Russian Journal of General Chemistry, Vol. 73, No. 11, 2003, pp. 1738–1741. Translated from Zhurnal Obshchei Khimii, Vol. 73, No. 11, 2003, pp. 1835–1838.

Reactions of Trialkyl Phosphites with Mono- and Diacylals of Halo-Substituted Acetic Acids

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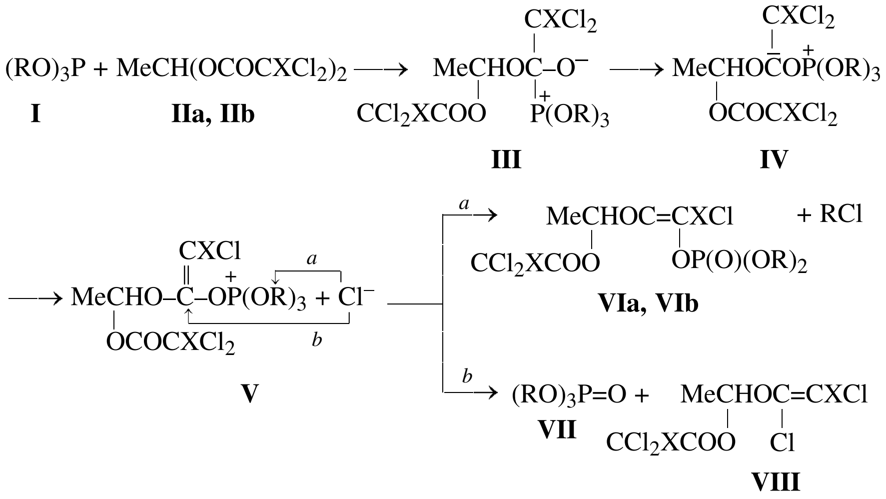
Received July 23, 2001

Abstract—Trialkyl phosphites react with diacylals of di- and trichloroacetic acids by the pathway of the Perkow reaction; with monoacylals of bromo- and iodoacetic acids, by the pathway of the classical Arbuzov reaction; and with monoacylals of di- and trichloroacetic acids, by the pathway of the nonclassical Arbuzov reaction.

Mono- and diacylals of unsubstituted acetic acid are fairly inert toward trialkyl phosphites **I**. As for the reaction of compounds **I** with trichloroacetic acid diacylal, only preliminary data are available [1].

Acylals of halo-substituted acetic acids contain three apparent electrophilic centers: carbon atoms of the methine, carbonyl, and halomethyl groups. Therefore, we expected that the reaction could occur along three pathways depending on the number and nature of halogen atoms and on the type of the acylal (mono- or di-).

We found that diacylals **IIa** and **IIb** derived from acetaldehyde and trichloroacetic and dichloroacetic acids, respectively, react with trialkyl phosphites with a considerable exothermic effect. The NMR spectra of the reaction mixtures and separate reaction products isolated in the individual form show that this reaction follows the pattern of the Perkow reaction, i.e., initially the phosphite attacks the carbonyl carbon atom to form bipolar ion **III**, which subsequently isomerizes into ion **IV** and then transforms into quasiphosphonium salt **V**, which is stabilized by pathways *a* and *b*.



II, VI, X = Cl (**a**), H (**b**).

The reaction yields functionally substituted vinyl phosphates **VIa** and **VIb**, which can also be considered as phosphorus-containing monoacylals of carboxylic acids, and trialkyl phosphate **VII**. Compounds **VIII** proved to be labile, and we failed to identify them.

It should also be noted that ethyl trichloroacetate reacts with triethyl phosphite only at a high tempera-

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ture [2]. The unusually easy reaction of **I** with diacylals of tri- and dichloroacetic acids is apparently due to additional electron-withdrawing effect of the substituted acyloxy group in position 1.

Below are the substituents R and X in compounds **VIa** and **VIb** and the NMR data [δ, ppm (*J*, Hz)]: R = Me, X = Cl: ^{1}H: 1.6 d (3H, Me, *J* 6.3), 3.8 d (6H, OMe, *J* 12.0), 6.48 q (1H, CH, *J* 6.3); ^{13}C: 19.5, 20.0 s (Me), 56.2 s (OMe), 89.0 s (CCl_3), 98.5, 99.5 s (CH), 136 d ($=CCl_2$, $^3J_{PC}$ 6.3), 146.1 d ($=CO_2$, $^2J_{PC}$ 7.6), 161.7 s (C=O); ^{31}P: –6. R = Et, X = Cl: ^{1}H: 1.25 t (6H, OCH_2Me, *J* 7.0), 1.58 d (3H, CH*Me*, *J* 6.3), 4.12 quintet (4H, OCH_2, *J* 7.0 and 7.0), 6.47 q (1H, CH, *J* 6.3); ^{31}P: –6. R = Et, X = H: ^{1}H: 1.26 t (6H, OCH_2Me, *J* 7.0), 1.6 d (3H, Me, *J* 6.3), 4.12 quintet (4H, OCH_2, *J* 7.0 and 7.0), 6.48 q (1H, CH, *J* 6.3), 6.4 s (1H, $CHCl_2CO$), 6.8–7.3 m (=CHCl); ^{31}P: –6.

Chloroacetic acid monoacylal shows a weak reactivity toward trialkyl phosphites. Bromoacetic acid monoacylal **IXa** reacts with trimethyl phosphite with a weak exothemic effect: As **Ia** is added dropwise to the monoacylal, the temperature of the reaction mixture grows from 18 to 23°C. At the same time, the reaction of monoiodoacetic acid acylal **IXb** occurs with a substantial exothermic effect: As **Ia** is added dropwise to **IXb**, the temperature of the reaction mixture grows from 18 to 33°C. However, in both cases, the strong odor of the phosphite remains after gradual spontaneous cooling of the mixture to 20°C. The odor disappears after heating the reaction mixture at 50–60°C for 2.5 h (Hlg = Br) or at 40–50°C for 2 h (Hlg = I). The ^{31}P NMR spectrum of the reaction mixture after removal of volatiles in a water-jet-pump vacuum contains a strong singlet with δ_P 23 ppm and a weak signal with δ_P 34 ppm. This fact suggests formation of two reaction products of the phosphonate structure. Therefore, we concluded that reaction of **I** with **IX** follows the pattern of the classical Arbuzov reaction yielding carboxylic acid monoacylal phosphorylated in the acid moiety (**X**) and methyl bromide or methyl iodide **XI**. The latter compounds enter into a competing reaction with the phosphite, yielding a methylphosphonic acid ester **XII**. The known δ_P value for **XII** is 35 ppm [3].

$$\mathrm{MeCH(OEt)OCOCH_2Hlg + (MeO)_3P}$$

$$\longrightarrow \mathrm{NeCH(OEt)OCOCH_2\overset{+}{P}(OMe)_3Hlg^-}$$

$$\longrightarrow \underset{\mathbf{X}}{\mathrm{MeCH(OEt)OCOCH_2P(O)(OMe)_2}} + \underset{\mathbf{XI}}{\mathrm{MeHlg}},$$

$$\mathrm{(MeO)_3P} \xrightarrow{\mathrm{MeHlg}} \underset{\mathbf{XII}}{\mathrm{MeP(O)(OMe)_2}},$$

$$\mathrm{MeCH(OEt)OCOCH_2P(O)(OMe)_2 + H_2O}$$

$$\longrightarrow \underset{\mathbf{XIII}}{\mathrm{(MeO)_2P(O)CH_2COOH}} + \mathrm{MeCHO + EtOH},$$

$$\mathbf{IX},\ \mathrm{Hlg = Br\ (\mathbf{a}),\ I\ (\mathbf{b})}.$$

To convert the initial acylal **IXa** or **IXb** completely, we took 1.2 molar equivalents of the phosphite. Dimethyl methylphosphonate **XII** and other volatiles were distilled off in a high vacuum into a trap cooled with liquid nitrogen. The residue, according to the ^{1}H and ^{31}P NMR spectra [δ, ppm (*J*, Hz)], was identified as compound **X**: 3.7 d (6H, POMe, *J* 12.0), 2.9 d (2H, PCH_2, *J* 20.8), 5.85 q (1H, O_2CH, *J* 6.0), 1.25 d (3H, CH*Me*, *J* 6.0), 3.6 q (2H, OC*H*$_2$Me, *J* 7.5), 1.1 t (3H, OCH_2Me, *J* 7.5); δ_P 23 ppm. By distillation of the condensate from the trap, we obtained dimethyl methylphosphonate; bp 70–71°C (10–12 mm Hg), n_D^{20} 1.4105. Published data: bp 67°C (12 mm Hg), n_D^{20} 1.4105 [4]. Its NMR spectra had the following characteristics, δ, ppm (*J*, Hz): 3.7 d (6H, POMe, *J* 12.0), 1.3 d (3H, P–Me, *J* 18.0); δ_P 34 ppm.

Since carboxylic acid monoacylals are readily hydrolyzed [5], compound **X** was subjected to hydrolysis under similar conditions: A mixture of the monoacylal of the phosphorylated acetic acid with water was kept at 50°C for 3 h. The volatiles were removed in a high vacuum. Crude acid **XIII** was identified by NMR spectroscopy, δ, ppm (*J*, Hz): 3.6 d (6H, POMe, *J* 11.5), 2.88 d (2H, PCH_2, *J* 21.0), 9.5 s (1H, COOH); δ_P 23 ppm.

Previously phosphorylated acetic acids were prepared by oxidation of the corresponding aldehydes [6]. Our method is a new route to these difficultly accessible substances.

Since the C–Cl is less polarized than the C–Br and C–I bonds and the ethoxy group is considerably less electron-withdrawing than the CCl_3COO and $CHCl_2 \cdot COO$ groups, monoacylals of trichloroacetic (**XIVa**) and dichloroacetic (**XIVb**) acids, compared to compounds **IIa**, **IIb**, **XIa**, and **XIb**, should be less reactive in the Perkow and classical Arbuzov reactions. On the other hand, the trichloro- and dichloroethanoate groups are sufficiently labile for occurrence of nucleophilic substitution at the methine carbon atom of the monoacylal under the action of trialkyl phosphite (nonclassical Arbuzov reaction).

Trichloroacetic acid monoacylal **XIVa** reacted with trimethyl phosphite with appreciable heat release: As **Ia** was added dropwise to the monoacylal, the temperature of the reaction mixture increased from 20 to 30°C. In the subsequent experiments, the temperature in the course of phosphite addition was kept no higher than 23°C. After adding the whole amount of **Ia**, the mixture was stirred for an additional 2 h. The ^{31}P NMR spectrum of the mixture contained two singlets with δ_P 27 and 1 ppm (ratio 1.5 : 1). The ^{1}H NMR spectrum of this mixture contains, among other signals, a strong singlet with δ 3.95 ppm belonging to methyl trichloroacetate **XVIa**. Distillation of the reaction mixture gave three fractions. The first consisted of trimethyl phosphate **VIIa**, δ 3.67 ppm (POMe, *J* 11.5 Hz), δ_P 1 ppm; the third, of dimethyl 1-ethoxyethylphosphonate **XVa**; and the second, of a mixture of **XVa** and **VIIa** in a 1.3 : 1.0 ratio. Below are the NMR data for **XVa**, δ, ppm (*J*, Hz): 4.15 m (1H, PCH), 3.7 d (6H, POMe, *J* 11.5), 3.6 q (2H, OCH_2, *J* 7.5), 1.2 d.d (3H, CH*Me*, *J* 7.5, 18.7), 1.02 t (3H, CH_2*Me*, *J* 7.5); δ_P 27 ppm.

Dichloroacetic acid monoacylal **XIVb** reacted with triethyl phosphite with a slight heat release: As triethyl phosphite was added dropwise to the monoacylal, the temperature of the reaction mixture increased from 20 to 23°C. The phosphite odor disappeared after keeping the reaction mixture at 50°C for 2 h and then at 80°C for 2.5 h. The ^{31}P NMR spectrum of the reaction mixture contained two singlets with δ_P 24 and 1 ppm (ratio 1.4 : 1.0), which were assigned to the phosphorus atoms of diethyl 1-ethoxyethylphosphonate **XVb** and triethyl phosphite **VIIb**. Vacuum distillation of the reaction mixture yielded ethyl dichloroacetate **XVIb**. Its ^{1}H NMR characteristics are as follows, δ, ppm (*J*, Hz): 6.25 s (1H, $CHCl_2$), 4.5 q (2H, OCH_2, *J* 7.0), 1.5 t (3H, Me, *J* 7.0). Unfortunately, we failed to fully separate **XVb** and **VIIb** by vacuum distillation; the fractions obtained contained these compounds in different ratios. The major fraction boiling at 98–103°C (10 mm Hg), according to the ^{31}P NMR spectra, contained these components in approximately equal amounts (singlets with δ_P 24 and 1 ppm of equal intensity). The ^{1}H NMR spectrum of this fraction contains the following signals, δ, ppm (*J*, Hz): 4.15 m (PCH, partially overlaps with the OCH_2 signals), 4.0, 4.07 q [$POCH_2$ (in phosphate and phosphonate), *J* 7.5 and 7.5], 3.5 q (OCH_2, *J* 7.5), 1.2 d.d (CH*Me*, *J* 7.5, 18.0), 1.17 t ($POCH_2$*Me*, *J* 7.5), 1.02 t ($CHOCH_2$*Me*, *J* 7.5).

The structures of **XV** and **XVI** suggest that these compounds are formed by nucleophilic substitution at the methine carbon atom of the acylal, i.e., the reaction follows the pattern of nonclassical Arbuzov reaction.

$$\underset{\textbf{XIVa, XIVb}}{\mathrm{MeCH(OEt)OCOCXCl_2}} + \mathrm{(RO)_3P}$$

$$\longrightarrow \underset{\textbf{XVII}}{\mathrm{MeCH(OEt)\overset{+}{P}(OR)_3\overset{-}{O}COCXCl_2}}$$

$$\longrightarrow \underset{\textbf{XVa, XVb}}{\mathrm{MeCH(OEt)P(O)(OR)_2}} + \underset{\textbf{XVIa, XVIb}}{\mathrm{XCl_2CCOOR}},$$

XIV, XVI = Cl (**a**), H (**b**); R = Me (**a**), Et (**b**).

Nucleophilic attack of the electrophilic methine carbon atom of the acylal with trialkyl phosphite yields quasiphosphonium salt **XVII**, which is stabilized by dealkylation under the action of the tri- or dichloroacetate anion. Unfortunately, although trialkyl phosphate is one of the major reaction products, we cannot suggest unambiguously the pathway of its formation.

EXPERIMENTAL

The NMR spectra were recorded on Bruker WP-80, Tesla BC-567A, and Bruker WP-250 spectrometers at 80, 100, and 250 (^{1}H); 25.2 (^{13}C); and 32.4 and 101.3 MHz (^{31}P). As solvents we used $CDCl_3$, CCl_4, and acetone-d_6 with addition of $CDCl_3$ for internal stabilization of the field. The ^{1}H and ^{13}C chemical shifts are given relative to TMS, and the ^{31}P chemical shifts, relative to 85% H_3PO_4.

Reaction of trimethyl phosphite with trichloroacetic acid diacylal. Trimethyl phosphite (4.67 g) was added dropwise with cooling to 19.93 g of trichloroacetic acid diacylal at a rate allowing the temperature of the reaction mixture to be maintained below 25°C. The low-boiling products were removed, and the residue was distilled in a high vacuum to give 0.86 g of a mixture of trimethyl phosphate and trichloroacetic acid diacylal, bp 31–92°C (1 mm Hg), δ_P 1 ppm; 6.25 g of the starting diacylal, bp 145–148°C (15 mm Hg); and 7.95 g (50.4%) of 1-[1-(*O,O*-dimethylphosphoryloxy)-2,2-dichloroethenyloxy]ethyl trichloroethanoate, bp 135–137°C (0.28 mm Hg). Found, %: Cl 41.64; P 7.22. $C_8H_{10}Cl_5O_7P$. Calculated, %: Cl 41.57; P 7.22.

Under similar conditions, the reaction of 26.44 g of trichloroacetic acid diacylal and 5.56 g of triethyl phosphite gave 1.79 g of a mixture of triethyl phosphate (δ_P 1 ppm) with the starting diacylal and 7.24 g (49.3%) of 1-[(*O,O*-diethylphosphoryloxy)-2,2-dichloroethenyloxy]ethyl trichloroethanoate, bp 137–138°C (0.14 mm Hg). Found, %: Cl 39.00; P 6.77. $C_{10}H_{14}\cdot Cl_5O_7P$. Calculated, %: Cl 39.00; P 6.81.

Under similar conditions, the reaction of 13.91 g of dichloroacetic acid diacylal and 5.44 g of triethyl phosphite gave 2.03 g of a mixture of triethyl phosphite (δ_P 1 ppm) with the starting diacylal and 6.09 g (47.9%) of 1-[(*O,O*-diethylphosphoryloxy)-2-chloroethenyloxy]ethyl dichloroethanoate, bp 132–134°C (0.12 mm Hg). Found, %: Cl 27.51; P 8.12. $C_{10}H_{16}\cdot Cl_3O_5P$. Calculated, %: Cl 27.58; P 8.03.

Reaction of trimethyl phosphite with monobromoacetic acid monoacylal. A mixture of 3.66 g of trimethyl phosphite with 5.2 g of monobromoacetic acid monoacylal was allowed to stand at 50–60°C for 2.5 h. The low-boiling products were distilled in a high vacuum into a trap cooled with liquid nitrogen to leave 4.22 g (71%) of 1-ethoxyethyl *O,O*-dimethylphosphorylethanoate. Found P, %: 12.93. $C_8H_{17}O_6P$. Calculated P, %: 12.89. Distillation of the condensate from the trap gave 0.79 g (25.9%) of dimethyl methylphosphonate, bp 70°C (12 mm Hg), n_D^{20} 1.4112.

Under similar conditions, the reaction of 5.8 g of monoiodoacetic acid monoacylal and 3.38 g of trimethyl phosphite gave 0.77 g (27.4%) of **XII**, bp 70–71°C (10–12 mm Hg), n_D^{20} 1.4115, and 3.66 g (67.2%) of 1-ethoxyethyl *O,O*-dimethylphosphorylethanoate.

Hydrolysis of 1-ethoxyethyl *O,O*-dimethylphosphorylethanoate. A mixture of 2.56 g of **X** and 0.29 g of water was heated at 50°C for 3 h. The volatiles were removed in a high vacuum to leave 1.64 g (91.6%) of *O,O*-dimethylphosphorylethanoic acid **XIII**.

Reaction of trimethyl phosphite with trichloroacetic acid monoacylal. Trimethyl phosphite (4.66 g) was added dropwise to 8.05 g of trichloroacetic acid monoacylal at a temperature not exceeding 23–25°C. The mixture was stirred for 2 h. Distillation gave 1.87 g (36.1%) of trimethyl phosphate, bp 22–24°C (0.45 mm Hg), n_D^{20} 1.4005; 1.31 g of a mixture of **VII** and **XVa**; and 2.45 g (39.6%) of dimethyl 1-ethoxyethylphosphonate, bp 94–98°C (0.45 mm Hg). Found P, %: 17.06. $C_6H_{15}O_4P$. Calculated P, %: 17.00.

Under similar conditions, the reaction of 5.3 g of triethyl phosphite with 6.42 g of dichloroacetic acid monoacylal gave 1.4 g (28%) of ethyl dichloroacetate, bp 48°C (7 mm Hg), n_D^{20} 1.4360 {published data: bp 56°C (10 mm Hg), n_D^{20} 1.4384 [7]}, and two fractions (2.75 and 6.09 g), bp 86–110°C (0.18 mm Hg) and 110–124°C (0.13 mm Hg), containing, according to the ^1H and ^{31}P NMR spectra, compounds **VII** (R = Et) and **XVb** in different ratios.

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