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Phosphorylation of Ethyl Urethane, Urea, and Acetamide with Bis(chloromethyl)phosphinic Chloride in the Presence of Potassium Carbonate

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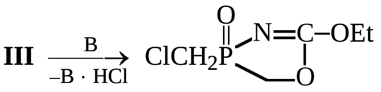
Abstract—Bis(chloromethyl)phosphinic chloride reacts with urethane to give phosphorylated urethane, whereas with urea and acetamide the final reaction product is bis(chloromethyl)phosphinic anhydride.

Recently we developed a procedure for preparing polyheterophosphacyclanes with endocyclic P–C bonds [1–5] by intramolecular cyclization of *P*-functionally substituted phosphorus chloromethyl derivatives. With the aim to examine the feasibility of preparing new functionally substituted chloromethylphosphinates and phosphacyclanes derived from them, we studied phosphorylation of urea, ethyl urethane, and acetamide with bis(chloromethyl)phosphinic chloride **I** in the presence of potassium carbonate.

Chloride **I** reacts with ethyl urethane **II** in the presence of potassium carbonate as a solid base with heat release, without adding a phase-transfer catalyst, to give phosphinyl urethane **III**. In the absence of potassium carbonate, the reaction occurs also, but it requires prolonged heating, and the final product is formed in a considerably lower yield.

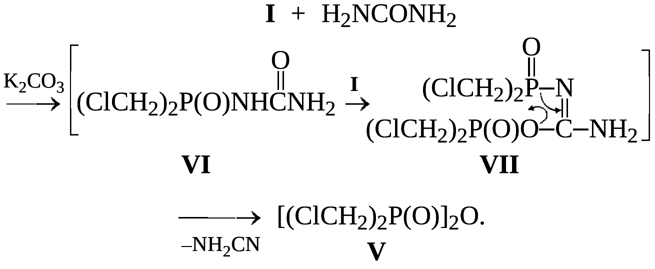
$$\underset{\mathbf{I}}{(ClCH_2)_2P(O)Cl} + \underset{\mathbf{II}}{H_2NCOOEt} \xrightarrow{K_2CO_3} \underset{\mathbf{III}}{(ClCH_2)_2P(O)NHCOOEt.}$$

Under the action of a base, phosphinyl urethane **III** readily eliminates HCl to give 1,3,4λ^5-oxazaphospholine **IV**. The composition and structure of **IV** were confirmed by elemental analysis and spectroscopic data. Whereas the IR spectrum of phosphorylated urethane **III** contains strong bands of the carbonyl (1725 cm^{-1}) and amide (3100 cm^{-1}) groups, in the spectrum of **IV** these bands are absent, but a C=N band appears at 1630 cm^{-1}.



IV

Attempted phosphorylation of urea with **I** in the presence of dry potassium carbonate yields bis(chloromethyl)phosphinic anhydride **V**. In view of high reactivity of **I** [8], it can be assumed that phosphinylurea **VI** (or, possibly, *O*-phosphorylation product) formed in the first stage reacts with the second phosphinic chloride molecule to give diphosphinyl derivative **VII**. As we showed previously [9], such derivatives readily undergo β-cleavage to give the final products.



$$\mathbf{I} + H_2NCONH_2 \xrightarrow{K_2CO_3} \left[\underset{\mathbf{VI}}{(ClCH_2)_2P(O)NHC(O)NH_2} \xrightarrow{\mathbf{I}} \underset{\mathbf{VII}}{(ClCH_2)_2P(O)N{=}C(NH_2)OP(O)(CH_2Cl)_2}\right] \xrightarrow[-NH_2CN]{} \underset{\mathbf{V}}{[(ClCH_2)_2P(O)]_2O.}$$

Phosphinylurea **VI** was prepared by a different pathway: addition of ammonia to bis(chloromethyl)phosphinic isocyanate **VIII**. Compound **VI** appeared to be stable in storage. When treated with **I** in the presence of potassium carbonate, compound **VI** transforms into **V**, confirming the suggested reaction pattern. In the presence of a base, phosphorylated urea **VI** undergoes cyclization via intramolecular alkylation of the terminal nitrogen atom with release of HCl and formation of 1,4,2-diazaphospholidine **IX**. Cyclization

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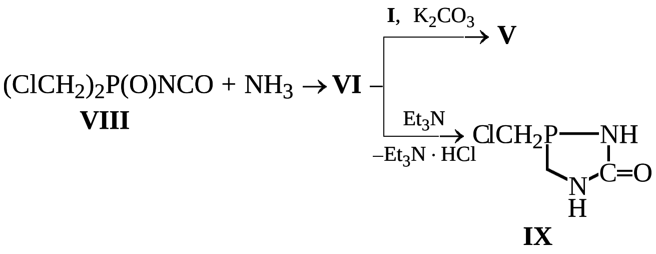
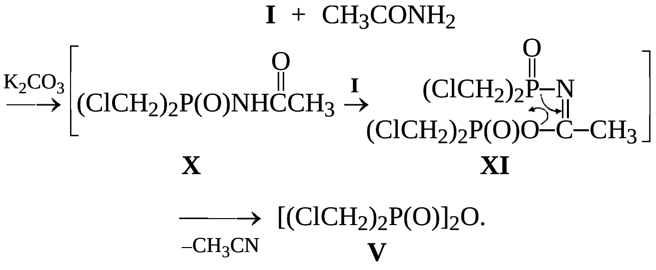
is accompanied by an upfield shift of the ^{31}P NMR signal and by an increase in the carbonyl absorption frequency from 1680 to 1720 cm^{-1}.



To prepare *N*-substituted derivative **X**, we attempted to phosphorylate acetamide with **I**. However, reaction of the equimolar amounts of these compounds in the presence of dry potassium carbonate also yielded **V**.



Apparently, the reaction pattern is similar to that proposed for phosphorylation of urea and involves formation and β-cleavage of intermediate **XI**. Formation of pyrophosphates (or pyrophosphonates) in phosphorylation of acylamides with phosphoric (or phosphonic) chlorides in the presence of amines was reported in [10, 11].

EXPERIMENTAL

The IR spectra (mulls in mineral oil) were taken on a UR-20 spectrometer. The ^{1}H and ^{31}P NMR spectra were recorded on Bruker WM-250 (^{1}H, 250.13 MHz) and Bruker MSL-400 (^{31}P, 166.93 MHz) spectrometers relative to residual solvent ($CDCl_3$) protons and external 85% H_3PO_4, respectively.

Bis(chloromethyl)phosphinic ethoxycarbonylamide III. *a*. A solution of 1.98 g of ethyl urethane in 10 ml of methylene chloride was slowly added with stirring to a mixture of 3.63 g of chloride **I** and 6.9 g of potassium carbonate in 40 ml of dry methylene chloride. After 2 h, the precipitate was separated, the filtrate was evaporated, and the residue was washed with hexane and dried in a vacuum (0.02 mm Hg). Compound **III** was obtained; yield 3.5 g (81%), mp 126–127°C. IR spectrum (KBr), ν, cm^{-1}: 1190 (P=O), 1725 (C=O), 3100 (NH). ^{1}H NMR spectrum (CD_3CN), δ, ppm (*J*, Hz): 1.03 t (3H, CH_3C, $^{3}J_{HH}$ 7), 3.77 d (4H, CH_2P, $^{3}J_{HP}$ 8), 3.90 m (2H, OCH_2), 10.76 br.s (1H, NH). ^{31}P NMR spectrum (C_6H_6), δ_P, ppm: 28.34. Found, %: C 24.83; H 4.16; N 5.74; P 13.18. $C_5H_{10}Cl_2NO_3P$. Calculated, %: C 25.65; H 4.30; N 5.98; P 13.23.

b. A mixture of 2.9 g of **I** and 1.42 g of ethyl urethane in 10 ml of anhydrous methylene chloride was refluxed for 10 h. The crystalline precipitate was washed with benzene and hexane. Compound **III** was obtained; yield 1.7 g (46%), mp 126–127°C. ^{31}P NMR spectrum, δ_P, ppm: 28.34. Found, %: Cl 30.24; P 13.43. $C_5H_{10}Cl_2NO_3P$. Calculated, %: Cl 30.32; P 13.23.

4-Oxo-4-chloromethyl-2-ethoxy-1,3,4λ^5-oxazaphospholine IV. A solution of 1 g of **III** and 0.43 g of triethylamine in 15 ml of dry benzene was kept at 20°C for 10 h. The precipitate of triethylamine hydrochloride was filtered off, the filtrate was evaporated, and the crystalline residue was washed with three portions of hexane. Compound **IV** was obtained; yield 0.65 g (77%), mp 147°C. IR spectrum, ν, cm^{-1}: 1630 (C=N). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.60 t (3H, CH_3C, $^{3}J_{HH}$ 7), 3.92 m (2H, OCH_2), 4.00 d (4H, CH_2P, $^{3}J_{HP}$ 8). ^{31}P NMR spectrum, δ_P, ppm: 60.23. Found, %: C 31.09; H 5.04; N 6.88; P 14.97. $C_5H_9ClNO_3P$. Calculated, %: C 30.39; H 4.59; N 7.09; P 15.69.

Bis(chloromethyl)phosphinic anhydride V. *a*. A mixture of 1.2 g of urea, 2.76 g of potassium carbonate, and 3.6 g of **I** in 50 ml of dry benzene was stirred for 8 h and allowed to stand for 3 days at 20°C. The precipitate was filtered off, the filtrate was evaporated, and the crystalline precipitate formed in the course of evaporation was recrystallized from methylene chloride. Compound **V** was obtained; yield 0.85 g (28%), mp 70°C [7]. ^{1}H NMR spectrum (CCl_4), δ, ppm: 3.86 d (8H, CH_2P, $^{3}J_{HP}$ 9). ^{31}P NMR spectrum, δ_P, ppm: 38.03.

b. A mixture of 2.05 g of **VI**, 2.65 g of dry potassium carbonate, and 1.8 g of **I** in 30 ml of dry benzene was stirred for 24 h at 20°C. The precipitate was filtered off, the filtrate was evaporated, and the crystalline precipitate formed in the course of evaporation was recrystallized from methylene chloride. Compound **V** was obtained; yield 1.1 g (36%), mp 70°C.

c. A mixture of 1.18 g of acetamide, 4.8 g of potassium carbonate, and 3.63 g of **I** in 50 ml of methylene chloride was kept for 3 days at 20°C. The precipitate was filtered off, the filtrate was evaporated, and the crystalline precipitate formed in the course of evaporation was recrystallized from methylene chloride. Compound **V** was obtained; yield 1.4 g (46%), mp 70°C.

2-Chloromethyl-2,5-dioxo-1,4,2λ^5-diazaphospholidine IX. Gaseous ammonia (0.5 g) was passed at –5°C through a stirred solution of 5.51 g of bis(chloromethyl)phosphinic isocyanate **VIII** in 70 ml of dry diethyl ether. The precipitate was filtered off and washed successively with anhydrous acetonitrile and diethyl ether. Bis(chloromethyl)phosphinylurea **VI** was obtained; yield 4.18 g (70%), mp 141°C. IR spectrum, ν, cm^{-1}: 690, 1390 (CH_2Cl), 1240 (P=O), 1620, 3390 (NH_2), 1680 (C=O), 3200 (NH). ^{31}P NMR spectrum, δ_P, ppm: 26.8. Found, %: C 17.21; H 3.18; Cl 35.09; P 15.37. $C_3H_7Cl_2N_2O_3P$. Calculated, %: C 17.58; H 3.45; Cl 34.59; P 15.11.

A mixture of 0.7 g of **VI**, 0.8 g of triethylamine, and 20 ml of anhydrous acetonitrile was refluxed for 7 h. The precipitate was filtered off and washed with dry CCl_4. Compound **IX** was obtained; yield 0.5 g (86%), mp 225°C. IR spectrum, ν, cm^{-1}: 1220 (P=O), 1720 (C=O), 3200 (NH). ^1H NMR spectrum $[(CD_3)_2N]_3PO$, δ, ppm: 3.7 d (2H, CH_2P, $^2J_{PCH}$ 8.5 Hz). ^{31}P NMR spectrum, δ_P, ppm: 20.0. Found P, %: 18.32. $C_3H_6N_2ClO_2P$. Calculated P, %: 18.38.

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