Arbuzov rearrangement in the 1,3,2-oxazaphosphinane series

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Reactions of 2-alkoxy-1,3,2-oxazaphosphinanes (including 3-alkyl derivatives) with methyl and ethyl bromoacetates give two types of Arbuzov rearrangement products (cyclic and acyclic ones). The ratio between their yields is virtually independent of the nature of the substituent in position 3 of the starting reagent, being mainly determined by the nature of the substituent in the phosphorus-bound alkoxy group and varying from 96 : 4 to 2 : 98. Acyclic products can be converted into cyclic ones.

Key words: 2-alkoxy-1,3,2-oxazaphosphinanes, 2-alkoxy-3-alkyl-1,3,2-oxazaphosphinanes, Arbuzov rearrangement, alkyl bromoacetates, 2-alkoxycarbonylmethyl-2-oxo-1,3,2λ^5-oxazaphosphinanes, 2-alkoxycarbonylmethyl-3-alkyl-2-oxo-1,3,2λ^5-oxazaphosphinanes, alkyl alkoxy[*N*-(3-bromopropyl)amino]phosphorylacetates, alkyl alkoxy[*N*-alkyl-*N*-(3-bromopropyl)amino]phosphorylacetates, cyclization.

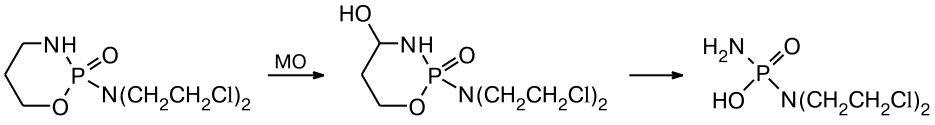
Arbuzov rearrangement is one of the basic and best investigated reactions in organophosphorus chemistry. A great number of original papers and several reviews have been devoted to Arbuzov rearrangement for tricoordinated acyclic esters of phosphorus acids and some of their cyclic analogs, namely, derivatives of 1,3,2-dioxaphospholane, phosphinane, and 1,3,2-oxazaphospholane (*e.g.*, see Refs 1—3). However, this rearrangement for 1,3,2-oxazaphosphinanes remains poorly studied. A few papers[4—8] published in the last decade are mainly concerned with asymmetric synthesis from the products of this reaction.

The goal of the present work was to use Arbuzov rearrangement in the 1,3,2-oxazaphosphinane series for obtaining new potential biologically active substances. From this viewpoint, corresponding derivatives of phosphorylacetic acid could be of particular interest since some representatives of this series were previously found to exhibit antiviral, antimicrobial, and some other biological activities.[9] It is also known that carcinolytic cyclophosphamide, which is a 1,3,2λ^5-oxazaphosphinane derivative, is not cytotoxic itself but is merely a good transport form. When in a cell, it metabolizes under the action of monooxygenases (MO) to give cytotoxic phosphoric diamide[10] (Scheme 1).

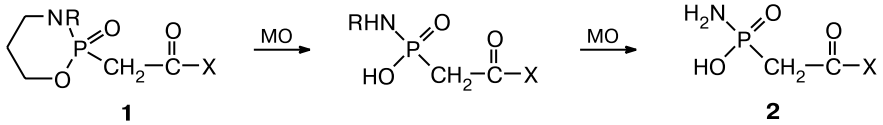
One could assume that oxazaphosphinane analogs of phosphorylacetic acid derivatives **1** (X = OH, AlkO, amino, and other groups; Scheme 2), when provided with a good "cell transport", would metabolize in a similar way to give prototype-close compounds **2** and can exhibit a variety of biological activity.

Since the aforementioned publications report no details of the Arbuzov reaction itself in this series of compounds, reactions of 2-alkoxy-3-alkyl-1,3,2-oxazaphos-

Scheme 1



Scheme 2



1 **2**

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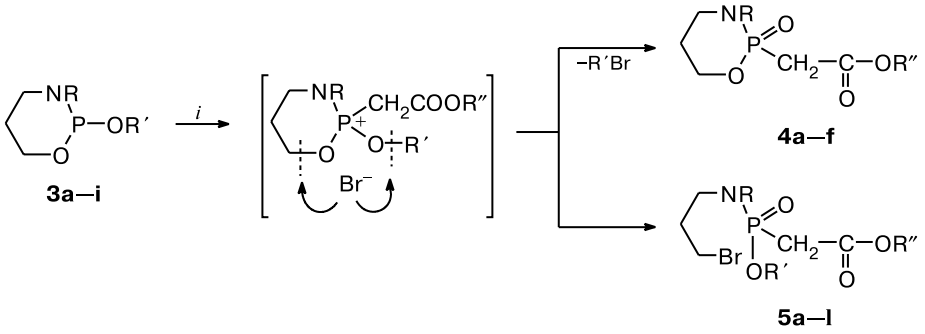
Scheme 3



i. $BrCH_2COOR''$, C_6H_6, 20 °C

Compound	R	R′	Compound	R	R′	R″	Compound	R	R′	R″
3a	Pr^i	Me	**4a**	Pr^i	—	Me	**5d**	Pr^i	Bu^n	Me
3b	Pr^i	Et	**4b**	Me	—	Me	**5e**	Pr^i	Pr^i	Et
3c	Pr^i	Bu^n	**4c**	H	—	Me	**5f**	Me	Me	Me
3d	Pr^i	Pr^i	**4d**	Pr^i	—	Et	**5g**	Me	Et	Me
3e	Me	Me	**4e**	Me	—	Et	**5h**	Me	Pr^i	Et
3f	Me	Et	**4f**	H	—	Et	**5i**	H	Me	Me
3g	Me	Pr^i	**5a**	Pr^i	Me	Me	**5j**	H	Me	Et
3h	H	Me	**5b**	Pr^i	Et	Me	**5k**	H	Et	Me
3i	H	Et	**5c**	Pr^i	Et	Et	**5l**	Me	Me	Et

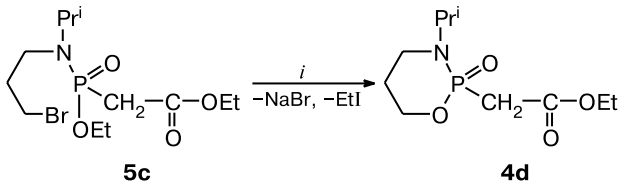
phinanes **3** with methyl and ethyl bromoacetates were studied thoroughly (Scheme 3). All reactions were carried out in benzene at 20 °C and yielded two major products, namely, cyclic (**4**) and acyclic ones (**5**). According to the ^{31}P NMR data, the ratio between their yields is virtually independent of the nature of the nitrogen-bound substituent R in oxazaphosphinanes **3** (Table 1). However, this ratio is sensitive to the nature of the substituent R′ in the alkoxy group at the phosphorus atom (Table 1). For instance, cyclic products are dominant for R′ = Me (ratio of **4** : **5** is 96 : 4 to 88 : 12), while acyclic products predominate for R′ = Et or Bu^n (**4** : **5** = 26 : 74 to 17 : 83). For R′ = Pr^i, acyclic compounds were obtained almost exclusively (**4** : **5** = 2 : 98). Thus, the reaction can be directed toward either cyclic or acyclic products by selecting a substituent R′. Obviously, such an effect of substituents in the alkoxy groups is associated with the ease of cleavage of the O—R′ bond in the intermediate phosphonium salt (Scheme 3). According to the ease of cleavage of this bond, alkyls can be arranged in the following order: Me > Et = Bu^n ≫ Pr^i. The best leaving group is R′ = Me (an analogous order is observed in the classic Arbuzov reaction). In other cases (especially for R′ = Pr^i), cleavage of the C—O bond in the ring becomes preferred.

Table 1. Effect of the structure of the starting compound **3** on the ratio between the products of its reaction with alkyl bromoacetates (according to ^{31}P NMR data (C_6H_6))

Starting reagents		δ		**4** : **5**
3	Bromoacetate, R″	**4**	**5**	
3a	Me	15.9 (**4a**)	26.0 (**5a**)	96 : 4
3b	Me	15.2 (**4a**)	23.9 (**5b**)	20 : 80
3b	Et	15.6 (**4d**)	24.7 (**5c**)	21 : 79
3c	Me	15.4 (**4a**)	23.9 (**5d**)	18 : 82
3d	Et	15.5 (**4d**)	22.8 (**5e**)	2 : 98
3e	Me	16.9 (**4b**)	25.9 (**5f**)	89 : 11
3e	Et	16.8 (**4e**)	26.1 (**5l**)	90 : 10
3f	Me	18.2 (**4b**)	24.9 (**5g**)	17 : 83
3g	Et	17.0 (**4b**)	23.1 (**5h**)	2 : 98
3h	Me	17.7 (**4c**)	25.3 (**5i**)	88 : 12
3h	Et	18.1 (**4f**)	26.1 (**5j**)	92 : 8
3i	Me	18.5 (**4c**)	24.6 (**5k**)	26 : 74

Note that an acyclic compound can undergo cyclization in boiling acetonitrile in the presence of NaI (Scheme 4).

Scheme 4



i. Δ, NaI/MeCN

The compounds obtained were isolated by column chromatography on anhydrous SiO_2. The compositions and structures of the compounds were confirmed by el-

Table 2. Yields of 2-alkoxycarbonylmethyl-3-alkyl(or H)-2-oxo-1,3,2λ^5-oxazaphosphinanes **4** and alkyl alkoxy[*N*-alkyl(or H)-*N*-(3-bromopropyl)amino]phosphorylacetates **5** and their elemental analysis data

Compound	R	R′	R″	Yield (%)	Found / Calculated (%)				Molecular formula
					C	H	Br	P	
4a	Pr^i	—	Me	90	46.05 45.96	7.87 7.71	—	13.20 13.17	$C_9H_{18}NO_4P$
4b	Me	—	Me	66	40.56 40.58	6.73 6.81	—	14.62 14.95	$C_7H_{14}NO_4P$
4c	H	—	Me	54	37.33 37.31	6.29 6.26	(—)*	—	$C_6H_{12}NO_4P$
4d	Pr^i	—	Et	15	47.44 48.19	8.14 8.09	(—)*	12.16 12.43	$C_{10}H_{20}NO_4P$
4f	H	—	Et	76	40.25 40.58	6.79 6.81	—	14.96 14.95	$C_7H_{14}NO_4P$
5b	Pr^i	Et	Me	62	38.37 38.38	7.11 6.75	22.03 23.22	9.15 8.99	$C_{11}H_{23}BrNO_4P$
5c	Pr^i	Et	Et	67	39.77 40.23	7.27 7.03	(—)*	8.52 8.65	$C_{12}H_{25}BrNO_4P$
5d	Pr^i	Bu^n	Me	74	43.01 41.95	7.58 7.31	—	8.87 8.32	$C_{13}H_{27}BrNO_4P$
5e	Pr^i	Pr^i	Et	84	42.61 41.95	7.52 7.31	20.71 21.45	—	$C_{13}H_{27}BrNO_4P$
5g	Me	Et	Me	66	34.44 34.19	6.44 6.06	24.56 25.28	9.73 9.80	$C_9H_{19}BrNO_4P$
5h	Me	Pr^i	Et	82	—	—	22.56 23.22	8.80 8.99	$C_{11}H_{23}BrNO_4P$
5k	H	Et	Me	38	31.79 31.80	5.64 5.67	25.01 25.44	9.93 10.24	$C_8H_{17}BrNO_4P$

* Found/calculated (%): N, 6.95/7.25 (**4c**); 5.34/5.62 (**4d**); 4.07/3.91 (**5c**).

emental analysis data (Table 2) and $^{31}P\{^1H\}$ (Table 1) and ^1H NMR spectra (Table 3).

Experimental

NMR spectra were recorded on a Bruker AMX-400 instrument (in $CDCl_3$ with a signal for the residual proton of the deuterated solvent as the internal standard (^1H) and in C_6H_6 with 85% H_3PO_4 as the external standard (^{31}P)).

The starting 2-alkoxy-3-alkyl(or H)-1,3,2-oxazaphosphinanes **3** were prepared according to known procedures.[11,12]

Products were isolated by column chromatography on anhydrous SiO_2 (Aldrich, 130—270 mesh, substance : SiO_2 ratio = 1 : 16 (w/w)) in hexane—acetone with a gradient from 100 : 1 to 3 : 2 or, for *N*-unsubstituted products, in $CHCl_3$—MeOH with a gradient from 100 : 1 to 100 : 15. The fractions were checked by TLC on the same stationary phase in hexane—acetone (3 : 2) or $CHCl_3$—MeOH (10 : 1).

2-Ethoxycarbonylmethyl-3-isopropyl-2-oxo-1,3,2λ^5-oxazaphosphinane (4d) and ethyl [*N*-(3-bromopropyl)-*N*-isopropylamino](ethoxy)phosphorylacetate (5c). A solution of phosphinane **3b** (1.91 g, 10 mmol) in 1 mL of C_6H_6 was slowly added dropwise to a stirred (with argon bubbles) solution of ethyl bromoacetate (2.50 g, 15 mmol) in 2 mL of C_6H_6. The addition rate was such that the temperature of the mixture did not exceed 20 °C. The reaction mixture was left in an argon flow at room temperature for 24 h and then analyzed by ^{31}P NMR spectroscopy (see Table 1). The solvent and the excess of bromoacetate were removed *in vacuo* (the final temperature was 60 °C (1 Torr)). The residue (3.45 g) was chromatographed on SiO_2 to give compounds **5c** (2.41 g, 67%) and **4d** (0.37 g, 15%) (see Tables 2, 3).

Other compounds **4** and **5** were obtained and isolated analogously. One or both were isolated, depending on the ratio of their yields (see Tables 1—3).

Cyclization of ethyl [*N*-(3-bromopropyl)-*N*-isopropylamino](ethoxy)phosphorylacetate (5c) into 2-ethoxycarbonylmethyl-3-isopropyl-2-oxo-1,3,2λ^5-oxazaphosphinane (4d). A solution of ester **5c** (2.19 g, 6 mmol) (^{31}P NMR (MeCN), δ: 26.1) and anhydrous NaI (1.05 g, 7 mmol) in 45 mL of anhydrous MeCN was refluxed for 12 h. According to ^{31}P NMR data, the degree of conversion of ester **5c** into **4d** was 91.5% (δ: 18.2 (MeCN)). The precipitate of NaBr was filtered off and MeCN was removed *in vacuo*. The residue was treated with CH_2Cl_2. The excess of NaI was filtered off and the filtrate was concentrated *in vacuo*. Chromatography on SiO_2 (29 g) gave individual product **4d** (1.23 g, 82%; ^{31}P NMR (C_6H_6), δ: 15.5).

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Table 3. ^{1}H NMR spectra ($CDCl_3$) of compounds **4** and **5**

Compound	δ, *J*/Hz
4a	1.09, 1.16 (both d, 3 H each, CHC$\underline{H}_3$, $^3J_{H,H}$ = 6.8); 1.79—1.86, 1.93—2.04 (both m, 1 H each, $CH_2C\underline{H}_2CH_2$); 2.97 (d, 2 H, $CH_2P(O)$, $^2J_{P,H}$ = 19.0); 2.93—3.04, 3.04—3.16 (both m, 1 H each, CH_2N); 3.68 (s, 3 H, MeO); 3.80—3.91 (m, 1 H, C$\underline{H}$Me); 4.14—4.36 (m, 2 H, CH_2OP)
4b[a]	1.73—2.06 (m, 2 H, $CH_2C\underline{H}_2CH_2$); 2.72 (s, 3 H, MeN); 2.89 (d, 2 H, $CH_2P(O)$; $^2J_{P,H}$ = 20.4); 3.14—3.21 (m, 2 H, CH_2N); 3.71 (s, 3 H, CH_3O); 3.96—4.03 (m, 2 H, CH_2OP)
4c[a]	1.95—2.06 (m, 2 H, $CH_2C\underline{H}_2CH_2$); 2.89 (d, 2 H, $CH_2P(O)$, $^2J_{P,H}$ = 20.8); 3.10—3.19 (m, 2 H, CH_2N); 3.71 (s, 3 H, MeO); 3.95—4.04 (m, 2 H, CH_2OP)
4d	1.09, 1.17 (both d, 3 H each, C$\underline{H}_3$CH, $^3J_{H,H}$ = 6.8); 1.25 (t, 3 H, C$\underline{H}_3CH_2$, $^3J_{H,H}$ = 7.2); 1.77—1.86 (both m, 1 H each, $CH_2C\underline{H}_2CH_2$); 2.97 (d, 2 H, $CH_2P(O)$, $^2J_{P,H}$ = 20.0); 2.98—3.17 (m, 2 H, CH_2N); 3.80—3.93 (m, 1 H, C$\underline{H}CH_3$); 4.14 (q, 2 H, C$\underline{H}_2CH_3$, $^3J_{H,H}$ = 7.2); 4.18—4.35 (m, 2 H, C$\underline{H}_2OP$)
4f	1.20 (t, 3 H, C$\underline{H}_3CH_2$, $^3J_{H,H}$ = 7.2); 1.66—1.71, 1.91—2.01 (both m, 1 H each, $CH_2C\underline{H}_2CH_2$); 2.95 (ABX-system, 1 H, H_B, $CH_2P(O)$, $^2J_{H,H}$ = 14.2, $^2J_{P,H}$ = 19.8); 2.97 (ABX-system, 1 H, H_A, $CH_2P(O)$, $^2J_{H,H}$ = 14.2, $^2J_{P,H}$ = 20.2); 3.15—3.32 (m, 2 H, CH_2N); 4.02 (br.s, 1 H, HN); 4.13 (q, 2 H, C$\underline{H}_2CH_3$, $^3J_{H,H}$ = 7.1); 4.18—4.38 (m, 2 H, C$\underline{H}_2OP$)
5b	1.03, 1.04 (both d, 3 H each, C$\underline{H}_3$CH, $^3J_{H,H}$ = 6.8); 1.16 (t, 3 H, C$\underline{H}_3CH_2$, $^3J_{H,H}$ = 6.8); 1.94—2.06 (m, 2 H, $CH_2C\underline{H}_2CH_2$); 2.75 (d, 2 H, $CH_2P(O)$, $^2J_{P,H}$ = 20.0); 2.89—3.00 (m, 2 H, CH_2N); 3.21—3.28 (m, 2 H, CH_2Br); 3.45—3.52 (m, 1 H, C$\underline{H}CH_3$); 3.56 (s, 3 H, C$\underline{H}_3O$); 3.74—4.00 (m, 2 H, C$\underline{H}_2OP$)
5c	1.14, 1.16 (both d, 3 H each, C$\underline{H}_3$CH, $^3J_{H,H}$ = 6.8); 1.24 (t, 3 H, C$\underline{H}_3CH_2OC$, $^3J_{H,H}$ = 7.2); 1.27 (t, 3 H, C$\underline{H}_3CH_2OP$, $^3J_{H,H}$ = 7.2); 2.01—2.19 (m, 2 H, $CH_2C\underline{H}_2CH_2$); 2.85 (ABX-system, 1 H, H_B, $CH_2P(O)$, $^2J_{H,H}$ = 14.0, $^2J_{P,H}$ = 20.0); 2.87 (ABX-system, 1 H, H_A, $CH_2P(O)$, $^2J_{H,H}$ = 14.0, $^2J_{P,H}$ = 20.0); 2.99—3.15 (m, 2 H, CH_2N); 3.31—3.40 (m, 2 H, CH_2Br); 3.54—3.67 (m, 1 H, C$\underline{H}$Me); 3.86—3.96, 4.03—4.10 (both m, 1 H each, $CH_3C\underline{H}_2OP$); 4.14 (q, 2 H, $MeC\underline{H}_2OC$, $^3J_{H,H}$ = 7.2)
5k	1.23 (t, 3 H, C$\underline{H}_3CH_2$, $^3J_{H,H}$ = 6.8); 1.93—2.00 (m, 2 H, $CH_2C\underline{H}_2CH_2$); 2.86 (ABX-system, 1 H, H_B, $CH_2P(O)$, $^2J_{H,H}$ = 4.8, $^2J_{P,H}$ = 20.4); 2.90 (ABX-system, 1 H, H_A, $CH_2P(O)$, $^2J_{H,H}$ = 4.8, $^2J_{P,H}$ = 20.4); 3.02—3.09 (m, 2 H, CH_2N); 3.41 (t, 2 H, CH_2Br, $^3J_{H,H}$ = 6.4); 3.64 (s, 3H, C$\underline{H}_3O$); 3.93—4.05 (m, 2 H, C$\underline{H}_2CH_3$)
5l	1.27 (t, 3 H, C$\underline{H}_3CH_2$, $^3J_{H,H}$ = 7.2); 2.04—2.13 (m, 2 H, $CH_2C\underline{H}_2CH_2$); 2.67 (d, 3 H, MeN, $^3J_{P,H}$ = 9.6); 2.92 (d, 2 H, $CH_2P(O)$, $^2J_{P,H}$ = 20.4); 3.08—3.25 (m, 2 H, CH_2N); 3.41 (t, 2 H, CH_2Br, $^3J_{H,H}$ = 6.8); 3.64 (d, 3 H, CH_3OP, $^3J_{P,H}$ = 11.2); 4.17 (q, 2 H, C$\underline{H}_2CH_3$, $^3J_{H,H}$ = 6.8)

[a] The spectrum was recorded in D_2O.

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