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# OXIDATIVE CONVERSION OF PHOSPHOROTHIOLATES TO PHOSPHINYLOXYSULFONATES PROBABLY VIA PHOSPHOROTHIOLATE S-OXIDES

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Summary. Phosphorothiolate S-oxides and their phosphinyloxysulfenate rearrangement products are probable intermediates in the facile conversion of phosphorothiolates to phosphinyloxysulfonates on peracid oxidation. They may also be intermediates in the biological oxidation of phosphorothiolates.

The phosphorothiolate moiety is an essential structural feature in about 15% of the current insecticides.[1] Phosphorothiolates act as acetylcholinesterase inhibitors both directly and when formed on oxidative desulfuration of phosphorodithioate insecticides.[2] Some phosphorothiolates may also require metabolic activation, perhaps involving sulfoxidation, although no activated products have been characterized.[3] Peracid oxidations are useful chemical models for the study of some activation reactions of thiophosphorus toxicants.[4] On attempting to prepare phosphorothiolate S-oxides we obtained instead a new class of phosphorus esters, the phosphinyloxysulfonates, whose formation probably involves a novel rearrangement reaction.

Profenofos (1A, Table I) reacts with three equivalents of m-chloroperoxybenzoic acid (MCPBA) on holding for one hr at 25°C in dry acetone to give a mixture of 25% 1A, 65-70% 2A + 3A and 5-10% 4A + 5A + 6A (eq 1, Ar = m-chlorophenyl, R defined in Table I). The first and

$$R_1R_2P(O)SR_3 \xrightarrow{\text{MCPBA}} \underset{1}{R_1R_2P(O)OS(O_2)R_3} + \underset{2}{R_1R_2P(O)OP(O)R_1R_2} + \underset{3}{R_1R_2P(O)OC(O)Ar} + \underset{4}{R_1R_2P(O)OH} + \underset{5}{HOS(O_2)R_3} \quad (1)$$

major product, 2A, was obtained pure by rapid extraction with cold aqueous $NaHCO_3$ of a similar compound mixture in $CHCl_3$ (ethanol free). Quenching with ethanol gave only 5A. Attempted isolation of 2A by TLC (silica gel) or HPLC (μPorasil) gave only 5A and 6A resulting from decomposition. The products are identified by $^{31}P$ and $^{1}H$ NMR, direct CI-MS on the mixture, and synthesis. Phosphinyloxysulfonate 2A (421, $[M+1]^+$) and anhydride 4A (453, $[M+1]^+$) were synthesized by reacting the dicyclohexylamine salt of 5A with propylsulfonic anhydride[5] and m-chlorobenzoyl chloride, respectively. Pyrophosphate 3A (611, $[M+1]^+$), prepared by di-

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Table I. $^{31}P$ NMR Chemical Shifts (10% Acetone-$d_6$ in Acetone)[a] for $R_1R_2P(O)X$[b]

| | $R_1$ | $R_2$ | $R_3$ | 1 X = $SR_3$ | 2 X = $OS(O_2)R_3$ | 3 X = $OP(O)R_1R_2$ |
|---|---|---|---|---|---|---|
| A | $C_2H_5O$ | 2-Cl-4-Br-$C_6H_3O$ | $C_3H_7$ | 28.24 | -16.60 | -17.42<br>-17.39 |
| B | $CH_3O$ | $CH_3O$ | $CH_3$ | 33.62 | - 8.41 | - 8.63 |
| C | $C_2H_5O$ | $C_2H_5O$ | $CH(CH_3)_2$ | 29.80 | -10.19 | -10.78 |
| D | $C_2H_5O$ | $C_2H_5O$ | $CH_2C(Cl)=CH_2$ | 28.36 | -10.30 | -10.82 |
| E | $C_2H_5O$ | $C_2H_5O$ | $CH_2C(Cl)=CHCl$[c] | 26.79 | -10.26 | -10.65 |
| F | $CH_3O$ | $NH_2$ | $CH_3$ | 37.42 | -10.01 | - 9.52 |
| G | $CH_3O$ | $NHC(O)CH_3$ | $CH_3$ | 29.44 | - 7.21 | - 9.12[d] |
| H | $CH_3O$ | $NH_2$ | $CH_2C(Cl)=CH_2$ | 34.80 | - 8.54 | - 8.73 |

[a]Referenced to 1% $(CH_3O)_3P(O)$ in $CDCl_3$. Signals upfield of this reference are given negative values. The signal of 85% $H_3PO_4$ appears 2.99 ppm upfield of that for $(CH_3O)_3P(O)$. Additional chemical shifts are: 4A -11.95, 4B -3.20, 4C -5.96, 4F -5.56, 4G -4.03, 5A -4.29, and 5G +1.55 ppm. Differences in the chemical shifts between 3C, 3D and 3E and between 3F and 3H are attributable to other solution components and concentration.

[b]Important insecticides are profenofos (1A), methamidophos (1F) and acephate (1G).

[c]*trans* isomer. Data for the *cis* isomer are 1 27.63 and 2 -10.22 ppm.

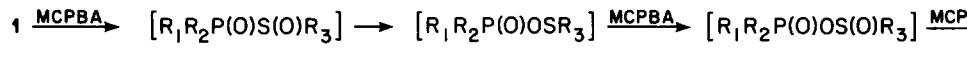
[d]Two signals in $CDCl_3$, -13.48, -13.77 ppm.

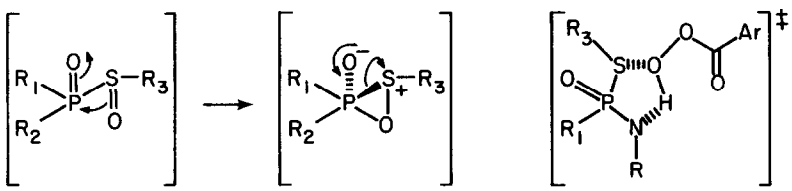
cyclohexylcarbodiimide-mediated coupling of 5A, gives two $^{31}P$ NMR signals ($\delta\Delta$ = 0.03 ppm, Table I, zero line broadening) consistent with two diastereoisomers. Products 3A and 4A, from MCPBA oxidation of 1A, are formed by secondary reactions of 2A with 5A and *m*-chlorobenzoic acid, respectively.

The reaction scheme in eq 1 appears to be generally applicable since a variety of phosphorothiolates react with excess MCPBA in dry acetone to give products analogous to those obtained with 1A (Table I).

Oxidative conversion of phosphorothiolates to phosphinyloxysulfonates is most easily rationalized by invoking a sequence of oxidation, rearrangement and further oxidation reactions (eq 2). Intermediates 7-9 have not been directly observed but two types of evidence indicate that if present they are oxidized faster than the starting material. First, NMR monitoring during the entire course of the reaction with excess MCPBA reveals only the starting material 1 and the terminal product 2, without detectable amounts of 7-9. Second, even on oxidation with 0.5-1.0 equivalent of MCPBA only 1 and 2 are evident with relatively little loss of starting material, consistent with most of the oxidant being consumed in further oxidation of 8 and 9. Thus, the rate-limiting step appears to be oxidation of 1 to 7 rather than the subsequent rearrangement of 7 to 8 and further oxidation to 9 and finally 2. The proposed conversion of 7 to 8 may involve a cyclic concerted rearrangement process via phosphoranoxide 10[6] or another mechanism such as a dissociation-recombination via a metaphosphate. An alternative to the

proposed P-S(O)-C → P-O-S-C (7 → 8) conversion is worthy of consideration with S-(2-chloroallyl) compounds D, E and H, i.e. [2,3] sigmatropic rearrangement to P-S-O-C derivatives[7,8] analogous to thiolcarbamate S-oxides; however, the conversion involves exclusively the former phosphorothiolate S-oxide → phosphinyloxysulfenate (7 → 8) rearrangement.[9]




Phosphoramidothiolates 1F-1H[10] undergo oxidation within seconds at -30 to -50°C[10] whereas phosphorothiolates 1A-1E require a temperature of >10°C for significant reaction. The reactivity sequence [methamidophos (1F) and 1H > acephate (1G) >> 1A-1E] suggests that oxidation is facilitated by the increased polarizability of the sulfur in the phosphoramidothiolates, as might occur on sulfoxidation via a transition state such as 11. Oxidation of the nitrogen does not appear to play a significant role since $^{15}N$ and $^{31}P$ studies[11] do not reveal $^{15}N$ signals in the region expected for N-oxides, i.e., 70-100 ppm downfield of the $^{15}N$ signal of 1G.[12] The insecticide sulprofos with three types of sulfur-containing moieties undergoes MCPBA oxidations in sequence at its methylthiophenyl, phosphorothionate and phosphorothiolate substituents.[13]

S-Oxides from S-alkyl and S-(2,3-dichloroallyl) N,N-dialkylthiocarbamates, important metabolic intermediates in their herbicidal and mutagenic activities, respectively, are easily isolated.[8] In contrast, the high reactivity of the proposed phosphorothiolate S-oxides (7) has until now precluded their isolation, except as two derivatives: the diethyl phosphates [e.g. $(C_2H_5O)_2P(O)OC_6H_3$-2-Cl-4-Br] from phosphorylation of the reaction solvent by the phosphorothiolate S-oxides on carrying out the MCPBA oxidation in ethanol;[14] the phosphinyloxysulfonates (e.g. 2A) formed in solvents not undergoing phosphorylation (e.g. acetone, $CHCl_3$ and $CH_2Cl_2$) on rapid rearrangement of the phosphorothiolate S-oxides to the phosphinyloxysulfenates which in turn are further oxidized by MCPBA. These findings provide models for cellular activation and deactivation processes of S-alkyl phosphorothiolate pesticides. Thus, initial cytochrome P450-catalyzed oxidation is expected to form the S-oxide capable of phosphorylating acetylcholinesterase or other sites important in the poisoning sequence. Alternatively, the S-oxide is probably detoxified by hydrolysis or preferably by rearrangement to the phosphinyloxysulfenate which is not likely to be a phosphorylating agent.

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5. The dicyclohexylamine salt of 5A yields 2A with propylsulfonic anhydride but exclusively 3A with propylsulfonyl chloride.
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9. A [2,3] sigmatropic rearrangement reaction of the S-(2-chloroallyl) sulfoxides would give P-S-O-C derivatives and, in the case of 1E, it would also give 2-chloroacrolein (Ref. 8), neither of which was present. Thus, monitoring by $^{31}P$ NMR revealed no formation of a P-S-O-C bond (which is easily distinguishable from the corresponding P-O-S-C bond) and $^{1}H$ NMR showed no aldehyde proton at 9.46 ppm as appropriate for 2-chloroacrolein. Finally, the Ames mutagenicity test which is extremely sensitive for 2-chloroacrolein (Ref. 8) also failed to detect any trace of this product.
10. More than 20 phosphorus-containing products were evident by $^{31}P$ NMR or warming the 1F reaction mixture to 25°C for 5 min.
11. NMR monitoring (0°C) by $^{15}N$ and $^{31}P$ reveals that 1G ($\delta$ $^{15}N$ 131.7 ppm, $^{J}31_{P-}{}^{15}_{N}$ = 10.9 Hz) at 2M in 10% acetone-$d_6$ in acetone with four equivalents of MCPBA gives two pairs of $^{15}N$ lines at a higher field (120.4 ppm, $^{J}31_{P-}{}^{15}_{N}$ = 38.9 Hz; 122.0 ppm, $^{J}31_{P-}{}^{15}_{N}$ = 36.5 Hz) corresponding to 2G and 3G, respectively. The $^{15}N$ peaks are referenced to external 95% nitromethane in acetone-$d_6$ [$\delta$ $^{15}N$ = 380.23 ppm downfield of liquid ammonia; P. R. Srinivasan and R. L. Lichter, J. Magn. Resonance 28, 227 (1977)].
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13. Oxidation of sulprofos or $C_3H_7S(C_2H_5O)P(S)OC_6H_4$-4-$SCH_3$ in 10% acetone-$d_6$ in acetone ($\delta$ $^{31}P$ = +95.06 ppm) gives in sequence the phosphorodithioate thioether S-oxide (+94.83) and sulfone (+94.62) and the phosphorothiolate sulfone (+26.23) prior to any phosphorothiolate oxidation. The first three oxidations occur rapidly at -30°C whereas the phosphorothiolate oxidation requires > 10°C for significant reaction.
14. No phosphorylation occurs on holding 1A in ethanol for 7 days.


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