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ORGANOSULPHUR COMPOUNDS—XXIX[1]

SYNTHESIS AND PUMMERER REARRANGEMENT OF β-PHOSPHORYL SULPHOXIDES

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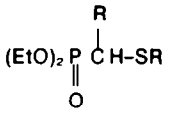
Abstract—β-Diethoxyphosphorylethyl sulphoxides **4**, prepared by selective oxidation of the corresponding sulphides **6** using bromine/potassium hydrogen carbonate as oxidising agent in a two-phase system, undergo the Pummerer rearrangement accompanied by elimination affording E-β-ethylthiovinylphosphonate **7**. The synthesis of Z-α-bromo-β-ethylthiovinylphosphonate **14** is also described.

α-Phosphoryl-substituted organosulphur compounds attracted recently much attention because of their importance in synthetic organic chemistry.[2] The presence in one molecule of the phosphonate grouping and an organosulphur moiety provides a unique opportunity for effecting a variety of interesting synthetic transformations. For example, the appropriately substituted α-phosphoryl sulphides **1** are key reagents in the synthesis of aliphatic[3] and aromatic ketones[4] while S,S-thioacetals of formylphosphonates **2** are the best starting materials for the synthesis of ketene thioacetals.[5]



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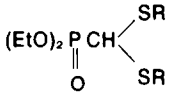

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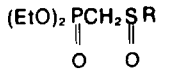

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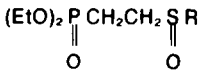

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Of considerable interest from both synthetic and stereochemical points of view are α-phosphoryl sulphoxides **3** which have been obtained in racemic and optically active forms in our laboratory.[6,7] Owing to the presence of the phosphonate moiety, they are key substrates in the synthesis of racemic and chiral α,β-unsaturated sulphoxides based on the Horner–Wittig reaction.

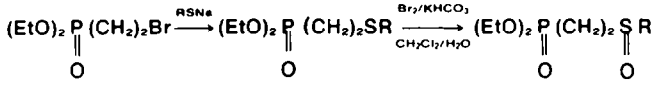
Up to now, however, the chemistry of β-phosphoryl-substituted organosulphur compounds and their synthetic application have received relatively little attention.[11] Only recently, the use of the suitably substituted β-phosphoryl sulphides in the synthesis of some natural products was reported.[12,13] In this paper we wish to report the simple and effective synthesis of β-phosphoryl sulphoxides **4** and their Pummerer rearrangement.

RESULTS AND DISCUSSION

We found that the reaction of the easily accessible diethyl β-bromoethanephosphonate **5**[14] with sodium mercaptides in ether-dimethoxyethane solution at room temperature gave the corresponding β-phosphorylethyl sulphides **6** in good yield. Only in the case of sodium methylmercaptide was the yield of **6c** lower, due to elimination of methane thiol from **6c** under the reaction conditions.

The β-phosphoryl sulphoxides **4** were prepared by the oxidation of sulphides **6** with bromine in the presence of potassium hydrogen carbonate under two-phase conditions.[15] Formation of the corresponding sulphones was not observed. The yields and physical and spectral data of β-phosphoryl sulphides **6** and sulphoxides **4** prepared are collected in Table 1.

In an extension of our previous study on the Pummerer rearrangements of α-phosphoryl sul-



5 **6** **4**

a, R = Et
b, R = Ph
c, R = Me

a, R = Et
b, R = Ph

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Table 1. Preparation and properties of β-phosphorylethyl sulphides **6** and sulphoxides **4**

	Product	Yield[a] %	n_D(°C) bp(°C)torr	^{31}P NMR($CDCl_3$) δ(ppm)	^{13}C NMR ($CHCl_3$) δ(ppm)
6a	$(EtO)_2P(O)(CH_2)_2SEt$	86	1.4650(22) 87/0.3	28.2	14.6($SCH_2\underline{CH_3}$);16.5(d,J_{POCC}=5.3 Hz,$POCH_2\underline{CH_3}$); 24.4(d,J_{PCC}=3.7 Hz,$PCH_2\underline{CH_2}$-);25.7($S\underline{CH_2}CH_3$); 27.0(d,J_{PC}=136.5 Hz,$P\underline{CH_2}CH_2$-);61.6(d,J_{POC}=6.3 Hz, $PO\underline{CH_2}CH_3$)
6b	$(EtO)_2P(O)(CH_2)_2SPh$	90	1.5230(23) 103/0.2	28.0	14.4(d,J_{POCC}=6.9 Hz,$POCH_2\underline{CH_3}$);24.6(d,J_{PC}=180.2 Hz, P-$\underline{CH_2}$-CH-);25.3(d,J_{PCC}=3.0 Hz,$P\underline{CH_2}CH_2$-);59.8(d, J_{POC}=8.8 Hz,$PO\underline{CH_2}CH_3$);124.8, 127.2, 128.1,1.133(aromatic)
6c	$(EtO)_2P(O)(CH_2)_2SMe$	55[b]	1.4600(20) 62/0.2	27.9	13.4($S\underline{CH_3}$);14.4(d,J_{POCC}=7.8 Hz,$POCH_2\underline{CH_3}$); 25.2 (d,J_{PCC}= =5.2 Hz,$PCH_2\underline{CH_2}$-);25.6(d,J_{PC}=145.6,$P\underline{CH_2}CH_2$-);60.1 (d,J_{POC}=7.8 Hz, $PO\underline{CH_2}CH_3$)
4a	$(EtO)_2P(O)(CH_2)_2S(O)Et$	90	1.4762(23)	27.9	6.8($SCH_2\underline{CH_3}$);16.4(d,J_{POCC}=5.8 Hz, $POCH_2\underline{CH_3}$);18.6 (d, J_{PC}=146.2 Hz, $P\underline{CH_2}CH_2$-); 44.0(d,J_{PCC}=4.3 Hz,PCH_2-$\underline{CH_2}$); 45.3($S\underline{CH_2}CH_3$); 62.0(d,J_{POC}=7.0 Hz, $PO\underline{CH_2}CH_3$)
4b	$(EtO)P(O)(CH_2)_2S(O)Ph$	88	1.5438(22)	27.1	14.4(d,J_{POCC}=5.2 Hz,$POCH_2\underline{CH_3}$);15.3(d,J_{PC}=189.6 Hz, PCH_2CH_2-); 47.1(d,J_{PCC}=5.2 Hz, $PCH_2\underline{CH_2}$-); 60.1 (d, J_{POC}=7.8 Hz, $PO\underline{CH_2}CH_3$); 127.3,127.9,129,3,140.7(aromatic)

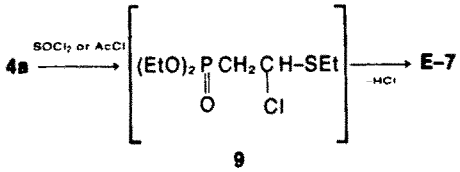
[a] Yield of a pure product. Satisfactory analytical data (±0,4% P,S) were obtained for all compounds listed in Table.
[b] Diethyl vinylphosphonate was also isolated in 40% yield.

phoxides 3[16] we investigated in detail the various Pummerer-type reactions of β-phosphoryl sulphoxide **4a**. At first, the classical Pummerer reaction of **4a** with acetic anhydride was carried out. The reaction was complete after 2 h in refluxing acetic anhydride and gave E-diethyl β-ethylthiovinylphosphonate (**7**) in 77% yield. None of the expected Pummerer reaction product, α-acetoxy β-diethoxyphosphorylethyl ethyl sulphide **8**, was isolated. Undoubtedly, it undergoes elimination of acetic acid to form **E-7**.

In accord with our recent observation that molecular bromine acts as an effective catalyst for the Pummerer reaction[17] we found that the addition of catalytic amounts of bromine to the mixture of **4a** and acetic anhydride completes the reaction within 2 h at 65°, as revealed by ^{31}P-NMR spectra.

Assignment of the E-geometry to the vinylphosphonate **7** formed was based on ^{1}H-NMR spectral data. Analysis of the vinylic ABX-system in the ^{1}H-NMR spectrum of **7** showed that olefinic protons absorb at $\delta = 5.53$ and 7.40 ppm. A simple calculation of the chemical shifts of the vinylic protons H_A and H_B in **7** by means of the additive increments method[18] indicated that the protons H_A and H_B in **E-7** should appear at $\delta = 5.62$ and 7.24 ppm whereas in **Z-7** at $\delta = 5.78$ and 7.03 ppm, respectively. Furthermore, the values of the coupling constants $^3J_{H\text{-}H} = 16.4$ Hz and $^3J_{P\text{-}H} = 21.1$ Hz provide independent proof of the E-geometry of **7**.

Vinylphosphonate **E-7** was found to be also formed as a result of the Pummerer-type reaction between **4a** and thionyl chloride or acetyl chloride carried out at room temperature. In this case too, the transiently formed Pummerer product, α-chloro-β-diethoxyphosphorylethyl ethyl sulphide **9**, eliminated hydrogen chloride spontaneously, and gave **E-7** as the final reaction product.



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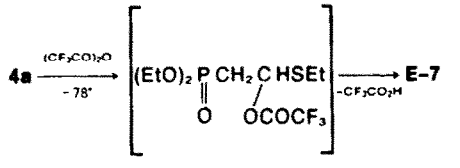

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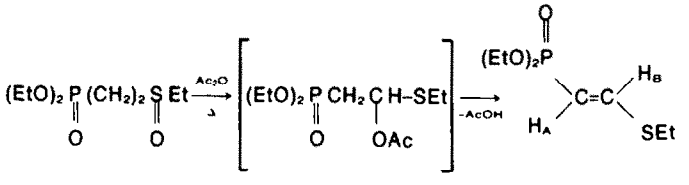


4a **8** **E-7**

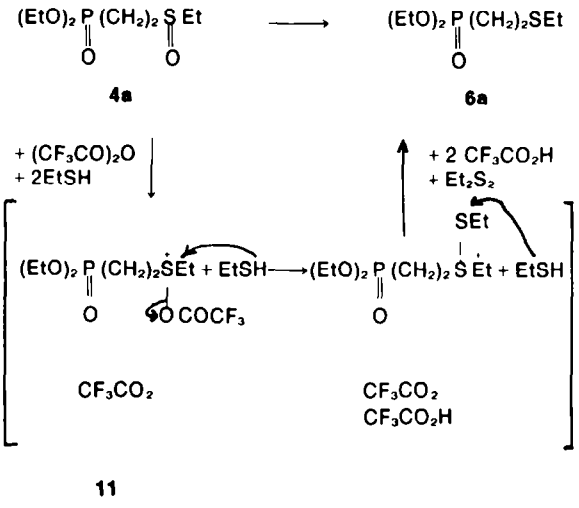
It should be pointed out that with the most reactive trifluoroacetic anhydride the Pummerer reaction of **4a** was complete after 15 min at *ca.*-78°. However, when the reaction mixture was warmed to room temperature the vinylphosphonate **E-7** was again isolated in 78% yield.

In order to obtain additional information on the course of the reaction of **4a** with trifluoroacetic anhydride we took advantage of the presence of phosphorus in sulphoxide **4a** and monitored this reaction by means of ^{31}P-NMR spectra (Fourier-transform technique with proton noise decoupling). Thus, a solution of **4a** in methylene chloride was treated with trifluoroacetic anhydride at −80°. The signal at δ_{31P} 27.8 ppm, characteristic of **4a**, disappeared immediately and a new signal at δ_{31P} 24.4 ppm was observed. It was assigned to the acyloxysulphonium salt **11** formed in the first stage of the Pummerer reaction. After a short time a new signal at δ_{31P} 22.7 ppm was formed at the expense of the signal absorbing at δ_{31P} 24.4 ppm. This stage of the reaction was completed at −40°. There is no doubt that the latter signal corresponds to the Pummerer reaction product, α-trifluoroacetoxy β-diethoxyphosphorylethyl ethyl sulphide (**10**). At the temperatures between 0° and 20° elimination of trifluoroacetic acid from **10** takes place resulting in appearance in the ^{31}P NMR spectrum of the already known resonance signal at δ_{31P} 17.2 ascribed to **E-7**.

The ^{31}P NMR spectral studies presented above allow to propose for the reaction of **4a** with trifluoroacetic anhydride the following main steps (Scheme I) i.e. the formation of sulphonium salt **11** and then of the ion pair **12** which undergoes the rearrangement to give the Pummerer reaction product **10** which, in turn, eliminates trifluoroacetic acid to form **E-7**.[19]

The fact that the trifluoroacetoxy sulphonium salt **11** is formed as a real intermediate, which is observed in the ^{31}P NMR spectra, is substantiated by our further observation that the Pummerer reaction of **4a** carried out in the presence of ethanethiol results in the quantitative reduction of **4a** to **6a** and oxidation of ethanethiol to diethyl disulphide.

Such a reaction course is consistent with the nucleophilic attack of the sulphur atom of thiol on the sulphur cation of **11** and has a precedent in the literature.[20]



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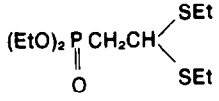
It is interesting to note that the reaction of ethanethiol with **12** should give S,S-diethyl thioacetal of α-phosphorylacetaldehyde (**13**)[21] as a result of nucleophilic attack of the sulphur atom of thiol on the carbon atom of the intermediate **12**.[22] However, the formation of **13** was not observed.



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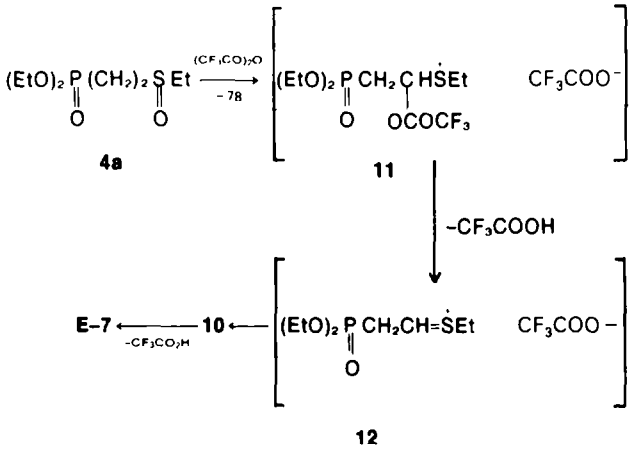
Finally, a comment should be made of the easy elimination of the HX-species (X = CH_3COO^-, CF_3COO^-, Cl^-) from various β-phosphoryl sulphur compounds which seems to be the general feature of such systems. A similar elimination of thiols and sulphenic acids from β-phosphoryl dithioacetals and their S-oxides has been reported earlier.[23,24]

We took advantage of this phenomenon and introduced a bromine atom at the α-position of the vinylphosphonate **E-7** by bromination of **E-7** fol-



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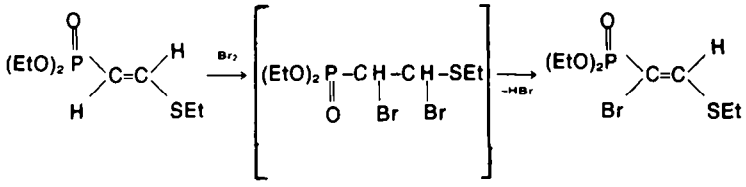
Scheme I.



E-7 14

lowed by spontaneous elimination of hydrogen bromide to give (**14**).

The elimination was found to be completely regio- and stereospecific because only one isomer **Z-14**, was formed. Its structure was assigned on the basis of the value of the phosphorus-hydrogen coupling constant, $^3J_{P\text{-}H}$, equal to 13 Hz which corresponds to the cisoidal configuration of both interacting nuclei.

EXPERIMENTAL

All b.ps and m.ps are uncorrected. Solvents and commercial reagents were distilled and dried by conventional methods before use. ^{1}H NMR spectra were recorded at 60 MHz with a R12B Perkin–Elmer spectrometer. ^{31}P- and ^{13}C-NMR spectra were obtained on a Jeol JNM-FX60 Fourier transform spectrometer with external 85% H_3PO_4 and internal Me_4Si as standards.

General procedure for synthesis of β-phosphorylethyl sulphides **6**

To a solution of diethyl β-bromoethanephosphonate (**5**) (7.34 g; 0.03 mol) in 20 ml ether and 20 ml dimethoxyethane an equimolar amount of sodium mercaptide was added. The reaction mixture was stirred for 3 h and allowed to stand overnight. The solvents were evaporated and the residue was dissolved in chloroform (20 ml). The chloroform solution was washed with water, dried and evaporated to afford the crude sulphide **6** which was purified by distillation. The yields and physical constants of sulphides **6** are given in Table 1.

General procedure for synthesis of β-phosphorylethyl sulphoxides **4**

Sulphoxides **4** were obtained by the oxidation of sulphides **6** (0.03 mol) by bromine/aqueous potassium hydrogen carbonate reagent in a two-phase system according to the procedure described by us earlier.[16] The crude products were purified by column chromatography on silica gel (benzene:acetone; 10:1). The yields and physical data of sulphoxides **4** are given in Table 1.

Reaction of β-diethoxyphosphorylethyl ethyl sulphoxide (**4a**) *with acetic anhydride*

Sulphoxide **4a** (2.42 g, 0.01 mol) was dissolved in 10 ml of acetic acid anhydride and refluxed for 2 h at 120°. After concentration under reduced pressure the crude product was purified by distillation to give E-diethyl β-ethylthiovinylphosphonate (**7**), 1.72 g (77%); b.p. 85°/0.1 mmHg; n_D^{23} 1.4870. ^{1}H NMR ($CDCl_3$)δ(ppm): 1.32 (t, 6, CH_3CH_2OP, $J_{H\text{-}H}$ = 7.1 Hz); 1.34 (t, 3, CH_3CH_2S, $J_{H\text{-}H}$ = 7.6 Hz); 2.82 (q, 2, CH_3CH_2S, $J_{H\text{-}H}$ = 7.6 Hz); 4.07 (dq, 4, CH_3CH_2OP, J_{PH} = 8.7 Hz); 5.53 (dd, 1, P-CH = C, J_{PH} = 16.5 Hz, $J_{H\text{-}H}$ = 16.4 Hz); 7.40 (dd, 1, P-CH = CH, $J_{P\text{-}H}$ = 21.1 Hz, $J_{H\text{-}H}$ = 16.4 Hz). ^{31}P NMR ($CDCl_3$)δ(ppm): 17.2. ^{13}C NMR ($CDCl_3$)δ(ppm): 13.7 (CH_3CH_2S); 16.3 (d, CH_3CH_2OP, $J_{P\text{-}C}$ = 4.9 Hz); 108.7 (d, P-CH = CH, $J_{P\text{-}C}$ = 192.7 Hz); 149.5 (d, P-CH = CH-, $J_{P\text{-}C}$ = 9.9 Hz. Found: C, 42.61; H, 7.50; P, 13.99. Calc for $C_8H_{17}O_3PS$: C, 42.85; H, 7.64; P, 13.8%.

The reaction of **4a** (2.42 g, 0.01 mol) with acetic anhydride (10 ml) in the presence of catalytic amounts of bromine was complete after 2 h at 65°C and gave after workup as described above 1.83 g (82%) of **E-7**.

Reaction of sulphoxide **4a** *with acetyl chloride*

Sulphoxide **4a** (2.42 g, 0.01 mol) and acetyl chloride (5 ml) were stirred at room temperature for 4 h. Excess acetyl chloride was removed *in vacuo* and the residue was distilled to give 1.45 g (65%) of **E-7**.

Reaction sulphoxide **4a** *with thionyl chloride*

To a solution of **4a** (2.42 g, 0.01 mol) in benzene (10 ml) thionyl chloride (1.19 g, 0.01 mol) was added. The reaction mixture was stirred for 3 h. After removal of benzene the residue gave **E-7** (1.52 g, 68%) on distillation.

Reaction of sulphoxide **4a** *with trifluoroacetic anhydride*

To a solution of sulphoxide **4a** (2.42 g, 0.01 mol) in 10 ml methylene chloride, trifluoroacetic anhydride (1 ml) was added at −78°. The reaction mixture was stirred at this temperature for 15 min. Then the temperature was raised to 20° and the resulting mixture was evaporated and distilled to give **E-7**; 1.74 g (78%).

Reaction of E-diethyl β-ethylthiovinylphosphonate **7** *with bromine*

To a solution of **E-7** (4.48 g, 0.02 mol) in 25 ml of carbon tetrachloride bromine (3.2 g, 0.02 mol) was slowly added. The reaction mixture was stirred at room temperature for 10 min. Evaporation of solvent and distillation gave α-bromo-β-ethylthiovinylphosphonate (**14**), 3.09 g (51%); b.p. 126–129°/0.01 mmHg; n_D^{21} 1.5130. ^{1}H NMR (CCl_4)δ(ppm): 7.91 (d, 1, P-C = CH, $J_{P\text{-}H}$ = 13.0 Hz). ^{31}P NMR ($CHCl_3$)δ(ppm): 8.3. ^{13}C NMR ($CDCl_3$)δ(ppm): 103.8 (d, P-C = CH-, $J_{P\text{-}C}$ = 211.2 Hz); 150.3 (d, P-C = CH, $J_{P\text{-}C}$ = 20.7 Hz). (Found: P, 9.98; Br, 26.14. Calc for $C_8H_{16}BrO_3PS$: P, 10.22; Br, 26.36%).

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[21]Compound **13** has been synthesised undependently by us from α-diethylphosphorylacetaldehyde diethylacetal and ethanethiol; $\delta_{31P} = 25.7$ ppm.
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