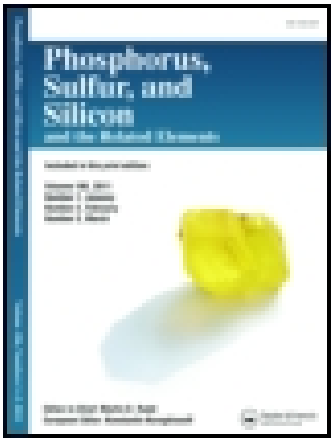

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Amidoalkylation of Phosphorus Trichloride with Acetamide and Alkyl Oxocycloalkanecarboxylates

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The course of the reaction between phosphorus trichloride, acetamide, and ethyl oxoalkanecarboxylates was studied in terms of the production of side-products. When alkyl 2-oxocycloalkanecarboxylates were used as substrates, together with the expected products—2-amino-2-phosphonocycloalkanecarboxylic acids—three side-products, namely 1-aminocycloalkanephosphonic acids (decarboxylation products of the latter compounds), 1-aminoethane-1,1-diphosphonic acids, and 1-hydroxyethane-1,1-diphosphonic acids were identified. Ethyl 1-oxocycloalkanecarboxylate afforded 4-amino-4-phosphonocyclohexane carboxylic acid in good yield.

Keywords Aminophosphonates; analogs of aspartic and glutamic acids; Oleksyszyn–Soroka reaction

INTRODUCTION

Aminoalkanephosphonic acids are generally defined as analogs of amino acids, in which the carboxylic group is replaced by a phosphonic acid function or a related moiety. Today they attract considerable interest because of their diverse and useful biological activities,[1–3] and consequently a wide variety of synthetic methods for their preparation has been elaborated.[1] The three-component amidoalkylation of trivalent phosphorus compounds is perhaps one of the simplest and most commonly used methods for the preparation of structurally diverse aminophosphonates. The final procedure of amidoalkylation, successfully introduced by Oleksyszyn et al.[4–6] and further modified by Soroka

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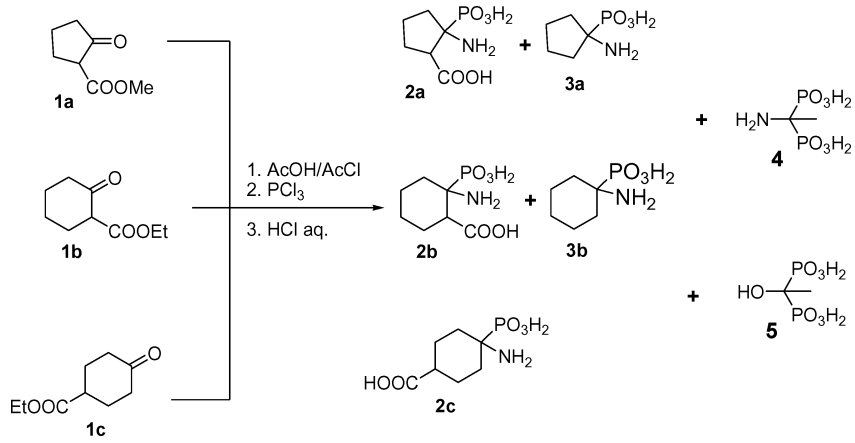
et al.,[7,8] has been found as the method of choice. The mechanism of this useful reaction is still not fully understood, and the formation of side products has not been reported in the literature.

In this article, we report the results of our studies on the reaction between phosphorus trichloride, acetamide, and ethyl oxoalkanecarboxylates, which upon application of the procedure introduced by Soroka,[7] yielded unexpected side products, thus showing the limitation of this reaction.

RESULTS AND DISCUSSION

Reaction of 2-oxocyclopentane carboxylate (**1a**) or ethyl 1-oxocyclohexane carboxylate (**1b**) with acetamide and phosphorus trichloride, followed by acid hydrolysis, afforded a set of four products. The expected diastereomers of the 2-amino-2-phosphonocycloalkane carboxylic acids (**2**) were accompanied by the products of their decarboxylation, namely the 1-aminocycloalkane phosphonic acids (**3**) together with substantial quantities of 1-aminoethane-1,1-diphosphonic acids **4** and small amounts of 1-hydroxyethane-1,1-diphosphonic acids **5** (Scheme 1). The presence of compounds **4** and **5** is not surprising, because they are usually prepared by reacting acetamide or acetic acid with phosphorus trichloride and phosphorous acid.[9] The formation of compounds **2**, **3**, and **4** was undoubtedly proven by comparing the ^{31}P NMR spectra of the mixture of reaction products with those of the pure compounds obtained by independent synthesis. The molar ratios of the components of the reaction mixtures calculated on the basis of their ^{31}P NMR spectra



SCHEME 1

TABLE I Compounds Present in the Reaction Mixtures Obtained by Amidolkylation of Phosphorus Trichloride with Acetamide and Alkyl Oxocycloalkane Carboxylates

	2 stereoisomer ratio	3	4	5
1a	64% 3:1	3%	29%	4%
1b	52% 9:1	23%	21%	4%
1c	90% 4:3	—	10%	—

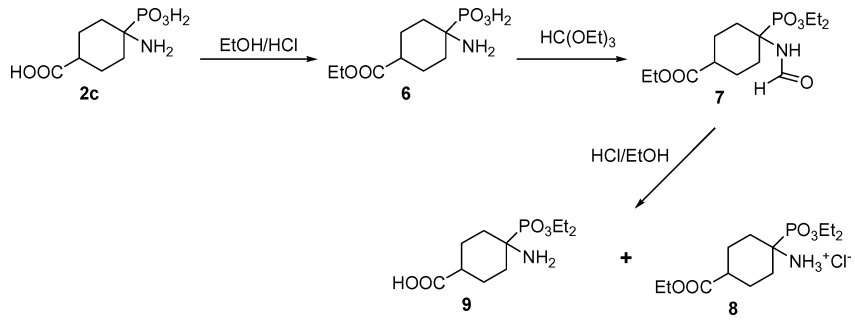
are given in Table I. Unfortunately we were only successful in isolation and characterization of some of the products (see the Experimental section).

For comparison, the reaction of ethyl 4-oxocyclohexane carboxylate (1c) was also studied. Interestingly, in this case the decarboxylation product and compound **4** did not form, and the desired product was isolated as a mixture of the *trans* and *cis* isomer in high (82%) yield. This indicates that steric hindrance present in the proximity of the reacting keto-group is governing the course of the reaction.

4-Amino-4-phosphonocyclohexane carboxylic acid (**2c**) was then converted into its various ethyl esters by standard procedures.[10,11] Direct reaction of **2c** with ethyl orthoformate did not yield the desired product **7**, and *C*-esterification was required prior to this reaction. Thus, the *C*-ethyl ester (**6**) was readily obtained by reacting **2c** with ethanol in the presence of HCl. Refluxing of compound 6 with ethyl orthoformate afforded crude triethyl 4-(*N*-formylamino)-4-phosphonocyclohexane carboxylate (**7**), which was not isolated but immediately converted into triethyl 4-amino-4-phosphonocyclohexane carboxylate hydrochloride (**8**) by the action of hydrogen chloride in ethanol. Interestingly this compound was accompanied by the diethyl ester **9**. In this manner all the possible esters of compound **2c** were obtained (Scheme 2). These esters might be further used in phosphonopeptide synthesis.[1]

EXPERIMENTAL

All reagents were obtained from commercial suppliers (Sigma-Aldrich, Merck, POCh) and used without further purification. Melting points were determined with a Boetius apparatus and are uncorrected. NMR spectra were recorded with a Bruker Avance DRX 300 or a Bruker AV instrument, operating at 300.13 MHz and 200.13 MHz (^{1}H), 121.499



SCHEME 2

MHz and 81.0 MHz (^{31}P), and 75.46 MHz and 50.32 MHz (^{13}C), respectively. Measurements were made in D_2O and $CDCl_3$. The relation of ^{13}C peaks to certain protons in ^{1}H NMR spectra was done on the basis of 2D ^{13}C-^{1}H HETCOR spectra. Microanalyses were performed by the Instrumental Analysis Unit of the Faculty of Chemistry, Wrocław University of Technology.

Amidoalkylation: General Procedure

The reaction was carried out introducing a small modification (optimized for a variety of substrates) in the procedure given by Soroka et al.[8] Acetamide (0.2 mol) was dissolved in acetic acid (40 mL) and cooled in an ice-bath. Then acetyl chloride (0.1 mol) was added with cooling, and the formation of a crystalline by-product was observed. After 15 min, compound **1** was added, and the mixture was kept for 30 min in the ice-bath and then left for **1** day at room temperature. Then the mixture was cooled again in an ice-bath, and phosphorus trichloride (0,1 mol) was added. The resulting mixture was kept in the bath for 30 min, then allowed to warm to room temperature, and finally heated for 1 h to 70–75°C. Evaporation of the volatile components of the reaction mixture resulted in an oily product, which was refluxed for 8 h in concentrated hydrochloric acid (100 mL). Then the acid was evaporated in vacuo, and the resulting product was dissolved in ethanol (50 mL) and left to complete the precipitation of ammonium chloride, which was filtered off, and the ethanol was evaporated under reduced pressure. The obtained oily residue was dissolved in ethanol (50 mL) and the aminophosphonate was precipitated by addition of pyridine.

Reaction of Methyl 2-Oxocyclopentane Carboxylate

After addition of pyridine fractional crystallization afforded the following:

Ammonium 1-aminoethane-1,1-dipohosphonate (ammonium salt of **4**): yield 20%; decomposition at 120–150°C. ^{31}P NMR (D_2O): $\delta = 14.1$. ^{1}H NMR (D_2O): $\delta = 1.50$ (t, $^{3}J_{PH} = 16.5$ Hz, CH_3). Elemental analysis: Calcd. for $C_2H_{12}N_2O_6P_2$(222,07): C, 10.75; H, 6.20; N, 10.85; Found: C, 27.59; H, 10.55; N, 10.66%.

1-Hydroxyethane-1,1-diphosphonic acid (**5**): yield 4%. ^{31}P NMR (D_2O): $\delta = 20.5$. ^{1}H NMR (D_2O): $\delta = 1.50$ (t, $^{3}J_{PH} = 16.5$ Hz, CH_3). ^{31}P NMR titration excluded the presence of an amino group.

Although their presence in the reaction mixture was evident, we were unable to obtain the other two components **2a** and **3a** in pure form either by crystallization or by ion-exchange chromatography.

Reaction of Ethyl 2-Oxocyclohexane Carboxylate

Fractional crystallization afforded the following:

1-Aminocyclohexane phosphonic acid: yield 18%; mp 258–264°C with decomposition (ref. [4]: mp 264–2655°C). IR (KBr pellet): $\nu = 3130$ (NH), 1202 (P=O), 1057, 1022 (PO_3H^-) cm^{-1}. The NMR are data identical with those reported in the literature.

2-Amino-2-phosphonocyclohexane carboxylic acid: yield 30%; mp 239–240°C with decomposition. IR (KBr pellet): ν 3236 (NH), 1670 (C=O), 1219 (P=O), 1109 (CO) cm^{-1}. ^{31}P NMR (D_2O): $\delta = 16.4$, which indicates that one diastereoisomer was isolated. ^{1}H NMR (D_2O): $\delta =$ 1.27–1.49 (m, $J =$ 3.5, 10.2 Hz, 2H, 6-CH_2), 1.59–1.72 (m, $J =$ 3.0, 12.3 Hz, 1H, CHCH_2), 1.76–1.88 (m, 3H, CHCH_2 and CH_2CH_2), 1.96 (ddd, $J =$ 3.0, 11.9, 15.3 Hz, 2H, CCH_2), 2.85 (ddt, $^{3}J_{HH} = 4.4$, 11.9 Hz, $^{3}J_{PH} = 12.7$ Hz, 1H, CCH).

Reaction of Ethyl 4-Oxocyclohexane Carboxylate

Upon addition of pyridine only 4-amino-4-phosphonocyclohexane carboxylic acid (**2c**) was isolated as a mixture of *cis*/*trans* isomers: yield 52%; mp 221–226°C. IR (KBr pellet): ν 3531 (NH), 1685 (C=O), 1240 (P=O), 1095 (PO_3H^-). ^{31}P NMR (D_2O): $\delta = 17.1$, 16.5 (7 : 6). ^{1}H NMR (D_2O): $\delta =$ 1.55–1.70 (m, $J =$ 4.0, 13.7, 9.5, 18.6 Hz, 2H, CHCH_2), 1.73–1.83 (m, $J =$ 4.0, 7.7, 10.9, 15.4 Hz, 2H, CCH_2), 1.82–2.03 (m, $J =$ 4.0, 13.3, 9.0, 17.8 Hz, 2H CHCH_2), 2.14 (dt, $^{3}J_{HH} = 4.1$, 7.6 Hz, 2H, CHCH_2), 2.45 (d of quint, $^{3}J_{HH} = 4.5$ Hz, $^{3}J_{PH} = 4.5$ Hz, 1H, CH).

Synthesis of Ethyl 4-Amino-4-phosphonocyclohexane Carboxylate (6)

Ethanol (100 mL) was cooled in an ice-bath and reacted with thionyl chloride (10 mL, added dropwise). Then 4-amino-4-phosphonocyclohexane carboxylic acid (0.1 mol) was added with stirring, and the mixture was left for 24 h. The volatile components of the reaction mixture were evaporated off, and the residue was dissolved in ethanol (100 mL). The product was precipitated by addition of pyridine (3 mL, to pH 5-6). Pure ester **6** was obtained in 82% yield. Mp 217–220°C. IR (KBr pellet): ν 1743 (C=O), 1235 (P=O), 1194, 1041, 938 (PO_3H^-). ^{31}P NMR (D_2O): $\delta = 16.5$. ^{1}H NMR (D_2O): $\delta = 1.15$ (t, $^3J_{HH} =$ 7.1 Hz, 3H, CH_3), 1.55–1.65 (m, $J = 4.6$, 7.3, 14.0 Hz, 2H, CHCH_2), 1.70–1.80 and 1.85–1.95 (m, $J = 5.7$, 11.6, 19.5 Hz, $^3J_{PH} = 7.7$ Hz, CCH_2), 2.06–2.19 (m, $J = 4.6$, 7.3, 14.0 Hz, 2H, CHCH_2), 2.48 (d of quint, $^3J_{HH} = 6.8$ Hz, $^3J_{PH} = 4.5$ Hz, 1H, CH), 4.07 (q, $^3J_{HH} = 7.1$ Hz, 2H, OCH_2).

Synthesis of Triethyl 4-Amino-4-phosphonocyclohexane Carboxylate Hydrochloride (8) and Diethyl 4-Amino-4-phosphonocyclohexane Carboxylic Acid (9)

Compound **6** (10 mmol) was dissolved in ethyl orthoformate (100 mL), and the mixture was heated for 3 h in a distillation apparatus to remove the produced ethanol. Solid impurities were filtered off, and the solvents were removed in vacuo. The *N*-formyl derivative **7** (^{31}P NMR ($CDCl_3$): $\delta = 23.2$, 23.8) was dissolved in a solution of hydrogen chloride in ethanol (15 mL, prepared as described above) and left for 24 h at room temperature. Evaporation of the ethanol yielded a residue, which was dissolved in chloroform (30 mL) and extracted with water (30 mL). The chloroform layer containing product **7** of satisfactory purity was dried over anhydrous magnesium sulfate, and the product was recovered upon evaporation of the chloroform with a total yield of 70%. ^{31}P NMR ($CDCl_3$): $\delta = 27.4$. ^{1}H NMR (D_2O): $\delta = 1.23$ (t, $^3J_{HH} = 7.1$ Hz, 3H, $COCH_2CH_3$), 1.31 and 1.35 (t, $^3J_{HH} = 7.1$ Hz, 3H, $POCH_2CH_3$), 1.73–1.83 and 2.46–2.58 (m, 2H, CHCH_2), 1.94–2.06 and 2.23–2.27 (m, 2H, CCH_2), 2.48 (d of quint, $^3J_{HH} = 6.8$ Hz, $^3J_{PH} = 4.5$ Hz, 1H, CHP), 4.04 (q, $^3J_{HH} = 7.1$ Hz, 2H, $COCH_2CH_3$), 4.16 (dq, $^3J_{HH} =^3 J_{PH} = 7.1$ Hz, 4H, $POCH_2$).

The water extract was evaporated to dryness and dissolved in ethanol (20 mL), and the product was precipitated by addition of pyridine. After recrystallization from a water-ethanol mixture, pure compound **9** was obtained in 15% yield. The yield of this product increases

upon prolonging the time of evaporation of the ethanol from the crude reaction mixture. ^{31}P NMR ($CDCl_3$): $\delta = 23.2$. ^{1}H NMR (D_2O): $\delta = 1.28$ (dd, $^3J_{HH} = 7.1$ Hz, 6 Hz, CH_3); 1.57–1.72 (m, $J = 4.6$, 7.3, 14.0 Hz, 2H, $CHCH_2$), 1.66–1.77 and 1.70–1.76 (m, $J = 5.7$, 11.6, 19.5 Hz, $^3J_{PH} = 7.7$ Hz, 2H, CCH_2), 2.47 (d of quint, $^3J_{HH} = 6.8$ Hz, $^3J_{PH} = 4.5$ Hz, 1H, CHP), 4.23 (qq, $^3J_{HH} = ^3 J_{PH} = 7.1$ Hz, 4H, $POCH_2$).

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