

# Glycidol Esters from Diethylamido-(4-phenylthiazolyl-2-amido)-ketophosphonates and Their Chemical Modification

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**Abstract**—Thiazolyl-containing esters of  $\alpha$ -ketophosphonic acids (KPE) unknown earlier were synthesized and investigated in Darzens–Claisen reaction. Reactions were demonstrated to proceed by a classic scheme to form the corresponding phosphorylated glycidol esters whose alkaline hydrolysis gave rise to phosphorylated aldehydes of interesting nature.

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Thiazole and its phosphorus-containing derivatives belong to heterocycles playing a significant role in the many vital activity processes, mainly in fauna. The thiazole ring is found in the composition of B<sub>1</sub> vitamin, of carboxylase enzyme, penicillin antibiotic, and many of other pharmacologic preparations [1].

Many simple types of heterocyclic systems with phosphorus-containing substituents are not easily accessible or have not been obtained at all despite the fact that these compounds are of significant theoretical and practical interest [2]. It has been known that the most general and simple method of synthesis of phosphorylated (thiophosphorylated) heterocyclic amines is the reaction of the corresponding amines with acid chlorides and isocyanates of phosphorus acids as well as by the Todd–Atherton method. The phosphorylated thiazoles with dialkylphosphoric acids residue in position 5 of thiazole ring and diphenylphosphonic acids residue in position 4 are also known [3, 4].

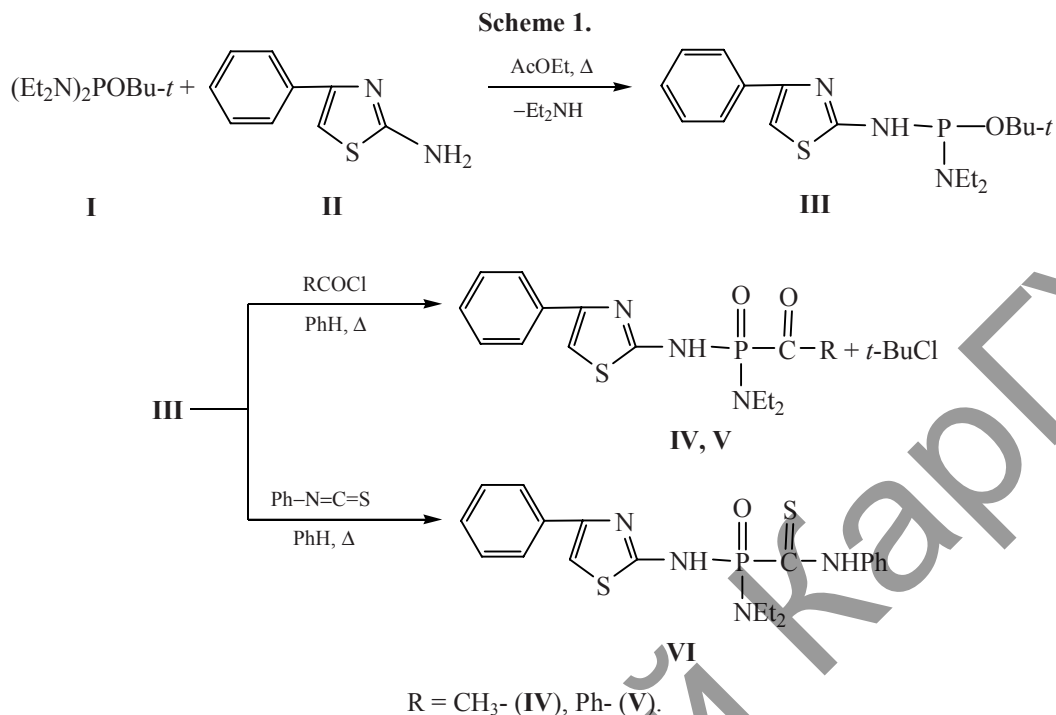
Earlier we succeeded to prepare *tert*-butyl diethylamido-(4-phenylthiazolyl-2-amido)phosphite **III** not described in the literature by transamidation of *tert*-butyl tetraethylamidophosphite **I** with 2-amino-4-phenylthiazole **II** [5, 6]. The complex polyfunctional structure of amidophosphite **III** obtained allows simultaneous electrophilic attack on several reaction centers. However, by the study of reaction of the latter with carboxylic acid halides it was established that this

reactions proceeded regioselectively involving the phosphorus(III) atom and affording the corresponding ketophosphonates **IV**, **V** and phosphono-substituted phenylthiocarbamate **VI** (Scheme 1).

$\alpha$ -Ketophosphonates (KPE) compose a class of highly reactive organophosphorus compounds. Despite the lability of P–C bond, KPE proved to be interesting key compounds for some syntheses basing on the use of increased activity of the carbonyl group, including the syntheses of  $\alpha$ -aminophosphonic acids and phosphorylcarbenes [7].

For the systematic evaluation of the synthetic potential of ketophosphonates **IV**, **V** obtained and to estimate their reactivity we studied a possibility of using KPE as basic structures for the synthesis of phosphorylated glycidol esters. The phosphorylated glycidol esters are known to be convenient synthons, which are appropriate for easy introduction of lipophilic phosphonolipid fragments into new and known potential drug structures to facilitate the trans-membrane transfer of biologically active substrates.

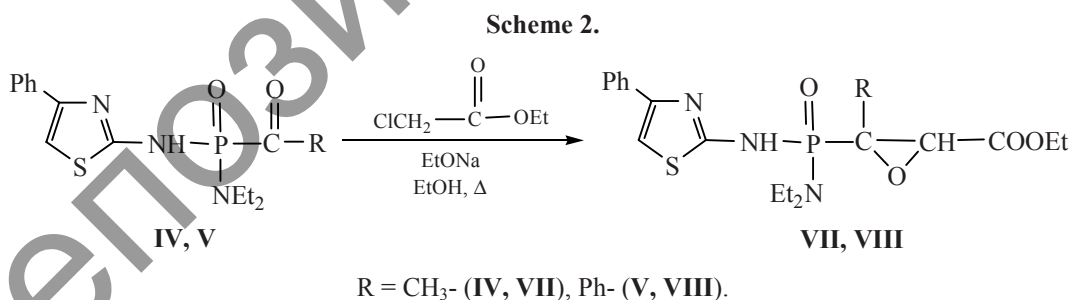
Brel and coworkers [8] carried out synthesis of 3-dialkoxyphosphorylpropyl glycidyl ethers by homolytic phosphorylation of allyl glycidyl ether with the corresponding dialkylphosphites in the presence of *tert*-butylbenzoylperoxide as initiator at 140–170°C and molar reagents ratio dialkylphosphite : allyl glycidyl ether : peroxide = 3.0–4.0:1.0:0.02–0.03.



Evaluation of the current status of this line shows that the known method of glycidol esters synthesis, Darzens–Claisen reaction, was not used earlier to obtain some phosphorus-containing esters of glycidic acid.

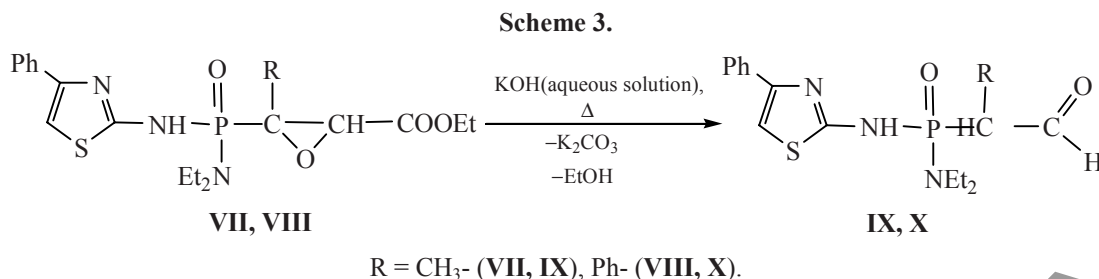
We established that ketophosphonates **IV**, **V** synthesized by a condensation reaction with ethyl monochloroacetate in the presence of sodium ethylate produce the corresponding 2-methyl-2-[diethylamido-*N*-

(4'-phenylthiazolyl-2'-amido)phosphono]ethyl epoxypropionate **VII** and 2-phenyl-2-[diethylamido-*N*-(4'-phenylthiazolyl-2'-amido)phosphono]ethyl epoxypropionate **VIII** in 75 and 76% yields respectively. Obviously the reaction is complicated by the formation of the alkoxyacetic ester. Nevertheless, the method described above is processible and suitable for the preparative synthesis of phosphorylated glycidol esters [9] (Scheme 2).



The interest to epoxy compounds is undoubtedly related to the possibility of their transformation into aldehydes and ketones containing by one carbon atom more than the initial carbonyl compounds. This transformation proceeds as a result of a common alkaline hydrolysis followed by decarboxylation of glycidic acid, and the aldehyde formation is accompanied by a rearrangement [10].

However, at the alkaline hydrolysis of epoxy compounds **VII** and **VIII** the prepared by us we observed that the formation of the corresponding phosphorylated aldehydes **IX** and **X** was possible even under the experimental conditions of the hydrolysis and did not require additional intermediate stages of isolation and work up that facilitated the preparation of the aldehydes (Scheme 3).



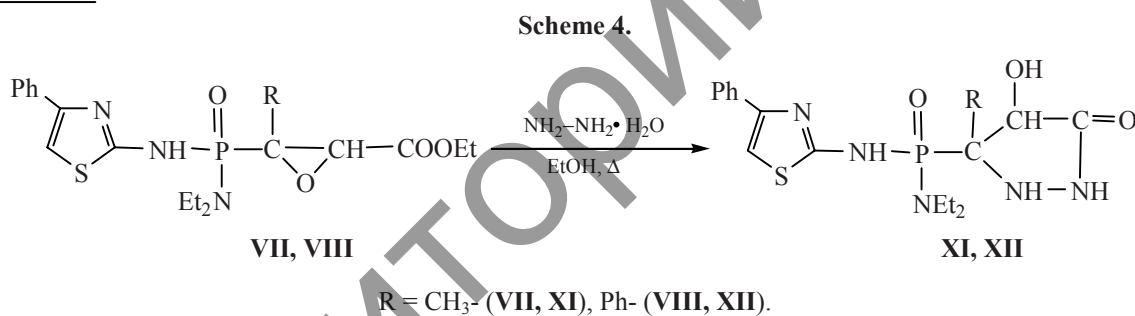
The high reactivity of the aldehyde group allows the compounds obtained to be considered as synthons for the synthesis of a great variety of compounds possessing useful properties.

Alongside the transformation into aldehydes and ketones, the glycidol esters are capable of entering into numerous reactions, which also are valuable for the fine organic synthesis.

Specifically, we studied reaction of epoxy compounds **VII** and **VIII** with amines, namely, with

hydrazine hydrate. This choice of reagent is determined by a possibility of obtaining cyclic compounds interesting by their structure, pyrazolidones, on the basis of some phosphorylated thiazolyl-containing glycidol esters **VII** and **VIII**.

4-R-4-[Diethylamido-(4'-phenylthiazolyl-2'-amido)-phosphono]-5-oxypyrazolidones [R = CH<sub>3</sub>- (**XI**), R = Ph- (**XII**)] were obtained as a result of the prolonged heating (10 h) of glycidol esters **VII** and **VIII** with hydrazine hydrate at 170–180°C and were characterized by physicochemical constants (Scheme 4).



Structure of compounds obtained was proved by IR and NMR spectroscopy and by independent syntheses.

#### EXPERIMENTAL

The IR spectra were registered on Specord IR-75 and Nicolet Avatar 360ESP spectrometers in thin layer in the range of 3700–400 cm<sup>-1</sup>. The <sup>1</sup>H NMR spectra were taken on a Bruker DRX500 spectrometer (500 MHz) relative to internal TMS.

**2-Methyl-2-[diethylamido-N-(4'-phenylthiazolyl-2'-amido)phosphono]ethyl epoxy-propionate (VII).** Sodium alkoxylate solution was prepared from 0.3 mol of sodium and 300 ml of anhydrous alcohol. After the completed dissolution to this solution was added dropwise a mixture of 3.67 g (0.03 mol) of ethyl monochloroacetate and 6.74 g (0.02 mol) of acetyl-

phosphonate **IV** while stirring and cooling with ice water. After the completion of reaction monitored by TLC the reaction mixture was left overnight at room temperature. Then it was neutralized with equimolar quantity of glacial acetic acid and poured into 100 ml of ice water. The water layer was extracted several times with ether. The extract was washed with water and dried over sodium sulfate. The solvent was evaporated and the residue was purified by recrystallization from ethanol. Yield 6.34 g (75%), mp 202–203°C. <sup>1</sup>H NMR spectrum, δ, ppm: 7.25–7.40 m (C<sub>6</sub>H<sub>5</sub>, CH), 1.15 t (CH<sub>3</sub>–CH<sub>2</sub>, 3H), 2.56 m (CH<sub>3</sub>–CH<sub>2</sub>, 4H), 7.8 s (NH, 1H). IR spectrum, ν, cm<sup>-1</sup>: 1749 (COOEt), 1483 (C=N), 1205 (P=O), 1442, 1547 (C=C), 3345 (NH). Found, %: C 53.76; H 6.67; N 9.45; P 7.18; S 7.84. C<sub>19</sub>H<sub>26</sub>N<sub>3</sub>O<sub>4</sub>PS. Calculated, %: C 53.90; H 6.15; N 9.93; P 7.33; S 7.56.

**1-Methyl-4-[diethylamido-(4'-phenylthiazolyl-2'-amido)phosphono]acetic aldehyde (IX).** A mixture of 4.24 g (0.01 mol) glycidol ester VII, 1.96 g (0.035 mol) of potassium hydroxide, 25 ml of water, and 50 ml of ethanol was refluxed for 4 h. After the completion of reaction the bulk of ethanol was evaporated. The residue was dissolved in a minimum volume of water and was acidified by hydrochloric acid to pH = 1 at cooling with ice. Then the reaction mixture was extracted with ether 4–5 times. Extracts were dried over anhydrous sodium sulfate. After the solvent removal the residue was recrystallized from ethanol. Yield 2.31 g (65%), mp 182°C. <sup>1</sup>H NMR spectrum, δ, ppm: 7.45–7.55 m (C<sub>6</sub>H<sub>5</sub>, CH), 1.20 t (CH<sub>3</sub>–CH<sub>2</sub>, 3H), 2.62 m (CH<sub>3</sub>–CH<sub>2</sub>, 4H), 7.82 s (NH, 1H), 7.15 s (thiazole, C<sup>5</sup>H), 8.57 (CH=O). IR spectrum, ν, cm<sup>-1</sup>: 1475 (C=N), 1194 (P=O), 1476, 1564 (C=C), 1685 (CH=O), 3372 (NH). Found, %: C 54.56; H 6.67; N 11.45; P 8.94; S 9.42. C<sub>16</sub>H<sub>22</sub>N<sub>3</sub>O<sub>2</sub>PS. Calculated, %: C 54.70; H 6.27; N 11.97; P 8.83; S 9.12.

**4-Methyl-4-[diethylamido-(4'-phenylthiazolyl-2'-amido)phosphono]-5-oxypyrazolidone (XI).** A mixture of 4.24 g (0.01 mol) of glycidol ester VII, 0.5 g of hydrazine hydrate in alcohol were heated at 150–180°C for 10 h. After the completion of reaction the precipitate was filtered off and recrystallized from alcohol. Yield 2.86 g (72%), mp 231°C. <sup>1</sup>H NMR spectrum, δ, ppm: 7.23–7.40 m (C<sub>6</sub>H<sub>5</sub>, CH), 1.15 (CH<sub>3</sub>, 3H), 7.8 s (NH, 1H), 7.2 s (thiazole, C<sup>5</sup>H). IR spectrum, ν, cm<sup>-1</sup>: 1461 (C=N), 1201 (P=O), 1463, 1582, (C=C), 1600 (C=O), 3260 (NH), 3435 (OH). Found, %: C 49.56; H 5.67; N 17.45; P 7.94; S 7.42.

C<sub>17</sub>H<sub>24</sub>N<sub>3</sub>O<sub>3</sub>PS. Calculated, %: C 49.88; H 5.87; N 17.11; P 7.58; S 7.82.

## REFERENCES

1. Ivanskii, V.I., *Khimiya geterotsiklicheskikh soyedinenii* (Heterocyclic Compounds Chemistry) Moscow: Vysshaya Shkola, 1978, p. 195.
2. Razvodovskaya, R.V., Grapov, A.F., Orlov, S.I., Khasan'yanova, E.Sh., and Mel'nikov, N.N., *Zh. Obshch. Khim.*, 1979, vol. 50, no. 2, p. 329.
3. Drach, B.S. and Lobanov, O.P., *Zh. Obshch. Khim.*, 1978, vol. 48, no. 9, p. 1994.
4. Prokof'eva, A.F., Aleshnikova, T.V., Negrebetskii, V.V., and Grapov, A.F., *Zh. Obshch. Khim.*, 1984, vol. 54, no. 3, p. 525.
5. Sal'keeva, L.K., Nurmaganbetova, M.T., and Minayeva, E.V., *Zh. Obshch. Khim.*, 2005, vol. 75, no. 12, p. 2065.
6. Sal'keeva, L.K., Nurmaganbetova, M.T., Minayeva, E.V., and Kokzhalova, B.Z., *Zh. Obshch. Khim.*, 2006, vol. 76, no. 9, p. 1456.
7. Zhdanov, Yu.A., Uzlova, L.A., and Glebova, Z.I., *Usp. Khim.*, 1980, vol. 49, no. 9, p. 1730.
8. Brel', A.K., Petrov, V.I., Ozerov, A.A., Gunger, A.A., and Sazhin, V.A., *Khim. Farm. Zh.*, 1992, no. 3, p. 86.
9. Sal'keeva, L.K., Nurmaganbetova, M.T., Minayeva, E.V., and Mantel', A.I., Abstracts of Papers, *Mezhdunarodnaya nauchnaya konferentsiya "Khimiya, khimicheskaya tekhnologiya i biotekhnologiya na rubezhe tysyachaletii"* (Int. Sc. Conf. "Chemistry, Chemical Technology, and Biotechnology on a Thousand Years Boundary"), Tomsk, 2006, p. 308.
10. *Organikum* (Organicum), Reutov, O.A., Ed., Moscow: Mir, vol. 2, 1992, p. 162.