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The Reaction of Alkyl 3-Alkoxy-2-bromopropanoate with Triethyl Phosphite

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Synopsis. Alkyl 3-alkoxy-2-bromopropanoate reacted with triethyl phosphite to give alkyl 2,3-bis(diethoxyphosphinyl)propanoate as the major product.

It is well known that alkyl 2-haloalkanoates react with trialkyl phosphite to give alkyl 2-(dialkoxyphosphinyl)alkanoates by means of an Arbuzov reaction.[1] However, when ethyl 2-bromo-3-ethoxypropanoate(**1**) was treated with triethyl phosphite, the expected product, ethyl 3-ethoxy-2-(diethoxyphosphinyl)propanoate (**2**), was not obtained at all; rather, ethyl 2,3-bis(diethoxyphosphinyl)propanoate(**3**) was obtained as the major product. We now wish to report on these unusual results.

$$\mathrm{ROCH_2CHBrCOOR' + 2P(OR'')_3 \longrightarrow (R''O)_2OPCH_2CH[PO(OR'')_2]COOR' + R''Br + ROR''} \qquad (1)$$

The reaction of **1** with three molar equivalents of triethyl phosphite began at 120 °C with the evolution of ethyl bromide, diethyl ether, and ethanol. From the residual mixture, **3**, triethyl phosphate, and ethyl 3-(diethoxyphosphinyl)propanoate(**4**) were obtained by distillation under reduced pressure. The reactions of other alkyl 3-alkoxy-2-bromopropanoates gave similar results, as is summarized in the table.

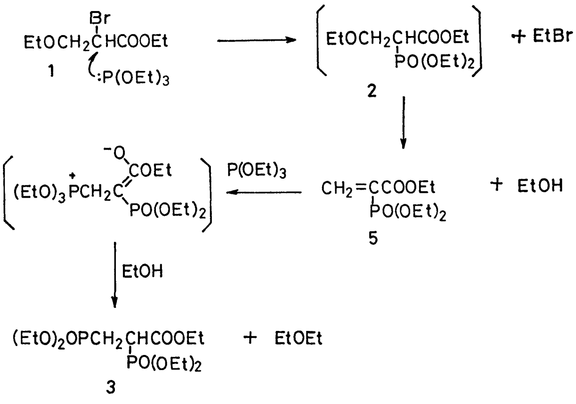
The yields of **3** were slightly decreased with an increase in the bulkiness of the alkyl group of R and/or R′. Even if an excess amount of triethyl phosphite was used, the yield of **3** did not increase. With an equimolar amount of triethyl phosphite, the yield of **3** was only 12%. In the reaction of **1** with trimethyl phosphite, none of the analogous product could be detected. From this mixture, dimethyl methylphosphonate was isolated almost quantitatively, and **1** was recovered, indicating that the rapid isomerization of trimethyl phosphite to dimethyl methylphosphonate by means of methyl bromide produced from the Arbuzov reaction occurred.

Table 1. Yields of alkyl 2,3-bis(dialkoxyphosphinyl)-propanoates from alkyl 3-alkoxy-2-bromopropanoates(**1**) with trialkyl phosphites

R	R′	R″	Bp/10^{-2} mmHg	Yield/%
CH_3	CH_3	CH_3	—	0[a]
CH_3	C_2H_5	CH_3	—	0[a]
CH_3	CH_3	C_2H_5	130—140	61[b]
C_2H_5	C_2H_5	C_2H_5	138—145	56[b]
n-C_3H_7	CH_3	C_2H_5	130—140	50[b]
i-C_3H_7	CH_3	C_2H_5	131—139	46[b]
n-C_4H_9	CH_3	C_2H_5	130—141	36[b]

a) Methyl or ethyl 2-bromo-3-methoxypropanoate respectively was almost entirely recovered. b) These were contaminated by products from the ester exchange.

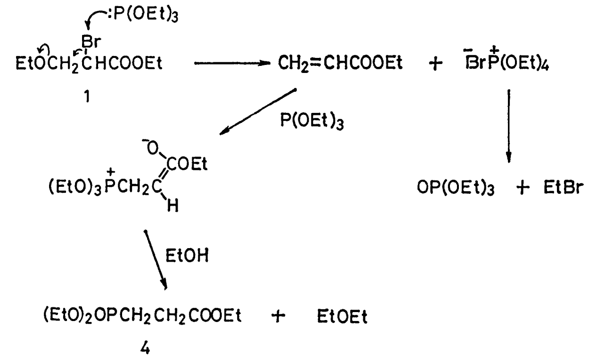
The reaction may proceed as is shown in Scheme 1; the unstable intermediate, **2**, which may be formed by the Arbuzov reaction of **1** with triethyl phosphite, immediately eliminates the ethanol to give ethyl 2-(diethoxyphosphinyl)propenoate(**5**), which reacts subsequently with triethyl phosphite to give **3**.



Scheme 1.

A facile elimination of ethanol has been found in the transformation of diethyl 2-(ethoxymethyl)propanedioate into diethyl 2-methylenepropanedioate.[2] When **5** prepared by another method[3] was treated with triethyl phosphite in the presence of ethanol at 110 °C for 0.5 h, **3** was given in a 62% yield.[5]

The formation of ethyl acrylate and **4** may be interpreted as in Scheme 2. The nucleophilic attack of triethyl phosphite may occur at the bromine center to give ethyl acrylate and tetraethoxyphosphonium bromide.[4] The former reacts with triethyl phosphite to give **4**,[5] and the latter decomposes to ethyl bromide and triethyl phosphate. The nucleophilic attack of triethyl phosphite might occur competitively at the carbon adjacent to the ethoxycarbonyl group and at the bromine, giving **3** and **4** respectively. The more nucleophilic diethyl phosphonate anion attacks preferentially at the bromine center to reduce **1** to



Scheme 2.

ethyl 3-ethoxypropanoate in a high yield at room temperature.

Experimental

The Reaction of Ethyl 2-Bromo-3-ethoxypropanoate (1) with Triethyl Phosphite. Ethyl 2-bromo-3-ethoxypropanoate (**1**, 15.0 g, 0.067 mol) and triethyl phosphite (33.2 g, 0.21 mol) were placed in a three-necked flask with a gas-inlet tube and a reflux condenser fitted with a tube connected to a trap cooled with Dry Ice–acetone. The mixture was heated at 120—130 °C for 5 h with the bubbling of nitrogen gas, until the evolution of volatile material ceased. The trapped volatile material (6.9 g) was identified as a mixture of ethyl bromide, diethyl ether, ethanol, and a trace amount of ethyl acrylate with GLPC (Shimadzu GC-3AF, a 3 m× 3 mmϕ column packed with 15% PEG 9000 on Uniport B, at 50 °C), but their relative ratio could not be defined with reproducibility. The residual mixture was distilled fractionally to give 1.0 g of a mixture of triethyl phosphate, a trace amount of diethyl ethylphosphonate, 2.1 g of **4** (bp 151—152 °C/1 mmHg,† identified with an authentic sample6)), and 14.0 g of **3**; bp 138—145 °C/10^{-2} mmHg†. M^+ 374. ^{1}H-NMR (CCl_4) $\delta=2.40$ (2H, m, CH_2), 3.28 (1H, m CH); ^{13}C-NMR ($CDCl_3$–TMS) $\delta=23.3$ (d-d, $J_{CP}=140$ Hz $J_{CCP}=3$ Hz, CH_2P), 40.0 (d-d, $J_{CP}=127$ Hz, $J_{CCP}=$ 3 Hz, CHP); ^{31}P-NMR ($CDCl_3$–85% H_3PO_4) $\delta=-21.1$ (d, $J_{PP}=69$ Hz, PCH), -27.6 (d, PCH_2).

The Reaction of Ethyl 2-(Diethoxyphosphinyl)propenoate (5) with Triethyl Phosphite. A mixture of **5** (11.8 g, 0.05 mol), triethyl phosphite (8.3 g, 0.05 mol), and ethanol (9.2 g, 0.2 mol) was heated at 100—110 °C for 2 h in a nitrogen atmosphere. After the reaction, a fraction (11.6 g, bp 139—145 °C/10^{-2} mmHg) was obtained by distillation under reduced pressure. It was found to be identical with **3** by a comparison of the NMR and GLPC data (an 1×3 mmϕ column packed with 10% Silicone SE-30 on Uniport B, at 200 °C).

The Reaction of Ethyl 2-Bromo-3-ethoxypropanoate (1) with Sodium Diethyl Phosphonate. Stripts of sodium (2.3 g, 0.1 atm) was added, portion by portion, into diethyl phosphonate (52 g, 0.4 mol). After the disappearance of the metal, the reaction mixture was cooled with ice water, and then **1** (11.3 g, 0.05 mol) was added, drop by drop. The resulting mixture was stirred at room temperature for 5 h and then poured into 5% sulfuric acid–ice water. The reaction product was extracted with ether, and the ethereal solution was washed with water and dried over sodium sulfate. After the removal of the ether, ethyl ethoxypropanoate was obtained by distillation (bp 66—68 °C/17 mmHg†,7) 5.3 g, 72% yield).

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† 1 mmHg≈133.3 Pa.