Organophosphorus Esters II

Novel Approach to the Synthesis of S-Alkyl Phosphorothioates *

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A simple procedure for the preparation of S-alkyl phosphorothioic acids (1) involving triethylammonium di-t-butyl phosphorothioate (2) as a thiophosphorylating agent for organic halides has been devised.

The need for a simple and efficient preparative procedure leading to S-alkyl phosphorothioates (1) emerged from increasing interest in the synthesis and chemistry of thionucleotides which has been aroused in recent years 1.

\[
\begin{align*}
R - S - P(\text{O})& - OH \\
\text{OH} &
\end{align*}
\]

The S-substituted phosphorothioic acids (1) synthesized earlier by others were prepared from the corresponding thiol with the aid of phosphorus oxychloride as a phosphorylating agent 2-6.

Two alternative procedures reported by ÄKERFELDT 7 consisted of: (a) reaction of mono- or polyfunctional alkyl halides with trilithium or trisodium phosphorothioate, and (b) addition of phosphorothioate anion to \(\alpha,\beta\)-unsaturated systems.

All methods mentioned, however, have several drawbacks: (a) thiols containing certain additional functional groups (OH, COOH, \(\text{NH}_2\) etc.) are liable to yield polyphosphorylated products (cf. l. c. 3); (b) the thiol group often reacts poorly with the phosphorylating agent, so the final yields of S-substituted phosphorothioic acids (1) are usually small; (c) the use of inorganic phosphorothioate as phosphorylating agent introduces certain purification and characterization problems and renders direct preparation of free S-alkyl phosphorothioic acids (1) impossible (cf. l. c. 7).

We wish to report now the successful application of a new thiophosphorylating agent for organic halides, viz. triethylammonium di-t-butyl phosphorothioate (2), which appears to be a reagent of choice for the direct preparation of free S-alkyl phosphorothioic acids (1).

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\begin{align*}
\text{Bu}^+\text{O}^-\text{P(S)}(\text{O})^\text{Et} &\xrightarrow{\text{R}-\text{X}} \text{Bu}^+\text{O}_2\text{P(0)}(\text{O})\text{SR}^\text{HCl} \text{CHCl}_3 \\
\text{2} &\rightarrow \text{R} - \text{S} - \text{P(0)}(\text{OH})_2 \\
\text{3} &\quad X = \text{Br} \text{ or I.}
\end{align*}
\]

The devised procedure involves the application of t-butyl groups as protecting groups in the synthesis of organic derivatives of phosphorothioic acid. It has been shown that t-butyl groups can be readily removed by dealkylation with dry hydrogen chloride in chloroform solution, the S-P bond being virtually unaffected by this treatment at low temperature.

Triethylammonium di-t-butyl phosphorothioate (2) is readily obtained in 76% yield from di-t-butyl phosphite by the addition of sulphur in benzene solution at 45 — 55°. Compound 2 undergoes reaction readily with organic bromides or iodides yielding the corresponding S-alkyl di-t-butyl phosphorothioates (3). The thiophosphorylation reactions were carried out in boiling dimethoxethane (DME) using stoichiometric amounts of the reagents. It was

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not necessary or desirable to isolate and purify the resulting phosphotriesters (3). The removal of t-butyl groups has been effected at 0 — 5° by passing dry hydrogen chloride through the solution of crude 3 in chloroform. The resulting S-alkyl phosphorothioic acids (1), obtained on evaporation of the solvent at slightly elevated temperature (40 — 50°), stretching vibrations. Additional proof of the thiol-structure of 1 and 3 was obtained from the examination of their 1H n.m.r. spectra. The phosphorus-hydrogen coupling constants (11 — 15 Hz) observed are too high to be ascribed to P — O — CH coupling, but they are fully consistent with the P — S — CH coupling.

| R   | Yield (crude salts) [%] * | M.p. [°C] | C   | H   | N   | P   | C   | H   | N   | P   |
|-----|--------------------------|----------|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Me  | 74                       | 159 — 160| 50.6| 8.8 | 4.5 | 10.1| 50.7| 8.8 | 4.4 | 10.2|
| Et  | 84                       | 157 — 158| 52.0| 9.3 | 4.3 | 9.6 | 52.2| 9.3 | 4.35| 9.9 |
| n-Br| 68                       | 161 — 162| 53.4| 9.5 | 4.15| 9.2 | 53.3| 9.5 | 4.6 | 9.1 |
| i-Pr| 35                       | 156      | 53.4| 9.5 | 4.15| 9.2 | 53.3| 9.5 | 4.2 | 9.55|
| n-Bu| 86                       | 157      | 54.7| 9.7 | 4.0 | 8.8 | 54.5| 9.6 | 4.0 | 8.8 |
| sec-Bu| 69                   | 146 — 147| 54.7| 9.7 | 4.0 | 8.8 | 54.2| 9.2 | 4.2 | 9.1 |
| i-Bu| 57                       | 154 — 155| 54.7| 9.7 | 4.0 | 8.8 | 54.3| 9.4 | 4.2 | 9.1 |
| allyl| 73                      | 164      | 53.7| 8.95| 4.2 | 9.25| 53.8| 8.7 | 3.9 | 9.4 |
| benzyl| 95                      | 151 — 152| 59.2| 8.3 | 3.6 | 8.05| 59.3| 8.8 | 3.5 | 8.1 |

Table I. Dicyclohexylammonium S-alkyl phosphorothioates (4).

* Calculated with respect to alkyl halide.

are colourless or pale-yellow, syrupy liquids of disagreeable odour. Because of their instability even at ambient temperature, they were characterized as dicyclohexylammonium salts (4) obtained by the action of dicyclohexylamine on benzene solutions of the freshly prepared corresponding acids 1. Yields, melting points and analytical data of the salts 4 thus obtained are summarized in Table I. They are colourless solids, almost insoluble in all known solvents and perfectly stable at room temperature. As shown by elemental analysis, they are satisfactorily pure when extracted with boiling acetone and dried, but they cannot be subjected to further purification by crystallization owing to their insolubility.

As dicyclohexylammonium S-alkyl phosphorothioates (4) could not be characterized by n.m.r. and their i.r. spectra were found to be of practically no diagnostic value, the structure of some intermediately formed S-alkyl di-t-butyl phosphorothioates (3) as well as the corresponding S-alkyl phosphorothioic acids (1) was unequivocally confirmed by spectral methods. All i.r. spectra of 3 exhibited characteristic strong absorption band at 1255 cm⁻¹; associated undoubtedly with the P — O...
388 SYNTHESIS OF S-ALKYL PHOSPHOROTHIOATES

Type of compd.  R  Characteristic i.r. absorption bands (cm⁻¹) ^H n.m.r. (δ, ppm; J, Hz)

| 3  | CAH₂—CBH₂—  | 1392 s, 1367 vs [But], 1255 vs [P=O], 1160 vs [C—O—(P)] | 1.34 (3HA, t, J=7.5), 1.50 (18H, s, C(CH₃)₃), 2.78 (2HB, 6 lines, JH—H = 7.5, Jp—s—CH₂ = 15.0) a | 3 (CAH₃)₂—CBH—CCH₂—

| 3  | (CAH₃)₂—CBH—CCH₂—  | 1395 s, 1370 vs [But], 1255 vs [P=O], 1160 s [C—O—(P)], 980 vs, 918 s [P—O—C(C)] b | 1.00 (6HA, d, J=6.3), 1.50 (18H, s, C(CH₃)₃), 1.68—2.20 (1HB, m), 2.64 (2HC, dd, JH—H = 6.8, Jp—s—CH₂ = 14.3) b | 1 (CAH₃)—CBH₂—

| 3  | CAH₃—CCH₃—CDH—  | 1398 s, 1373 vs [But], 1255 s [P=O], 1163 vs [C—O—(P)], 980 vs, 920 s [P—O—(C)] b | 1.00 (3HA, distorted t, J=6.9), 1.40 (2HB, d, J=7.2), 1.54 (18H, s, C(CH₃)₃), 1.25—1.88 (2HC, m), 3.25 (1HD, m) b | 3 (CAH₃)₂—CBH—CCH₂—

| 3  | CAH₃—CBH₂—  | 2315 s, 1650 s, br [P(O)OH], 1110 vs, br [P=O, bonded?] b | 1.28 (3HA, t, J=7.1), 2.77 (2HB, 6 lines, JH—H = 7.1), 7.14 (1s, OH) a | 1 (CAH₃)—CBH₂—

| 1  | (CAH₃)₂—C₃H₇—  | 2315 s, 1650 s, br [P(O)OH], 1175 vs, br [P=O, bonded?] b | 0.95 (6HA, d, J=6.0), 1.51—2.18 (1HB, m), 2.63 (2HC, dd, JH—H = 6.4, Jp—s—CH₂ = 13.1), 7.20 (s, br, OH) a | 1 (CAH₃)—C₃H₇—

| 1  | CAH₅—C₃H₇—CDH—  | 2280 s, br, 1650 s, br [P(O)OH], 1140 vs, br [P=O, bonded?] e | 1.00 (3HA, distorted t, J=7.1), 1.43 (2HB, d, J=7.1), 1.25—1.88 (2HC, m), 3.30 (1HD, m), 7.34 (s, OH) c | 1 (CAH₅—C₃H₇—

| 1  | Ph—CH₂—  | 1080 s (C—O—[P]), 980 vs, 950 vs (P—O—[C]), 700 s (P=S—?) cm⁻¹. | 3.98 (2H, d, Jp—s—CH₂ = 11.0, CH₂), 7.30 (s, OH, H arom.) f | 1 (Ph—CH₂—

Tab. II. n.m.r and i.r.r spectral assignments of some O,0-di-t-butyl-S-alkyl phosphorothioates (3) and S-alkyl phosphorothioic acids (1) a.

- All spectra were measured on crude samples.
- b Taken on neat sample.
- c In CHCl₃ solution.
- d In CCl₄ solution.
- e In CDC₁₃ solution.
- f In DMSO—D₆ solution.

Abbreviations used: s, strong; vs, very strong; br, broad; s, singlet; d, doublet; dd, double doublet; t, triplet; m, multiplet.

S-Alkyl O,O-di-t-butyl phosphorothioates (3).

General procedure

A mixture of triethylammonium salt 2 (8.19 g, 0.025 mole), alkyl bromide or iodide (0.025 mole), and dimethoxyethane (30 ml) was refluxed gently with stirring for 2 hours. Triethylammonium halide was filtered off and the filtrate evaporated in vacuo. Benzene (50 ml) was added to the residue and the solution was washed with water (2 × 10 ml), dried over anh. MgSO₄, and evaporated in vacuo to give the crude phosphotriester 3. Crude 3 could not be distilled in vacuo without decomposition.

The solution of S-methyl O,O-di-t-butyl phosphorothioate (prepared from 2 and methyl iodide used in 100% excess) could not be washed with water. Traces of triethylammonium iodide were removed from it by refrigeration.

Dicyclohexylammonium S-alkyl phosphorothioates (4).

General procedure

A rapid stream of dry, gaseous hydrogen chloride was passed through a solution of crude phosphotriester 3 (ca. 0.02 mole) in chloroform (20 ml) at 0—5° with stirring and efficient external cooling.

After 1.5 hours solvent was evaporated at room temperature, the residue dissolved in benzene (25 ml), and evaporated again at 40—45°. Crude S-alkyl phosphorothioic acid (1) thus obtained was dissolved in benzene (20 ml) and treated with 20% excess of dicyclohexylamine (the amount calculated with respect to the crude 1). Immediately formed dicyclohexylammonium salt 4 was filtered off, washed with benzene, and purified by continuous extraction with boiling acetone (3—4 hours). Dicyclohexylammonium S-benzyl phosphorothioate was prepared from the crude thioacid (colourless, crystalline solid, m.p. 92—94°) in DMSO solution.