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Reactions of *tert*-Butyl *N*,*N*-Diethyl-*N*'-(4-phenylthiazol-2-yl)-phosphorodiamidite with Electrophilic Reagents

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Abstract — Previously unknown amidophosphorous acid derivatives were prepared by transamidation of *tert*-butyl *N*,*N*-diethyl-*N*'-(4-phenylthiazolyl)phosphorodiamidite with 2-amino-4-phenylthiazole, and their reactions with acetyl and benzoyl chloride were studied. These reactions are shown to proceed regioselectively according to the Arbuzov scheme to give the corresponding ketophosphonates. The reaction of the phosphorodiamidite with acetyl chloride in a 1 : 2 molar ratio involves formation of acetophosphonate that reacts in the enol form to give the corresponding (1-acetoxy)vinylphosphonate.
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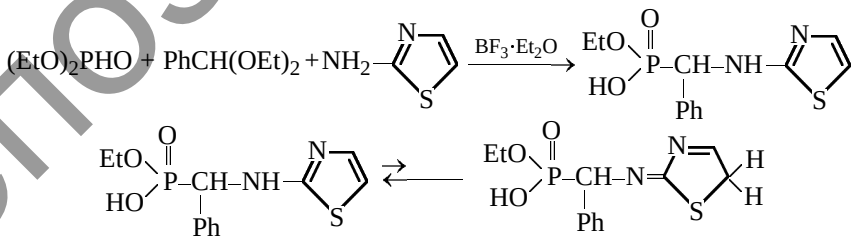
One of the most important and promising directions of the synthesis of biologically active compound is chemical modification of previously known compounds having pharmacophoric groups, such as readily available 2-aminothiazole derivatives. Thiazoles and their derivatives are known to exhibit pharmacological activity. Among them, antimicrobial, antihistaminic, antiparasitic, antihelminthic, antipyretic, and antiviral preparations were found. Norsulfazol, phthalazol, and related compounds are thiazole derivatives widely used in medical practice. The thiazole ring is present in such natural compounds as vitamin B_1 (thiamine), penicillin, and carboxylase enzyme [1]. Thiazole series compounds are widely used as antioxidants for petroleum products, vulcanization accelerators, and photochromic compounds [2, 3].

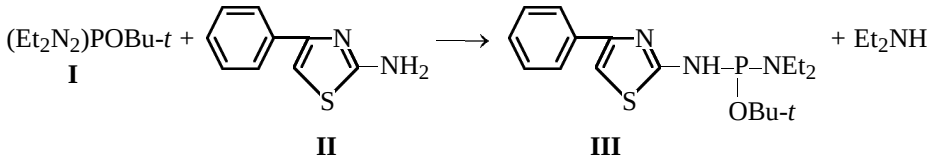
Attempts to prepare phosphorus-containing derivatives of thiazole and its homologs were undertaken at different times. Specifically, attempted involvement of 2-aminothiazole in direct condensation with aromatic aldehydes and dialkyl hydrogen phosphites in the presence of alkali metal alkoxides failed, evidently because of its low basicity (pK_a 5.39) [4]. 2-Aminothiazole could be phosphonomethylated with the dialkyl hydrogen phosphite–benzaldehyde diethyl acetal system in presence of boron trifluoride etherate [5]. The possibility of equilibrium between the amino and imino forms was shown, and the fact that the equilibrium is strongly shifted to the amino form was established.



We previously showed that transamidation of *tert*-butyl tetraethylphosphorodiamidite (**I**) with 2-amino-4-phenylthiazole (**II**) results in formation of previously unknown *tert*-butyl *N*,*N*-diethyl-*N*'-(4-phenylthiazol-2-yl)phosphorodiamidite (**III**) [6].

The imino form of phosphorodiamidite **III** is even less possible, because the phenyl radical significantly decreases the basicity of the thiazole amino group.

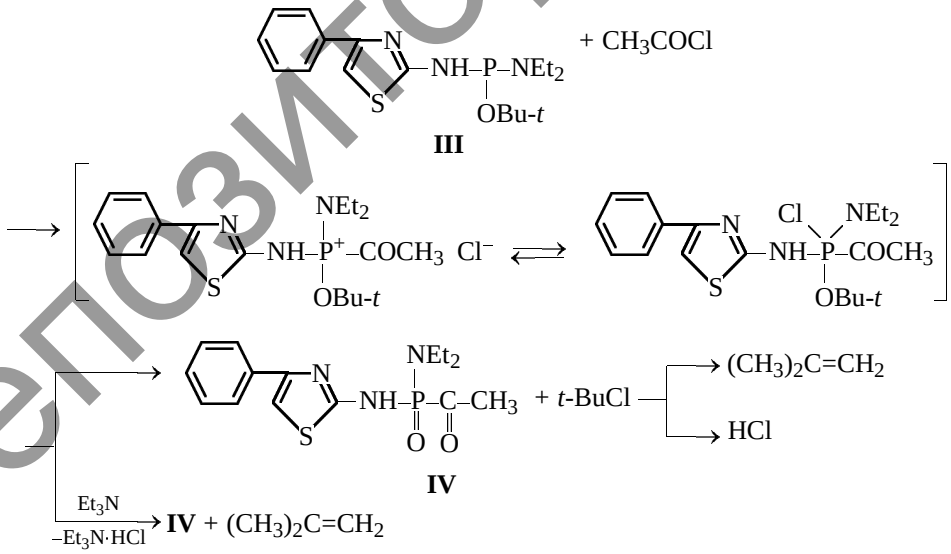
The reaction was carried out by heating equimolar



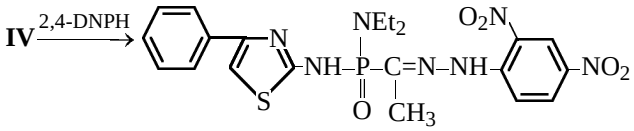
amounts of phosphorodiamidite **I** and 2-amino-4-phenylthiazole in ethyl acetate with simultaneous distillation of diethylamine. The latter was identified as hydrochloride. The reaction progress was monitored by TLC. The amount of the hydrochloride formed characterized the reaction completion. Compound **III** was purified by crystallization from benzene. It is a white crystalline substance soluble in water and polar solvents.

Transamidation of phosphorodiamidite **I** with two mol of thiazole **II** resulted in liberation of one mole of diethylamine only. After addition of one more mole of compound **I**, phosphorodiamidite **III** was isolated and identified. Hence, two 2-amino-4-phenylthiazole groups cannot be introduced to the P(III) atom, probably, by steric reasons. Phosphorodiamidite **III** was further used for chemical modification.

Compound **III** has a polyfunctional structure due to the simultaneous presence of a P(III) atom, on the one hand, and nucleophilic diethylamino and aminothiazolyl nitrogen atoms on the other. As known [7], such structures can exhibit dual reactivity. In view of known factors, we considered it interesting to study the behavior of phosphoroamidite **III** in the Arbuzov reaction with various electrophiles. Hence, by reacting compound **III** with acetyl chloride under various conditions we showed that the reaction proceeds regioselectively by the P(III) atom to give the corresponding acetylphosphonic diamide **IV**. The process is accompanied by liberation of equimolar amount of isobutylene. The reaction mechanism evidently includes the nucleophilic attack of the phosphorus atom, leading to a quasiphosphonium compound of the pentacovalent or ionic structure, depending on the nature of the solvent. The quasiphosphonium intermediate quickly decomposes with isobutylene liberation. Its amount was established volumetrically. Indirect evidence for the proposed mechanism is provided by the isolation of equimolar amount of triethylamine hydrochloride in the reaction in presence of triethylamine. The structure of acetylphosphonic diamide **IV** was confirmed by the formation of a colored hydrazone precipitate under the action of 2,4-dinitrophenylhydrazine.

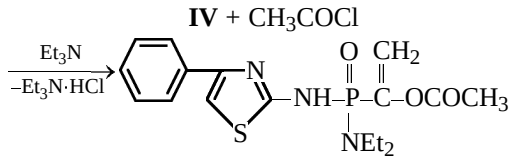


The structure of phosphonate **IV** suggests existence of the enol form in equilibrium with the keto form. To obtain evidence for this possibility, we treated phosphorodiamidite **III** with acetyl chloride in a 1 : 2 molar ratio and also in presence of two mole of triethylamine. It was found that diamide **IV** formed in



V

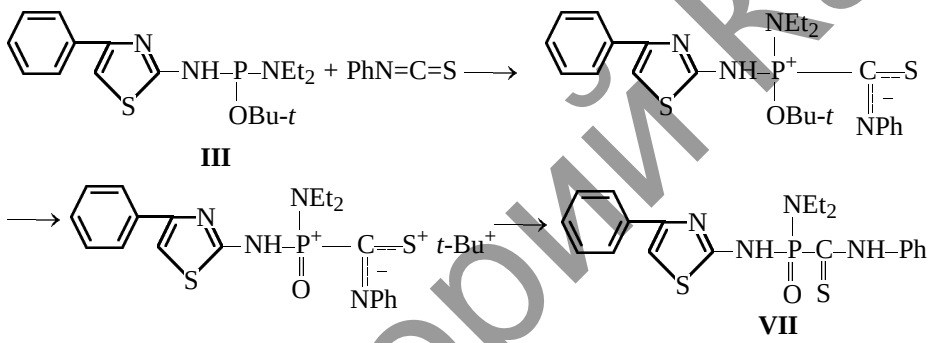
the first stage reacts in the enol form with the second acetyl chloride molecule to give acetoxyvinylphosphonic diamide **VI**.



VI

The reaction of phosphorodiamidite **III** with benzoyl chloride proceeds analogously to give the corresponding benzoylphosphic diamide in high yield. This result is evidently explained by the fact that the resulting benzoylphosphic diamide cannot be further benzoylated, because it lacks, unlike acetylphosphonic diamide **IV**, the enol form.

Continuing these investigations, we performed reaction of phosphorodiamidite **III** reaction with phenyl isothiocyanate to obtain phosphorylated phenylthiocarbamate **VII** in high yield. It is a stable substance readily soluble in organic solvents. Compound **VII** present interest in terms of biologic activity.



VII

EXPERIMENTAL

The IR spectra were recorded on Specord IR-75 spectrometer (3700–400 cm^{-1}, thin film) and Nicolet Avator-360 instruments. The ^1H NMR spectra were taken on a Bruker DRX-500 spectrometer (500 MHz) against internal TMS.

***tert*-Butyl *N*,*N*-diethyl-*N*'-(4-phenylthiazol-2-yl)-phosphorodiamidite (III).** *tert*-Butyl tetraethylphosphorodiamidite, 4.96 g, was treated with 3.52 g of 2-amino-4-phehylthiazole in 100 ml of ethyl acetate. The reaction mixture was heated until diethylamine no longer distilled. The amount collected, 1.34 g (92%), was stoichiometric. The diethylamine obtained was identified as hydrochloride, mp 221°C (reference data: mp 221°C). Free diethylamine, bp 54–55°C, n_D^{20} 1.3873 (reference data: bp 55.5°C, n_D^{20} 1.3878), was isolated by treatment with alkali. Compound **III** was purified by crystallization from benzene. Yield 5.97 g (85%), mp 141–142°C. IR spectrum, ν, cm^{-1}: 1475, 1620, (C=C), 1685 (C=N), 3365 (NH), 1060 (P–O–C). ^1H NMR spectrum, δ, ppm: 7.22–7.48 m (CH, C_6H_5), 1.21 s [9H, $(CH_3)_3C$], 1.07 t (6H, CH_3, $^3J_{HH}$ 7 Hz), 2.59 m (4H, CH_2), 4.0 (1H, NH). Found, %: C 58.45; H 7.22; N 11.78; P 8.98. $C_{17}H_{26}NO_3PS$. Calculated, %: C 58.12; H 7.40; N 11.96; P 8.83; S 9.12.

***N*,*N*-Diethyl-*N*'-(4-phenylthiazol-2-yl)(acetyl)-phosphonic diamide (IV).** To a solution of 7.02 g of compound **III** in benzene, 1.57 g of acetyl chloride was added, and the resulting mixture was refluxed. Isobutylene liberated and was measured volumetrically. The liberated amount, 412 ml (92%), is stoichiometric. The precipitate formed was filtered off and crystallized from ethanol to give 5.05 g (75%) of compound **IV**, mp 178°C. IR spectrum, ν, cm^{-1}: 1462, 1599 (C=C), 1623 (C=O), 3375 (NH), 1203 (P=O). Found, %: C 53.12; H 5.40; N 12.54; P 9.43; S 9.22. $C_{15}H_{20}N_3O_2PS$. Calculated, %: C 53.41; H 5.93; N 12.46: P 9.20; S 9.50.

[(Diethylamino)[(4-phenylthiazol-2-yl)amino]-phosphinoyl](methylene)methyl acetate (VI). To a solution of 7.02 g of compound **III** and 4.04 g of tri-

ethylamine in benzene, 3.14 of acetyl chloride was added at 20°C. The resulting mixture was refluxed until 421 ml (94%) of isobutylene liberated (by volumetry). The precipitate formed was filtered off and washed with several portions of distilled water to remove triethylamine hydrochloride and then crystallized from ethanol to obtain 6.06 g (80%) of compound **VI**, mp 205–206°C. IR spectrum, ν, cm^{-1}: 1442, 1549 (C=C), 1644 (C=O), 3167 (NH), 1302 (P=O). Found, %: C 53.76; H 5.67; N 11.26; P 8.56; S 8.32. $C_{17}H_{22}N_3O_3PS$. Calculated, %: C 53.83; H 5.80; N 11.08; P 8.18; S 8.44.

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