

Reaction of γ -benzylideneaminopropanol with dialkyl phosphorochloridites

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Reactions of dialkyl phosphorochloridites with 3-(*N*-benzylideneamino)propan-1-ol follow two pathways giving rise to linear dialkyl 1-(3-chloropropylamino)benzylphosphonates and diastereomeric cyclic 2-alkoxy-2-oxo-3-phenyl-1,4,2-oxazaphosphepanes.

Key words: dialkyl phosphorochloridites, 3-(*N*-benzylideneamino)propan-1-ol, α -amino-phosphonates, phosphepanes, phosphorylation.

Recently,¹ we have demonstrated that the reaction of β -aldiminoalcohols with dialkyl phosphorochloridites involves many steps and proceeds through the intermediate formation of β -iminophosphites. The intramolecular reaction of the P^{III} atom with the C=N bond in the latter compounds leads to their stereoselective transformation into 1,4,2-oxazaphosphorinanes in high yields. This reaction provides a new efficient procedure for the synthesis of six-membered phosphacyclanes. With the aim of examining the scope of this reaction and preparing larger heterocycles, we studied the possibility of using γ -aldiminoalcohols as the starting reagents. In this case, the analogous reaction would be expected to give seven-membered phosphepane heterocycles due to an increase by one CH₂ unit in the alkylene group, which links the reactive centers in imino alcohol.

The starting 3-(*N*-benzylideneamino)propan-1-ol (**1**) was prepared by condensation of 3-aminopropan-1-ol with benzaldehyde in toluene using water azeotropic distillation.² It should be noted that well-known^{3,4} ring-chain tautomerism occurs in a CDCl₃ solution of γ -imino alcohol **1**, where 2-phenyltetrahydro-1,3-oxazine (**1'**) is the second tautomer. This is evidenced by the ¹H NMR spectrum of imino alcohol **1** in CDCl₃, which shows, along with the characteristic signal for the proton of the CH=N fragment (δ 8.13), the minor signal for the methine proton at the C(2) atom of the oxazine ring in **1'** (δ 5.05). The ratio of tautomers **1** and **1'** was estimated at 3 : 1 by integrating these signals.

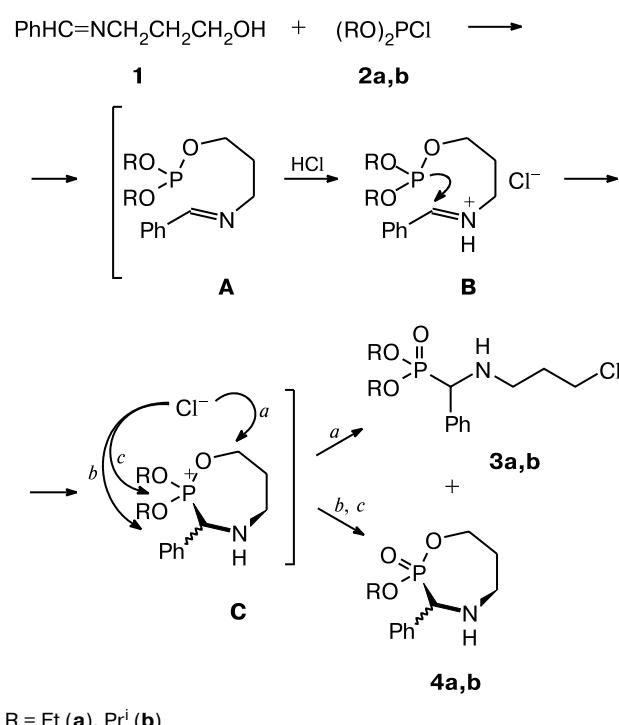
The reactions of γ -aldiminoalcohol **1** with diethyl and diisopropyl phosphorochloridites **2a,b** in chloroform at 0 °C afford three phosphorus-containing products (³¹P{¹H} NMR spectroscopic data, after the dis-

appearance of the signals of the starting dialkyl phosphorochloridites). For example, the ³¹P NMR spectrum of the products prepared by the reaction with diethyl phosphorochloridite **2a** shows a singlet at δ 21.85 and two singlets with similar chemical shifts (δ 25.00 and 25.10). The integral intensity ratio of these peaks is 1.77 : 1 : 1.23, respectively. The compounds characterized by upfield chemical shifts appeared to be more mobile during their separation by column chromatography. These compounds were isolated in ~32% yield as crystals. Subsequent recrystallization from a ~1 : 1 Et₂O–petroleum ether mixture afforded single crystals of these compounds suitable for X-ray diffraction. These compounds were demonstrated to be dialkyl 1-(3-chloropropylamino)benzylphosphonates **3a,b** (Scheme 1, Fig. 1). The crystals of both compounds are centrosymmetric (see the Experimental section) and exist as racemates consisting of independent enantiomeric molecules of phosphonates **3a,b**.

The geometric parameters (bond lengths and bond angles) in the phosphonate fragment of molecules **3a** and **3b** have standard values and are consistent with the analogous parameters of acyclic phosphonates. The phosphorus atom in these molecules has a typical distorted tetrahedral coordination. The O=P–C and O=P–O bond angles are larger, whereas the O–P–C and O–P–O bond angles are smaller than the ideal value (109°). The molecule occurs in a staggered conformation along the P–C bond. This conformation is sterically favorable for this fragment.

The isopropyl groups in molecule **3b** adopt a usual transoid conformation. The ethyl groups in molecule **3a** have different conformations (*trans* and *cis*), which are

Scheme 1



rarely observed in alkyl phosphonates. This is associated with the presence of the C—H... π interaction between the hydrogen atom of one of the ethoxy groups and the benzene ring in molecule **3a**.

According to the IR and ^{31}P and ^1H NMR spectroscopic data, the products characterized by similar down-field chemical shifts are mixtures of diastereomers of oxazaphosphepanes **4a,b**. We failed to separate these mixtures by chromatography.

Treatment of compounds **4a,b** with picric acid afforded well-crystallized picrates. The structure of the picrate of oxazaphosphepane **4b** was additionally confirmed by EI mass spectrometry. The mass spectrum of this compound is the sum of the mass spectra of compound **4b** and picric acid, which may be attributed to decomposition of the salt upon its transition to the gas phase in the inlet system of the instrument.

Based on the structures of the final products, we hypothesize that the reaction of aldiminoalcohol **1** with dialkyl phosphorochloridites **2** proceeds by the mechanism shown in Scheme 1. The first step involves the replacement of the chlorine atom at the phosphorus atom under the action of the hydroxy group of imino alcohol to form intermediate iminophosphite **A**. The reaction of the latter with hydrogen chloride that is eliminated produces imine salt **B**, which can undergo intramolecular cyclization to give intermediate quasiphosphonium salt **C**. Then the chloride anion, in accordance with the second step of the Arbuzov

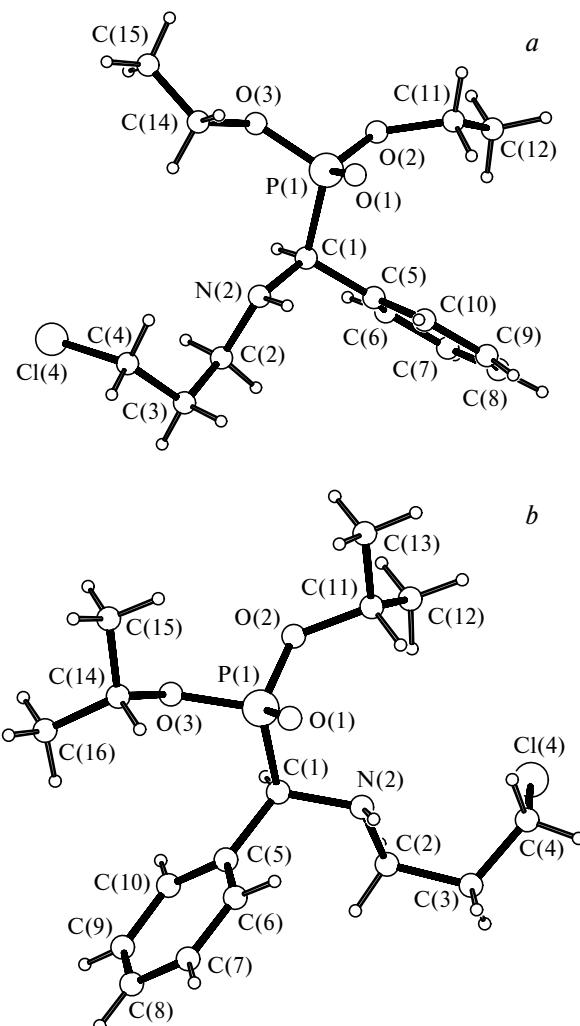


Fig. 1. Molecular structures of diethyl 1-(3-chloropropylamino)benzylphosphonate (**3a**) (a) and diisopropyl 1-(3-chloropropylamino)benzylphosphonate (**3b**) (b). Independent molecules are shown.

reaction, can either attack the carbon atom at position 7 of the ring to form linear phosphonate **3** (path *a*) or dealkylate one of the diastereotopic alkoxy groups at the phosphorus atom to give diastereomers **4** (paths *b* and *c*). Unlike the reactions of β -aldiminoalcohols with dialkyl phosphorochloridites,¹ which afford exclusively six-membered cyclic products, the reaction of higher homolog **1** produces both cyclic and linear compounds. This is apparently associated with lower stability and higher tendency of the seven-membered phosphepane ring in the intermediate compounds to undergo ring opening compared to the six-membered phosphinane ring.

To summarize, the above-described reaction provides a new procedure for the synthesis of seven-membered phosphepane heterocycles containing the α -aminophosphonate fragments.

Experimental

The $^{31}\text{P}\{\text{H}\}$ NMR spectra were recorded on a CXP 100 spectrometer in CDCl_3 with 85% H_3PO_4 as the external standard. The ^1H and ^{13}C NMR spectra were measured on a Bruker MSL-400 instrument in CDCl_3 . The IR spectra were recorded on a Vector 22 Fourier-transform IR spectrometer (Bruker). The mass spectra were obtained on a TRACE MS Finnigan MAT instrument (ionizing electron energy was 70 eV, the ion source temperature was 200 °C, the evaporator tube of the direct inlet system was heated in the programmed mode from 35 to 150 °C with a step of 35 °C min^{-1}). The mass-spectrometric data were processed using the Xcalibur program.

Reactions of dialkyl phosphorochloridites 2a,b with 3-(*N*-benzylideneamino)propan-1-ol (1) (general procedure for the synthesis of compounds 3a,b and 4a,b). A solution of 3-(*N*-benzylideneamino)propan-1-ol (1) (5.7 mmol) in dry CHCl_3 (5 mL) was added dropwise with stirring to a solution of dialkyl phosphorochloridite 2a,b (5.7 mmol) in dry CHCl_3 (10 mL) under dry argon at 0 °C. The reaction mixture was stirred at ~20 °C for 2 h. Then the solvent was removed *in vacuo*. The residue (oil) was chromatographed on SiO_2 (Chemapol, L 100/160 mm) in the 1 : 4 acetonitrile–toluene system; the eluate was monitored by TLC on Silufol UV-254 plates.

Diethyl 1-(3-chloropropylamino)benzylphosphonate (3a). The yield was 32%, colorless crystals, m.p. 56–57 °C. Found (%): Cl, 11.09; N, 4.35; P, 9.68. $\text{C}_{14}\text{H}_{23}\text{ClNO}_3\text{P}$. Calculated (%): Cl, 11.11; N, 4.38; P, 9.70. ^{31}P NMR, δ : 21.6. ^1H NMR, δ : 1.10 and 1.26 (both t, 6 H, $\text{CH}_3\text{CH}_2\text{CO}$); 1.87 (m, 2 H, CCH_2C); 2.61 (m, 2 H, CH_2N); 3.57 (m, 2 H, CH_2Cl); 3.72–4.12 (m, 4 H, $\text{CH}_3\text{CH}_2\text{O}$); 3.98 (d, 1 H, PCH, $^2J_{\text{H},\text{P}} = 20.3$ Hz); 7.12–7.63 (m, 5 H, Ph). IR (Nujol mulls), ν/cm^{-1} : 1021, 1059 (P=O–C), 1237 (P=O), 3284 (NH).

Diisopropyl 1-(3-chloropropylamino)benzylphosphonate (3b). The yield was 32%, colorless crystals, m.p. 59.0–59.5 °C. Found (%): Cl, 10.11; N, 4.01; P, 8.90. $\text{C}_{16}\text{H}_{27}\text{ClNO}_3\text{P}$. Calculated (%): Cl, 10.21; N, 4.03; P, 8.92. ^{31}P NMR, δ : 22.5. ^1H NMR, δ : 0.93, 1.18, 1.24, and 1.26 (all d, 12 H, Me); 1.83 (m, 2 H, CCH_2C); 2.59 (m, 2 H, CH_2N); 3.55 (m, 2 H, CH_2Cl); 3.89 (d, 1 H, PCH, $^2J_{\text{H},\text{P}} = 20.4$ Hz); 4.44 and 4.65 (both m, 2 H, OCHMe_2); 7.11–7.38 (m, 5 H, Ph). IR (Nujol mulls), ν/cm^{-1} : 1025, 1052 (P=O–C), 1231 (P=O), 3282 (NH).

2-Ethoxy-2-oxo-3-phenyl-1,4,2-oxazaphosphepane (4a). The yield was 53%, colorless viscous oil. Found (%): N, 5.44; P, 12.15. $\text{C}_{12}\text{H}_{18}\text{NO}_3\text{P}$. Calculated (%): N, 5.49; P, 12.16. ^{31}P NMR, δ : 25.00, 25.10. ^1H NMR, δ : 0.95 and 1.05 (both t, 3 H each, $\text{CH}_3\text{CH}_2\text{O}$ of diastereomers, the integral intensity ratio was 1 : 1.4); 1.81–2.32 (m, 2 H, CCH_2C); 2.82 and 3.41 (both m, 2 H, CH_2N); 3.65–4.40 (m, 6 H, $\text{CH}_2\text{O} + \text{OCH}_2\text{CH}_3$); 3.85 and 4.18 (both d, 1 H each, PCH, $^2J_{\text{H},\text{P}} = 9.3$ Hz); 7.20–7.43 (m, 5 H, Ph). IR (thin layer), ν/cm^{-1} : 1032 (P=O–C), 1245 (P=O), 3303, 3446 (NH).

2-Isopropoxy-2-oxo-3-phenyl-1,4,2-oxazaphosphepane (4b). The yield was 52%, viscous oil. Found (%): N, 5.19; P, 11.50. $\text{C}_{13}\text{H}_{20}\text{NO}_3\text{P}$. Calculated (%): N, 5.20; P, 11.52. ^{31}P NMR, δ : 26.6, 26.7. ^1H NMR, δ : 0.78, 0.88, 1.19, and 1.21 (all d, 3 H each, Me of two diastereomers, the integral intensity ratio was 1 : 1.2); 1.87–2.33 (m, 2 H, CCH_2C); 2.85 and 3.44 (both m, 2 H,

CH_2N); 3.94–4.50 (m, 4 H, $\text{CH}_2\text{O} + \text{OCHMe}_2$); 3.91 and 4.23 (both d, 1 H each, PCH, $^2J_{\text{H},\text{P}} = 10.7$ Hz); 7.23–7.43 (m, 5 H, Ph). IR (thin layer), ν/cm^{-1} : 1031 (P=O–C), 1248 (P=O), 3302, 3424 (NH).

Picrate of compound 4a. A solution of picric acid (0.1 g, 15% excess) in ethanol (1 mL) was added to a solution of compound 4a (0.1 g) in ethanol (1 mL). The reaction mixture was allowed to stand for ~14 h. The crystals that precipitated were filtered off and dried *in vacuo*. The picrate was obtained as yellow crystals in a yield of 0.18 g (96%), m.p. 199–200 °C. Found (%): N, 11.49; P, 6.38. $\text{C}_{18}\text{H}_{21}\text{N}_4\text{O}_{10}\text{P}$. Calculated (%): N, 11.57; P, 6.40.

Picrate of compound 4b was prepared analogously, the yield was 94%, yellow crystals, m.p. 192–193 °C. Found (%): N, 11.23; P, 6.21. $\text{C}_{19}\text{H}_{23}\text{N}_4\text{O}_{10}\text{P}$. Calculated (%): N, 11.24; P, 6.22. MS, m/z (I_{rel} (%)): 269 [M_1^+] (2.4), 229 [M_2^+] (7.2), 227 (15.0), 226 (33.0), 213 (0.63), 210 (8.4), 199 (11.8), 91 (100.0), 77 (39.6), 47 (5.0), 46 (4.8), 41 (76.4).

X-ray diffraction study of compounds 3a,b. At +20 °C, crystals of $\text{C}_{14}\text{H}_{23}\text{ClNO}_3\text{P}$ (3a) are triclinic, $a = 8.111(1)$ Å, $b = 10.826(2)$ Å, $c = 10.849(2)$ Å, $\alpha = 69.58(2)$ °, $\beta = 79.17(2)$ °, $\gamma = 74.46(1)$ °, $V = 855.4(3)$ Å 3 , $Z = 2$, $M = 319.75$, $d_{\text{calc}} = 1.24$ g cm $^{-3}$, $F(000) = 340$, space group $P\bar{1}$. Crystals of $\text{C}_{16}\text{H}_{27}\text{ClNO}_3\text{P}$ (3b) are triclinic, $a = 9.266(2)$ Å, $b = 10.449(1)$ Å, $c = 10.965(1)$ Å, $\alpha = 76.20(1)$ °, $\beta = 76.40(1)$ °, $\gamma = 78.44(1)$ °, $V = 990.2(2)$ Å 3 , $Z = 2$, $M = 347.81$, $d_{\text{calc}} = 1.17$ g cm $^{-3}$, $F(000) = 372$, space group $P\bar{1}$. No absorption correction was applied because of its low value ($\mu(\text{Mo}) = 3.23$ and 2.80 cm $^{-1}$ for 3a and 3b, respectively). The intensities of 3665 (3a) and 2132 (3b) reflections, of which 2454 (3a) and 1479 (3b) reflections were with $I > 2\sigma(I)$, were measured on an Enraf Nonius CAD-4 diffractometer at 20 °C ($\lambda(\text{Mo-K}\alpha)$, $\omega/2\theta$ scanning technique, $2\theta_{\text{max}} < 53.8$ °). The structures were solved by direct methods using the SIR program⁵ and refined first isotropically and then anisotropically using the SHELXL97 program package.⁶ The H atoms were located from difference electron density maps. The contributions of the hydrogen atoms to the structure amplitudes were taken into account with fixed positional and isotropic thermal parameters in the final step of the refinement. All calculations were carried out using the WinGX program package.⁷ The final R factors were as follows: $R = 0.0493$, $R_w = 0.1360$ using 3463 independent reflections for 3a and $R = 0.0499$, $R_w = 0.1343$ using 1995 independent reflections for 3b. The unit cell parameters, the intensities of reflection, and the absorption corrections were measured on an Enraf Nonius CAD-4 diffractometer controlled by an Alpha Station 200 using the MolEN program package.⁸

The structures were deposited with the Cambridge Structural Database (CCDC 272838 (3a) and CCDC 272839 (3b)).

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