Oxidation of O-Alkyl-O-(subst. phenyl) phenylphosphonothioates

Sir:

The well-known explanation of the mechanism of action of organophosphorus insecticides, especially the O,O-dialkyl-O-(subst. phenyl) phosphorothioate*1 series, is that these are oxidized by enzymes to the corresponding phosphorates in vivo, which inhibit the acetylcholinesterase in the central nervous system and cause the death of animals1). Interesting investigations have already been reported on the correlation between the acetylcholinesterase inhibition rates of the phosphorates or alkylphosphonates and the hydrolysis rates of inhibitors2,3). Concerning to O-alkyl-O-(subst. phenyl) phenylphosphonothioates, whether the correlation described above holds true or not is unknown because the O-alkyl group change has not yet been reported. In order to confirm the correlation, a simple method of synthesizing various pure phenylphosphonates (III) has to be found. In this report, (A) consists of the condensation of phenylphosphonochloridates (I) and alkaline phenolates (II), their slight modifications have been already reported3-5). Similar methods6) are applicable to phosphorothioates (IV), though they are oxidized to phosphorates (V) by nitric acid as well7), (B). But the oxidation of phenylphosphonothioates (VI) to the corresponding phenylphosphonates (VII) has not been tried. To obtain pure phenylphosphonates (VII) without difficulty, the present authors oxidized phenylphosphonothioates (VI) with nitric acid, and found that the reactions proceed accordingly to the following equation (C):

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\begin{align*}
B & \rightarrow \text{IV} \\
\text{HNO}_3 & \rightarrow \text{V}
\end{align*}
\]

R stands for a lower alkyl group.

\[
\begin{align*}
\text{A} & \rightarrow \text{B} \\
\text{I} & \rightarrow \text{II} \\
\text{III} & \rightarrow \text{IV} \\
\end{align*}
\]

R stands for a lower alkyl group.

Sixty-seven grams of nitric acid (d=1.42) was added at 15~20°C with stirring to 30 grams

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*1) Chemical names of phosphorus compounds in this paper are based upon the Drake Committee's Report (Chem. Eng. News, 30, 4515 (1952)).


of supercooled liquid O-ethyl-O-4-(nitrophenyl) phenylphosphonothioates (VI a) (m.p. 36−38°C). During the addition much heat and nitrogen monoxide evolved. After the addition, the reaction mixture was stirred continuously for a period of 2 hours, and for additional 2 hours maintained at the same temperature under reduced pressure, then poured into ice-water. An organic layer was separated and extracted with three portions of 100 ml of ether. The extract was washed thrice with cold water, then five times with 5% sodium bicarbonate aqueous solution, again with cold water until the washing was neutral to litmus, and dried with sodium sulfate. After the solvent was removed, 19 grams of a pale yellow liquid was obtained which was purified by chromatography. This pure substance has a refractive index n^25_D 1.5674. (Reported^3,4), n^27_D 1.5678 and n^30_D 1.5621.) The analitic data of this compound agree with formula C_{14}H_{14}N_2O_5P. Anal. Found. P, 10.0; N, 4.55. Calcd. for P, 10.1; N, 4.56%.

The IR spectrum of the product shows a strong absorption at 1260 cm\(^{-1}\) originated by a P=O stretching vibration^8); but the starting material O-ethyl-O-(4-nitrophenyl) phenylphosphonothioate (VI a) does not cause any absorption in the region of 1260 cm\(^{-1}\). (see Fig. 1). From the IR spectra and the quantitative analyses of the elements, the product

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was identified with O-ethyl-O-(4-nitrophenyl) phenylphosphonate (VII a).

By this method phenylphosphonate will be easily obtained from phenylphosphonothioates. For example, oxidation of O-ethyl-O-(4-cyanophenyl) phenylphosphonothioate (VI b) (m.p. 83°C) gave a yellow oily liquid, which has a P=O band at 1260 cm⁻¹ (see Fig. 2) and n_D 1.5535. *Anal. Found.* P, 10.6; N, 4.68.

Thus the compound was identified with O-ethyl-O-(4-cyanophenyl) phenylphosphonate (VII b).

The details about the inhibition rates of the acetylcholineesterase and the hydrolysis rates of phenylphosphonates will be presented in another report on this journal.

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