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SYNTHESIS AND INVESTIGATION OF PHOSPHORYLATED THIAZOLES

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The monograph summarizes data on the preparation, structure and properties of the main representatives of aminothiazoles. The modification and functionalization of new organophosphorus derivatives of aminothiazoles have been considered.

The monograph is indented for researchers, teachers, doctoral students, master students and undergraduates.

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INTRODUCTION

More than sixteen millions of individual compounds were created over nearly two centuries of history of organic chemistry. Synthesis of new organic compounds is becoming more and more widespread, which is dictated by the need to solve fundamental problems, for example, to reveal the interrelation between the chemical structure of compounds and their reactivity. But no less rapid development of organic chemistry is provided by the practical needs of society. One of such needs is the availability of an arsenal of affordable, reliable and effective medicines for the prevention and treatment of human diseases.

Thiazole derivatives are known to be of great importance for pharmaceutical production, biochemistry, technology, clinical and experimental medicine. Mercaptothiazoles used for the synthesis of various sulfanilamide and anti-tuberculosis drugs are among the practically significant derivatives of thiazole on an industrial scale. The thiazole cycle is a structural fragment of some natural biologically active compounds, for example, antibiotics of the penicillin and thiamine group. Some thiazole derivatives took an important place as intermediates for the synthesis of amino acids, peptides, and purines.

An in-depth study of aminothiazoles to expand the boundaries of their use and create new approaches to the production of practically important heterocyclic compounds remains one of the most important tasks of the current stage in the development of the chemistry of nitrogen-containing heterocycles. The purpose of this monograph is to study phosphorylated aminothiazoles in chemical modification reactions, which is of considerable interest in solving important theoretical and practical issues in interpreting the mechanisms of reactions of polyfunctional systems. The monograph deals with the synthesis of phosphorylated aminothiazoles aimed at obtaining compounds with a wide range of practically useful properties.

The monograph is intended for a wide range of readers interested in the problems of modern organic chemistry in general and the chemistry of heterocyclic compounds in particular.

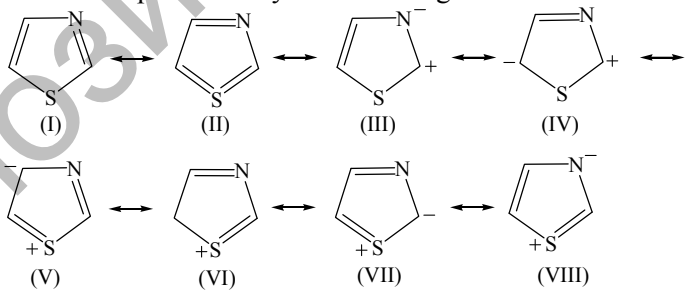
Chapter1

SYNTHESIS, STRUCTURE, CHEMICAL AND BIOLOGICAL ACTIVITY OF THIAZOLE DERIVATIVES

1.1 Structural features and physico-chemical properties of thiazole derivatives

Thiazole is a five-membered heterocycle with two heteroatoms, namely nitrogen and sulfur in the ring that are in relation to each other at the β-position. 1,3-Thiazole is a very stable compound that is not susceptible to self-oxidation. Thiazole is a water-miscible liquid with a pyridine-like odor. The boiling point of thiazole is 117-118°C. The thiazole density is slightly higher than the density of water and is 1.198 g/cm^3 due to the presence of a sulfur atom. The refractive index for the sodium D-line is 1.5969. Thiazole, like pyridine, has pronounced basic properties (pKa 2.53); substituents having an electron-donating effect enhance the basic properties of the heterocycle, pKa is 3.07 for 4-methylthiazole [1].

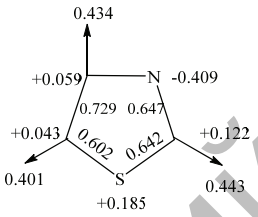
Thiazole, like other azoles, has a 6-π-electron heteroaromatic system, which makes it similar to pyridine and thiophene by its chemical properties. The distribution of electron charges in the thiazole corresponds to a certain set of resonant structures, the main ones of which are represented by the following series:



Here, the decent structure is taken into account, which can occur only when the electrons are distributed over the d-orbitals [2].

The energy of delocalization of the thiazole ring is approximately 84 kJ/mol. The molecular diagram of thiazole (1) allows us to draw several important conclusions. The distribution of the electron density

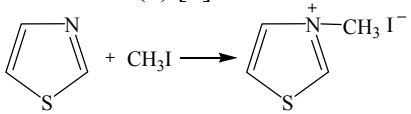
in the ring indicates a significant contribution of V, VI, VII structures to the total hybrid of the resonance structures of thiazole. A positive charge on the sulfur atom indicates the presence of a screening effect in the electronic shell of the sulfur atom and, consequently, the strong delocalization of its external electrons. The negative charge on the nitrogen atom and the positive charges on the carbon atoms agree with the experimental facts: an electrophilic attack on the nitrogen atom is possible; electrophilic substitution on carbon atoms is not characteristic; nucleophilic substitution passes through the carbon atom C2 most readily [3].



(1)

The bond orders confirm the arrangement of double bonds in the classical formula of thiazole. However, one can speak of the lability of the double bond 2-3 and its shift to the 1-2 position. This circumstance indicates a formal value of the resonance structure VIII. The ratio of bond orders in the thiazole molecule indicates a significant deviation of the geometric form of the thiazole from the regular pentagon [4]. Values of indices of free valence show that the center of the highest reactivity of thiazole is located on the C2 carbon atom [5].

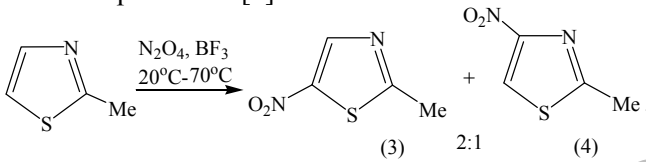
Although thiazole is a weak base (pKa 2.53), it is able to form fairly stable salts with acids. Thiazoles react with active alkylating agents forming thiazolium salts (2) [6].



(2)

As noted above, thiazole derivatives hardly undergo electrophilic substitution reactions, which is due to N-protonation or complexation with Lewis acids under the reaction conditions. Under conditions that exclude these reactions, nitration with N-nitropicolinium tetrafluoroborate goes to the position 5 and leads to the formation of

compounds (3) and (4) in acetic anhydride. Nitration to the 5-position of the thiazole proceeds fairly easily when there is a strong electron-donor substituent in position 2 [7].

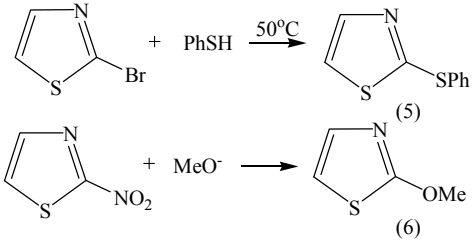


Electrophilic substitution occurs only in the para position of the benzene ring at nitration of phenylthiazoles. Other electrophilic substitution reactions, namely sulfonation and halogenation can be successfully carried out at position 4 and 5 also only in the presence of electron-donating substituents in the ring. Halogenation at the C2 carbon atom takes place with very great difficulty. Thus, the bromination of thiazole in position 2 is carried out in the vapor phase at a temperature of 250-400°C in a small yield. Under these conditions, the halogenation reaction most likely proceeds by a radical mechanism [8, 9].

Thiazoles are sulfonated under harsh conditions requiring high temperatures and the presence of mercury (II) sulfate as a catalyst [10].

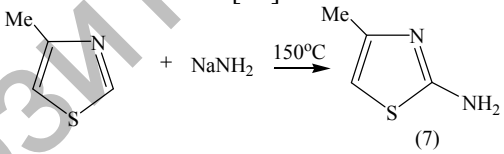
The reactivity of various positions of the thiazole cycle in the electrophilic substitution proceeding through the cationic σ-complex decreases in the series: 5-> 4-≥2-position. It is necessary to have electron-donating substituents, in which case the attack is predominantly based on position 5, to accelerate the reactions of electrophilic substitution [11].

Passivity of the thiazole ring in the electrophilic substitution reactions resembles the attitude of pyridine to these reactions. The analogy between thiazole and pyridine is also clearly visible with regard to these heterocycles to the action of nucleophilic reagents. Thiazoles posessing good leaving groups in position 2 readily react with nucleophiles to form substitution products, for example, (5) and (6) [12].

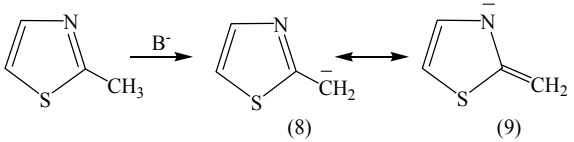


2-Chlorothiazole is about 100 times more reactive than 2-chloropyridine in nucleophilic substitution reactions, and 2-chlorobenzothiazole is even more active. More surprisingly, 4- and 5-halothiazoles can also undergo nucleophilic substitution reactions, although the relative rates of reactions of halothiazoles with different nucleophiles vary greatly [13]. It is known the example of the nucleophilic amination of thiazoles with the formation of the product (7). The process obviously proceeds analogously to the reaction of Chichibabin for pyridines [14].

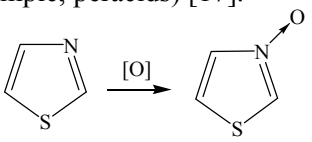
Neutral thiazoles are deprotonated by strong bases also predominantly at position 2; for example, thiazole forms an organomagnesium compound by reaction with ethylmagnesium bromide and is lithiated at position 2 by phenyllithium at -60°C. Metallized thiazoles react with aldehydes, carbon dioxide and other electrophiles in the usual manner [15].



The methyl substituents at position 2 of the thiazoles activated by the C=N bonds of the cyclic system have significant CH acidity and can be deprotonated with alkyllithium reagents and other strong bases to form anionic intermediates (8, 9) [16].

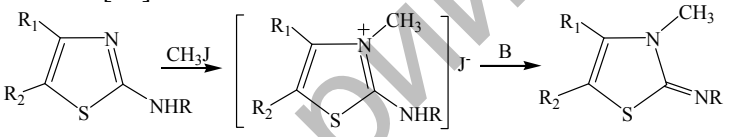


Thiazole and its derivatives are oxidized to the corresponding N-oxides (10) capable of 1,3-dipolar addition under the action of oxidizing agents (for example, peracids) [17].



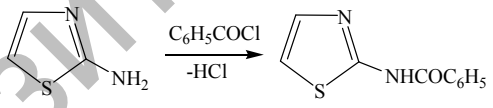
(10)

Aminothiazoles, especially 2- and 5-aminothiazoles, have been most thoroughly studied among the thiazole derivatives. 4-Aminothiazoles are known only in the form of their N-acyl derivatives. The cases of tautomerism of amine groups are not described. The nitrogen of the ring is usually attacked with the formation of thiazolium salts (11) followed by their transition to compounds of the general formula (12) in the alkylation of 2- and 5-aminothiazoles [18]:



(11) (12)

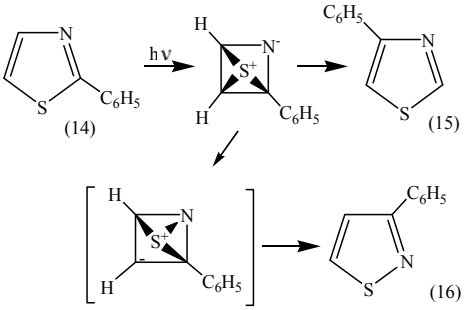
Acylation of 2- and 5-aminothiazoles, on the contrary, proceeds only through the amino group, for example, to form compound (13) [19]:



(13)

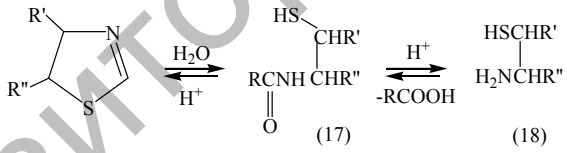
2- and 5-Aminothiazoles exhibit typical properties of aromatic amines undergoing diazotization reaction and condensation with aldehydes.

The rearrangement of 2-phenylthiazole (14) into 4-phenylthiazole (15) with the intermediate formation of a tricyclic sulfonium cation deserves attention among the photochemical transformations of thiazole compounds:

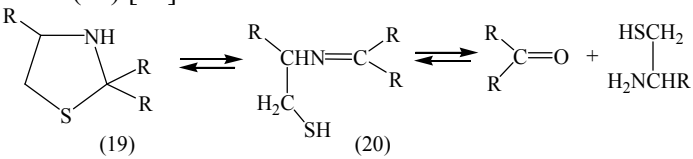


3-Phenylisothiazole (16) is formed as a by-product. The mechanism of rearrangement is confirmed by deutero-exchange [20].

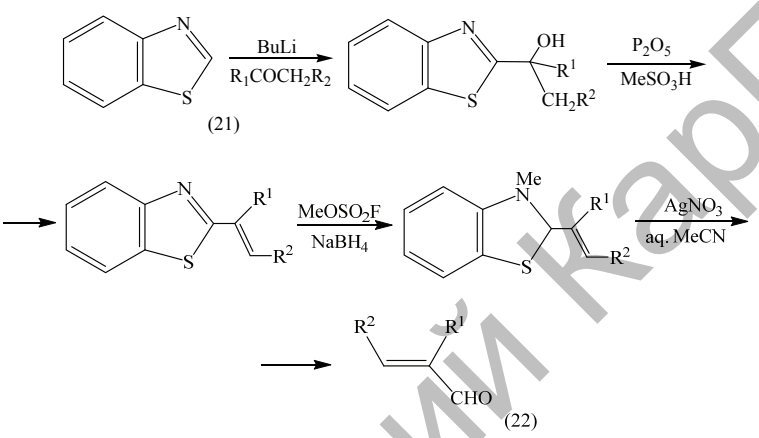
The reduced forms of thiazole, namely thiazolines and thiazolidines are well studied. It was not possible to obtain thiazolines by direct reduction of thiazoles, and they were usually synthesized by other methods. Thiazolines are no longer aromatic compounds and behave like acyclic amines. Acid chlorides, ketenes and their derivatives can be easily attached to double bond of 2-thiazolines. The thiazoline ring is easily opened in the presence of concentrated hydrochloric acid (formation of mercaptoalkylamines (17, 18)) [21].



The fully reduced form of thiazole, namely thiazolidine has all the properties of a secondary amine. It is easily alkylated and acylated at the nitrogen atom. The thiazolidine ring is not stable. Thiazolidine (19) is in equilibrium with the open thiol form (20) even in a neutral aqueous medium or the starting materials, from which this thiazolidine is synthesized (19) [22]:



The heterocycles of the 1,3-azole group are widely used as reagents in organic synthesis, since position 2 of this cyclic system is a hidden or protected carbonyl group. This use of the benzothiazole ring system (21) results in the formation of protected aldehyde (22) [23].

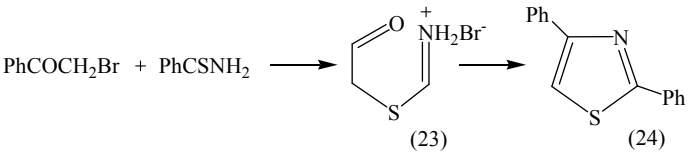


(21) (22)

1.2 Methods for the synthesis of thiazole derivatives

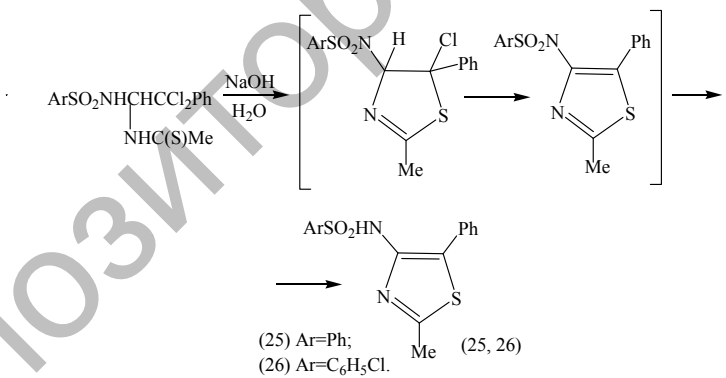
The chemistry of thiazole derivatives and their synthesis are discussed in detail in the literature, which is due to the interest that these compounds evoke from different points of view [24].

Methods for the synthesis of thiazole are based mainly on the use of substituted carbonyl compounds. The most important of these methods is the Hantzsch method developed in 1888. The method is based on the reaction of α-halocarbonyl compounds with thioamides. The reaction is carried out not only with amides and thioamides, but also with thioureas, thiosemicarbazides and other compounds containing the -N-C=S structural fragment. A nucleophilic attack of the sulfur atom takes place at the halogen substituted carbon atom during the reaction; the resultant acyclic intermediate was isolated in some cases. The formation of such an intermediate (23) is illustrated by the synthesis of 2,4-diphenylthiazole (24) [25].



Most often, the Hantzsch method is used for the synthesis of thiazoles containing alkyl, aryl and heterocyclic substituents. Using this method, it is possible to obtain mono-, di- and trisubstituted thiazoles with any combination of substituent groups. The synthesis of various 2-aminothiazoles from thiourea, as well as from N-substituted thioureas, is of great interest [26].

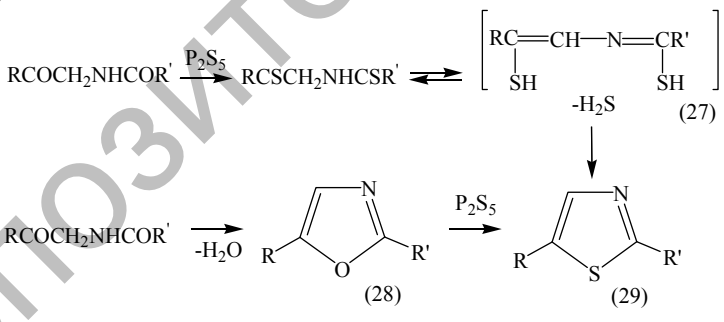
The reaction described adjoins closely the reaction of ammonium dithiocarbamate with α-halo ketones, which underlies the best method of synthesis of 2-mercaptothiazole, as well as the synthesis of 4-(arylsulfonyl)amino-2-methyl-5-phenyl-1,3-thiazoles (25, 26) from polyfunctional halogen-containing arenesulfone-amides, which can be easily prepared from N,N-dichloroarenesulfonamides, phenylacetylene and thioacetamide [27, 28].



The third method of synthesis of thiazoles, important from the preparative point of view, is the interaction of α-acylaminocarbonyl compounds with phosphorus pentasulfide. This reaction is analogous to the known synthesis of thiophenes from 1,4-diketones and is a convenient method for obtaining di- and trialkyl- (or aryl-)thiazoles, as well as 5-alkoxy-substituted derivatives [29].

There are two noteworthy assumptions regarding the mechanism of formation of the thiazole ring during the interaction of acylaminocarbonyl compounds with phosphorus pentasulfide. According to the first of these, the oxygen atom of the carbonyl group is replaced by a sulfur atom, after which the reaction product (27) undergoes cyclization with the loss of the hydrogen sulfide molecule and formation of the compound (29). According to the second assumption, the cycle closes first (as a result of water elimination), and then the oxazole formed (28) reacts with phosphorus pentasulfide [30].

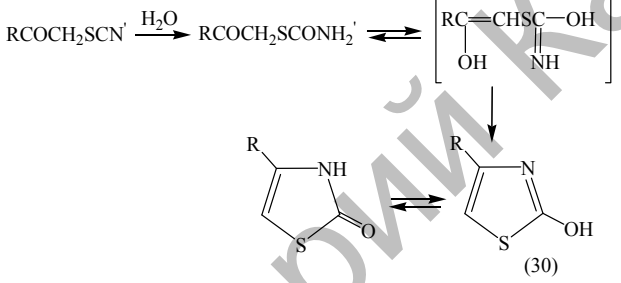
The first assumption is more plausible for the following two reasons. First, phosphorus pentasulfide reacts with water very slowly [31], and therefore it is difficult to expect that oxazole can be formed directly from the acylaminocarbonyl compound by such a weak dehydration agent. Secondly, the presence of oxazole was not proved in other reactions, in which oxazole formation should precede the formation of thiazole (for example, in the reaction of a mixture of acetamide and chloroacetone with phosphorus pentasulphide [32]). The known conversion of amides and ketones to their sulfurous analogs, which occurs under the action of phosphorus pentasulphide, also proves the first assumption on the mechanism of the reaction [33].



Another method for the preparation of substituted thiazoles is the rearrangement of α-rhodanketones in aqueous solutions, which allows the preparation of 2-hydroxy thiazoles (30) substituted at positions 4 or 4 and 5. The rearrangement occurs in aqueous solutions and is strongly dependent on the presence of acids or alkalis. The choice of reaction conditions is essential, since several compounds are often

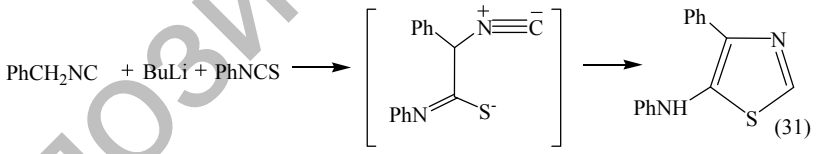
formed as a result of rearrangement. It is possible to achieve excellent yields with proper selection of conditions in some cases [34].

It is difficult to conclude on the extent to which the reaction under consideration is general due to the small number of examples described in the literature. It was studied in detail only with the example of rhodanacetone and rhodanacetophenone. In the case of the latter compound, the use of concentrated hydrochloric acid as a hydrolysing medium made it possible to isolate the intermediate-formed phenacylthiocarbamate $C_6H_5COCH_2SCONH_2$. Using dilute hydrochloric acid, 2-hydroxy-4-phenylthiazole is formed with quantitative yield [35].



(30)

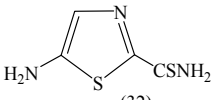
There are a number of convenient methods for the synthesis of thiazoles. Thiazoles not substituted at position 2, in particular compound (31), can be obtained by cyclization of isonitriles [36].



(31)

Benzothiazoles are most often obtained by the interaction of 2-aminophenols or 2-aminothiophenols with acid chlorides and other similar acylating agents [37].

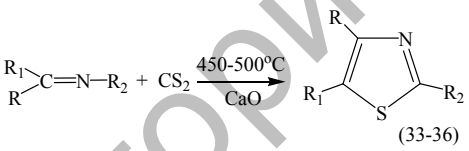
The synthesis of the so-called chrysean from hydrogen sulfide and potassium cyanide should be also mentioned [38]. This reaction was studied in detail by Helsing [39], who suggested that chrysean was 5-amino-2-thiocarbamylthiazole (32).



(32)

Subsequently, this assumption was confirmed [40], but the mechanism of the reaction is still unclear. Attempts to raise the yield of the chrysean more than 15-20% remained unsuccessful [41].

The reference [42] provides a vapor phase synthesis of thiazoles along with the above-described classical methods for forming the thiazole ring. 2-R^2-4-R-5-R^1-thiazoles (33-36) (where R=Me, R_1=R_2 =H, R=Ph, R_1=R_2 =H, R=R_1=H, R_2=Ph, R=R_2=H, R_1=Me) and benzothiazole in 70%, 26%, 40%, 20% and 40% yield, respectively, were obtained by the cyclization of enamines of structure $RCR_1{=}NR_2$ (where R=R_1=R_2=Me, R=Ph, R_1=R_2=Me, R=R_1=Me, R_2=$PhCH_2$, R=Et, R_1=H, R_2=Me) or methyliminocyclohexanes with carbon disulfide at 450-500°C in the presence of the catalyst (CaO, MgO, 1% ZrO_2).



(33-36)

1.3 Synthesis, structure and reactivity of phosphorylated thiazole derivatives

Organoelement derivatives of thiazole, namely organic compounds of phosphorus on the basis of the thiazole itself and its functional derivatives are of considerable practical and theoretical interest [43].

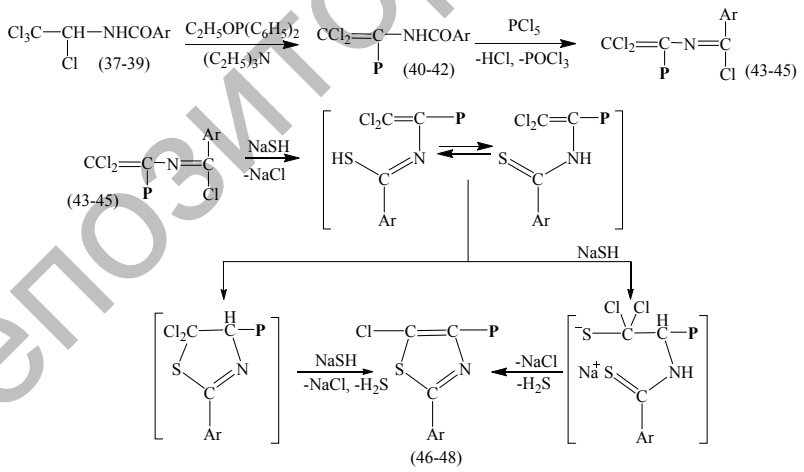
However, there are few publications devoted to the methods of synthesis of phosphorylated thiazole derivatives as analysis of literature data shows. For example, only one type of phosphorylated thiazoles with residues of dialkylphosphoric acids in the 5-position of the thiazole ring is known [44].

The authors of [45] succeeded in obtaining previously unknown substituted thiazoles containing the residue of diphenylphosphinic

acid at the 4-position of the ring. The readily available condensation products of N-1,2,2,2-tetrachloroethylamides of aromatic acids (37-39) with ethyl diphenylphosphinic acid were used for this synthesis, which are converted to phosphorylated 2,2-dichlorovinyl amides (40-42) after treatment with triethylamine. When the enamides (40-42) and phosphorus pentachloride are heated, the corresponding enimide chlorides (43-45) are formed which react smoothly with sodium hydrosulfide in a molar ratio of 1:2 at 20-25°C in dimethylformamide and give biphenyl(5-chloro-2-aryl-4-thiazolyl)phosphineoxides (46-48).

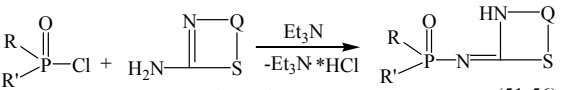
Phosphorylated thiazoles (46-48) are yellow, crystalline substances that are readily soluble in polar solvents. They have such low basicity that they do not dissolve even in concentrated hydrochloric acid. Solutions of these compounds in concentrated sulfuric acid at 20-25°C are completely stable and the compounds (46-48) are released unchanged after their dilution with water.

The most common and simple method of phosphorylation (thiophosphorylation) of heterocyclic amines consists in their reaction with acid chlorides and isocyanates of phosphorus acids, and also by the Todd-Atherton method [46].



where **P**=P(O) $(C_6H_5)_2$;
Ar=C_6H_5, *n*-$CH_3C_6H_4$, *n*-ClC_6H_4.

Thus, L.V. Razvodskaya and co-workers [47, P. 330] showed that only 2-phosphinylamino derivatives (51-56) were formed in all cases when 2-aminothiazoline (49) or 2-aminothiazole (50) reacted with phosphonic acid chlorides.

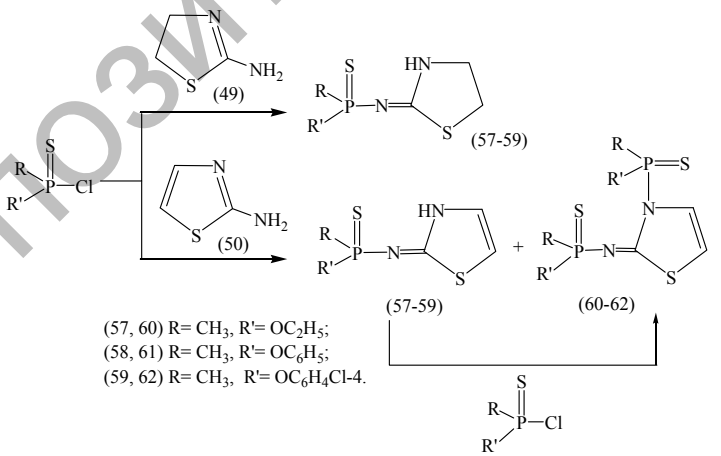


(49, 50) (51-56)

(49) Q= CH_2CH_2;
(50) Q= CH=CH.

(51) Q= CH_2CH_2, R= CH_3, R'= OC_2H_5;
(52) Q= CH_2CH_2, R= CH_3, R'= OC_6H_5;
(53) Q= CH_2CH_2, R= CH_3, R'= OC_6H_4Cl-4;
(54) Q= CH=CH, R= CH_3, R'= OC_2H_5;
(55) Q= CH=CH, R= CH_3, R'= OC_6H_5;
(56) Q= CH=CH, R= CH_3, R'= OC_6H_4Cl-4.

The reactions with phosphorus thioacid chlorides proceed specifically for each amine. 2-Aminothiazoline (49) with thiophosphonic acid chlorides forms products of thiophosphorylation at the exocyclic nitrogen atom (57-59). A mixture of thiophosphorylation products (60-62) is obtained both over the exocyclic and both nitrogen atoms in the reaction with 2-aminothiazole (50) as indicated in the scheme:



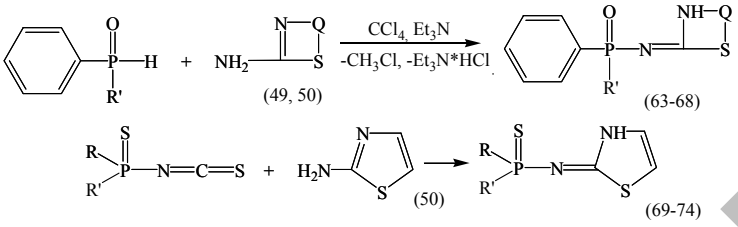
(57, 60) R= CH_3, R'= OC_2H_5;
(58, 61) R= CH_3, R'= OC_6H_5;
(59, 62) R= CH_3, R'= OC_6H_4Cl-4.

The bisphosphorylation products (60-62) are also isolated under the action of O-arylmethylthiophosphonic acid chloride on 2-aroxymethylthiophosphinylaminothiazole in the presence of triethylamine. This supports the stepwise mechanism of the formation of bis (thiophosphinyl)iminothiazoline [47, P. 333].

Taking as a basis the stepwise mechanism of substitution, the authors explain the differences during the thiophosphorylation reaction by lowering the nucleophilicity of the endocyclic nitrogen atom in the series of thiophosphorylated 2-aminoimidazoline, 2-aminothiazole and 2-aminothiazoline. The absence of bisphosphorylation products in the phosphonic acid series is probably the result of a decrease in the electron density at the endocyclic nitrogen atom in phosphinylaminoheterocycles compared to their thiophosphinyl analogues due to the stronger electron-acceptor effect of the phosphinyl group, and also because of the strong intramolecular hydrogen bond between phosphoryl oxygen and a proton at the nitrogen atom in position 3 [47, P. 334].

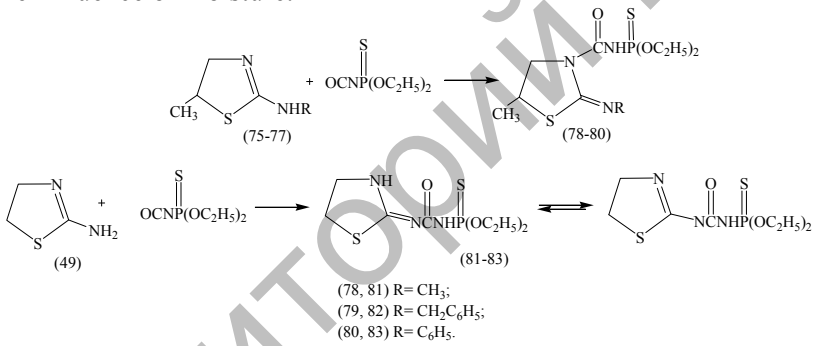
Other methods for the synthesis of phosphorylated (thiophosphorylated) heterocyclic amines are the reaction of O-alkylphenylphosphonites with the corresponding aminoheterocycles (49, 50) in carbon tetrachloride in the presence of triethylamine (Todd-Atherton reaction) or in the reaction of amines with thiophosphinyl isothiocyanates, resulting in the formation of (63- 68) and (69-74), respectively [47, P 335].

The authors of reference [48] showed that the 2-substituted aminothiazolines (75-77) formed substitution products on the endocyclic nitrogen atom of the heterocycle (78-80), when reacted with thiophosphoryl isocyanate, and 2-aminothiazoline (49) unsubstituted at amino group reacted with thiophosphoryl isocyanate via an extra-cyclic nitrogen atom to form products (81-83).



(63, 69) Q =CH_2CH_2, R =CH_3, R'= OC_2H_5;
(64, 70) Q =CH_2CH_2, R =CH_3, R'= OC_6H_5;
(65, 71) Q =CH_2CH_2, R =CH_3, R= OC_6H_4Cl-4;
(66, 72) Q =CH=CH, R =CH_3, R'= OC_2H_5;
(67, 73) Q =CH=CH, R =CH_3, R'= OC_6H_5;
(68, 74) Q =CH=CH, R =CH_3, R'= OC_6H_4Cl-4.

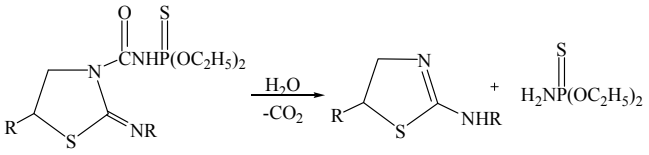
Ureas (81-83) are not stable enough and decompose easily under the influence of moisture.



(78, 81) R= CH_3;
(79, 82) R= $CH_2C_6H_5$;
(80, 83) R= C_6H_5.

The most common method for the synthesis of compounds containing the P(O)-C-N-H structural fragment is the Kabachnik-Fields reaction or the addition of phosphites to azines. However, it is not possible to introduce 2-aminothiazole into direct condensation with aromatic aldehydes and dialkyl phosphites in the presence of sodium alcoholate catalysts, which is due to the low basicity of 2-aminothiazole (pKa 5.39). The use of acetals of aromatic and aliphatic aldehydes, as well as orthoester, in the Kabachnik-Fields reaction leads to the synthesis of compounds of different structures [49-51].

So, A.F. Prokof'yeva et al. found that benzaldehyde diethyl acetal reacted with diethylphosphite and 2-aminothiazole (50) in alcohol in the presence of boron trifluoride etherate to form O-ethyl-α-(2-aminothiazolyl)-benzylphosphonic acid (84).

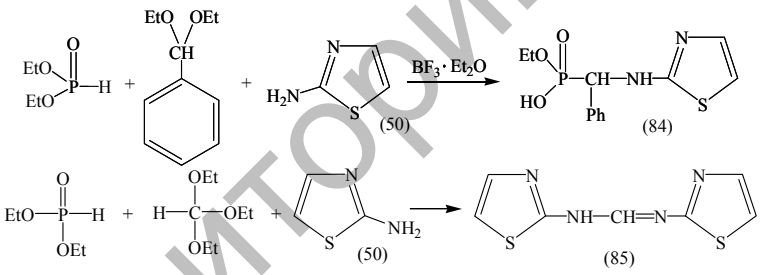


(81-83)

(81) R= CH_3;
(82) R= $CH_2C_6H_5$;
(83) R= C_6H_5.

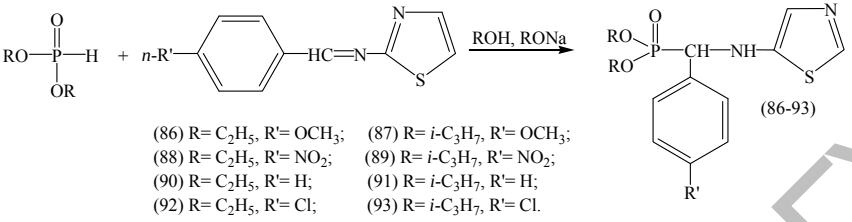
There is a broad absorption band of NH_2^+ cation in the 2300-2400 cm^{-1} region in the IR spectrum of compound (84), and also at 1610 cm^{-1}, which indicates that the compound apparently exists as an internal salt. Diethyl acetal of acetaldehyde does not undergo the reaction under the same conditions [52, p. 525].

N,N'-bis(2-thiazolyl)formamidine (85) was obtained as a result of condensation of diethylphosphite, 2-aminothiazole (50) and 4-fold amount of orthoester [52, P. 525].



Synthesis of O,O-dialkyl-α-(2-aminothiazolyl)-benzyl-phosphonates (86-93) was achieved by the addition of dialkyl phosphites to the corresponding Schiff bases in an alcohol medium and in the presence of sodium alcoholate catalysts [52, P. 526].

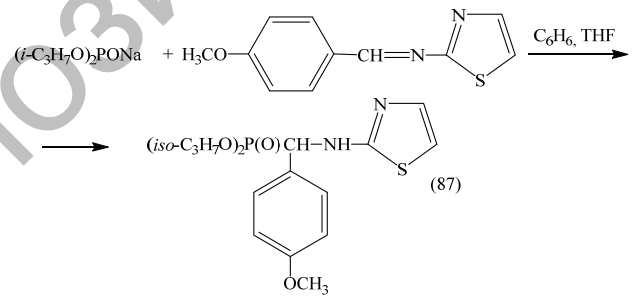
A.F. Prokof'yeva and co-workers explained the low yields of thiazolylaminobenzylphosphonates (86-93) obtained by this reaction by the low stability of Schiff's bases for the action of sodium alcoholates. It was shown that the yield of thiazolylaminobenzylphosphonates (87) could be increased to 58% in some cases using equimolecular amounts of sodium dialkylphosphite and carrying out the reaction in a mixture of absolute benzene and tetrahydrofuran [52, P. 527].



(86) R= C_2H_5, R'= OCH_3; (87) R= *i*-C_3H_7, R'= OCH_3;
(88) R= C_2H_5, R'= NO_2; (89) R= *i*-C_3H_7, R'= NO_2;
(90) R= C_2H_5, R'= H; (91) R= *i*-C_3H_7, R'= H;
(92) R= C_2H_5, R'= Cl; (93) R= *i*-C_3H_7, R'= Cl.

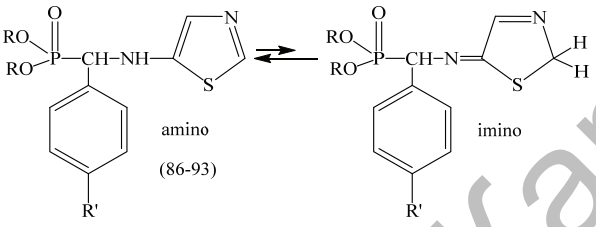
The authors considered that the introduction of a strong electron-withdrawing nitro group in the para position of the phenyl ring had a significant effect on the electron density distribution in compounds (86-93). At the same time, the acidic properties of the PCH proton increase, which leads to its partial deuteration by prolonged exposure (~10-20 h) of the solution in $(CD_3)_2CO$ at a temperature of 50-60°C. It is interesting to note that deuteration of the S-CH proton of 2-aminothiazole (50) is also observed here. Deuteration of the S-CH proton can be realized as a result of a tautomeric process, the equilibrium position of which is strongly shifted toward the amino form.

A.F. Prokof'yeva and co-workers assumed that the introduction of the nitro group to the para position of the phenyl ring promoted some stabilization of the imino form, which was not observed spectrally. For other substituents R'other than the nitro group, as well as for the 2-aminothiazole (50), P-CH and S-CH protons deuteration practically does not occur and with longer heating [52, P. 528].



There are few papers devoted to thiazole systems containing a phosphonium moiety. In particular, thiazolylmethylphosphonium salts are formed by condensation of β-acyl- or

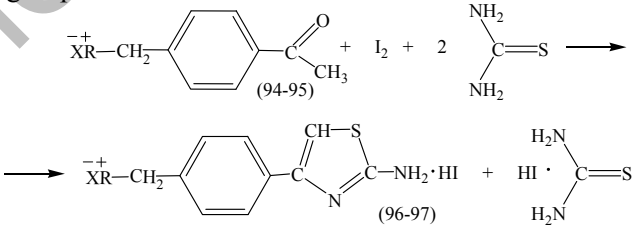
(cyano)vinyltriphenylphosphonium salts with thiourea, thioamides and thioacetamide, and phosphorus-containing thiazole derivatives are synthesized on the basis of certain substituted vinyl phosphonium salts [53].



R= C_2H_5, *i*-C_3H_7; R' =OCH_3, NO_2, H, Cl.

The synthesis of thiazole derivatives is known to be fulfilled by several methods. The main ones are the Dodson-King method; Hantzsch reaction and alkylation of 2-aminothiazole with quaternary phosphonium compounds containing a bromo-acetyl group [54].

In [55], the authors present results on the synthesis of a number of thiazole derivatives based on the cyclization reactions of certain acylphosphonium salts and the alkylation of the thiazole ring. Thus, I.N. Chernyuk and co-workers used triphenylphosphonium (94) and pyridine (95) salts, which were obtained by reacting *p*-bromomethylacetophenone with triphenylphosphine or pyridine, respectively, in the case of synthesis by the Dodson-King method. A condensation reaction of the resulting salts (94, 95) with iodine and thiourea in an absolute alcohol medium was carried out to synthesize thiazole derivatives (96, 97) containing triphenylphosphonium and pyridine groups.



(94, 96) R= Ph_3P, X=I ;

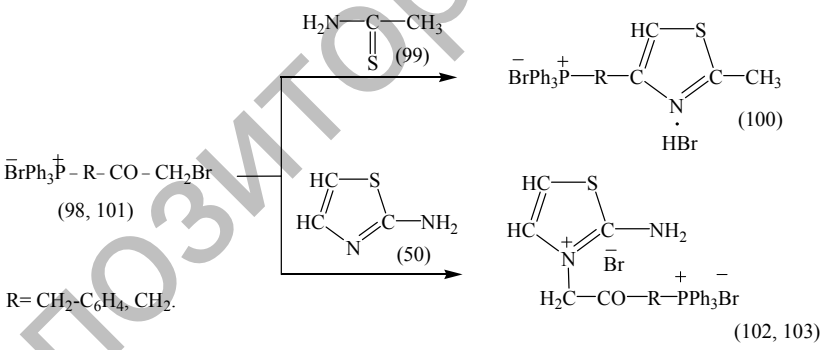
(95, 97) R= C_5H_5N, X=ClO_4.

It was previously established that an exchange of the bromine anion with iodine took place during the Ortolev-King reaction with bromides of phosphonium salts. Therefore, the authors used the reaction to prepare the compounds (96) and (97) in the form of iodides (94) or perchlorates (95) [56, P. 2690].

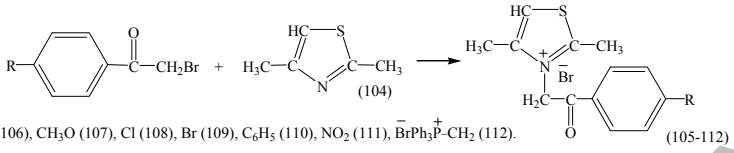
According to the Hantzsch method, the reaction was carried out by condensation of *p*-triphenylphosphonium methyl-ω-bromoacetophenone (98) bromide with thioacetamide (99) in absolute alcohol, which led to the preparation of 4-(2-methyl-3-hydrobromide-4-thiazolyl)benzyltriphenylphosphonium bromide (100) [56, P. 2691].

As a result of alkylation of 2-aminothiazole (50) with phosphonium salt (101) and bromoacetylmethylene-triphenylphosphonium bromide (98), phosphorus-containing derivatives of aminothiazole (102, 103) were synthesized [56, P. 2691].

Condensation of 2,4-dimethylthiazole (104) with a series of *para*-derivatives of phenacyl bromide in toluene or nitromethane also resulted in the synthesis of quaternary salts with various substituents on the phenacyl phenyl nucleus (105-112) [56, P. 2692].

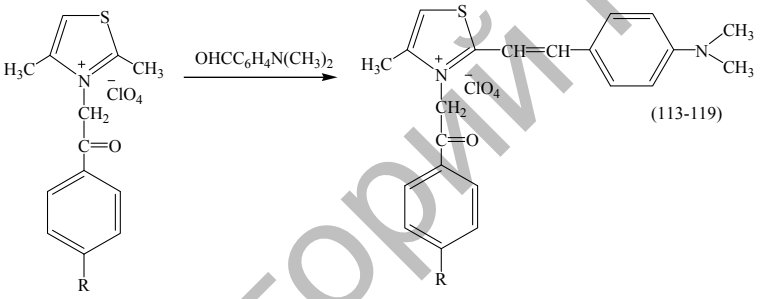


The presence of an active CH_3 group in the second position of the thiazole ring in quaternary salts synthesized allowed condensation in acetic anhydride with *p*-dimethylaminobenzaldehyde and a number of styryl dyes (113-119) [56, p. 2693].



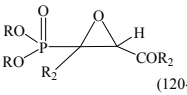
R=H (105), CH_3 (106), CH_3O (107), Cl (108), Br (109), C_6H_5 (110), NO_2 (111), $\overset{-}{B}rPh_3\overset{+}{P}-CH_2$ (112). (105-112)

E. Oehler et al. [57] synthesized compounds (120-123) containing an impurity $(RO)_2P(O)CH_2COEt$ (where R=Me; Et; Ph) by the reaction of $(RO)_2P(O)C(R^1)=CHCOR^2$ (where R=*i*-Pr, R_1=H, R_2=Me; =*i*-Pr, R_1=H, R_2 =Et; R=R_2=*i*-Pr, R_1=H; R=Et, R_1=Ph, R_2=Me; R=*i*-Pr, R_1=H, R_2=Et) with H_2O_2 in methanol. It was shown that the reaction of (120-123) with $RC(=S)NH_2$ (where R=Me, Ph, NH_2, COOEt) in boiling alcohol led to compounds (124-127).

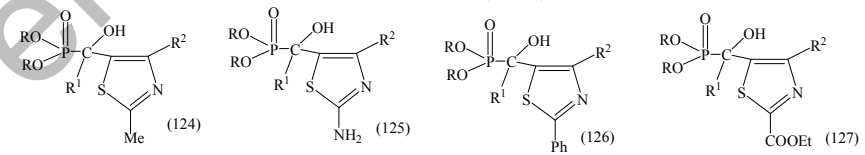


R=H (113), CH_3 (114), CH_3O (115), Cl (116), Br (117), C_6H_5 (118), NO_2 (119).

The team of authors supervised by Oehler E. [58] also managed to synthesize a thiazole ring based on the reaction of thiourea and diethyl bromoacetylphosphonate.



(120-123)

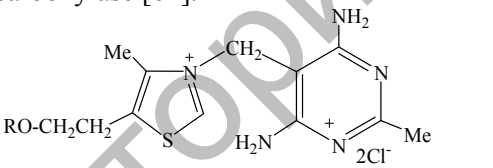


(124) (125) (126) (127)

1.4 Practical significance of thiazole derivatives

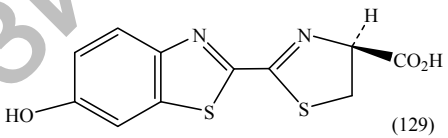
The thiazole fragment is a very common structure in living nature. So, for example, the molecule of the most important natural compound thiamine (vitamin B1) (128) includes a fragment of the thiazolium salt. Bleomycin antibiotics with antitumor activity are complex aminoglycoside structures containing thiazole fragments. Luciferin (129) of fireflies is a benzothiazole derivative, which has bioluminescent properties due to photooxidation at the asymmetric center. Some semisynthetic β-lactams contain fragments of 2-aminothiazole in the side chain, for example cefotaxime (130) [59, 60].

Vitamin B1 (128) is usually in the form of thiamine pyrophosphate (129) in the human body. Phosphorylation of free thiamine occurs (mainly in the liver) to form mono-, di- and triphosphate esters. This vitamin is involved in important metabolic processes in the form of thiamine pyrophosphate (131) called coenzyme co-carboxylase [61].

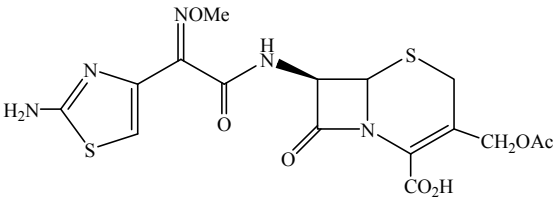


(128, 131)

R= H (128), PO(OH)-O-PO-(OH)$_2$ (131).

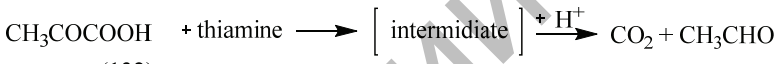


(129)



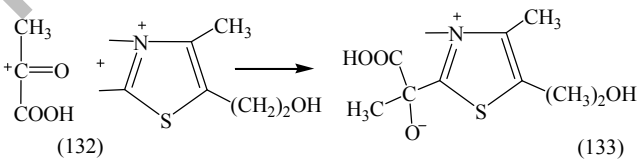
(130)

It is known that the energy necessary to maintain the existence of a living organism is obtained by the "burning" of glucose entering the body with food. "Burning" of glucose occurs gradually, as the conditions of this process are very soft and accurate. The temperature of the "living stove" is very stable and cannot be changed even by one degree. Pyruvic acid (132) is formed at one of the last stages of glucose "burning". This is an important intermediate in the exchange providing energy to the functional activity of the nervous system. Pyruvic acid (132) is also obtained by the deamination of amino acids. The pyruvic acid (132) formed in this, and in the other case, undergoes further "combustion". Otherwise, carbohydrate metabolism in the brain and transmission of nerve impulses are disturbed. The "burning" of pyruvic acid (132) begins with its decarboxylation, which is carried out with thiamine pyrophosphate (131) as a part of the carboxylase enzyme [62].



(132)

The catalytic action of thiamine is determined by the mobility of the hydrogen atom at the 2-position of the thiazole ring. Indeed, this atom is unusually mobile due to the features of the electron density distribution in the thiazole cycle. The mobility of the hydrogen atom in position 2 is enhanced by the positive charge of the thiazole ring and the electron-withdrawing action of another heterocycle, pyrimidine. The catalytic act consists in attaching the pyruvic (132) acid molecule to the carbon atom of the thiazole ring, which has lost the mobile proton and, therefore, carries a negative charge with the formation of (133) [63].



(132) (133)

The attached molecule of pyruvic acid in the form of (133) is activated by thiamine (128), a redistribution of the electron density

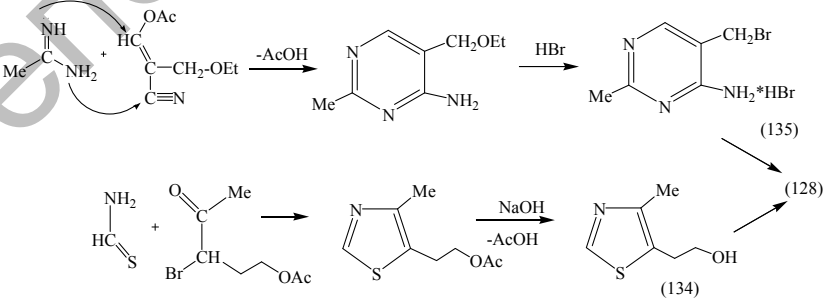
takes place, as a result of which the carboxylic group of pyruvic acid (132) breaks easily, releasing the CO_2 molecule [64].

Currently, the world production of vitamin B1 (128) is hundreds of tons. It is widely used as a food additive and in the pharmaceutical industry. Thiamin (128) is prescribed for ulcers of the stomach and duodenum, intestinal atony, liver diseases, myocardial dystrophy, dermatoses, and also for the treatment of neuritis, radiculitis, neuralgia and peripheral paralysis [65].

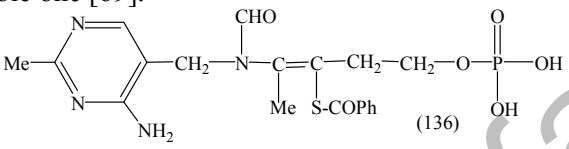
The synthetic thiamine (128) is prepared by quartenisation of the substituted thiazole (134) with bromomethylpyrimidine (135). Bromomethylpyrimidine (135) was synthesized by cyclization of acetamidine with the acrylonitrile derivative and bromination of the intermediate ethoxymethyl pyrimidine with hydrobromide. The thiazole synthon (134) is formed by cyclocondensation of thioformamide with 3-bromo-4-oxo-1-acetoxypentane followed by alkaline hydrolysis of the ester. The counterion (anion) in thiamine (128) can be Cl^-, Br^-, $H_2PO_4^-$ [66].

The analogue of thiamine (128) with the open thiazole cycle, which is benfotiamine (136), is pharmacologically similar to vitamin B1 and co-carboxylase. It penetrates through biomembranes more easily and is more resistant to the action of thiamine, which destroys thiamine. It is used for treatment of avitaminosis, arrhythmia, cardio and atherosclerosis [67].

The development of antibiotic chemistry in the years of the Second World War led to the discovery of penicillin and related compounds of thiazolidine cycles. Penicillin is an antibiotic produced by the green mold of the genus *Pennicillium*. Penicillin group includes a large number of antibiotics having a single penicillin base [68].



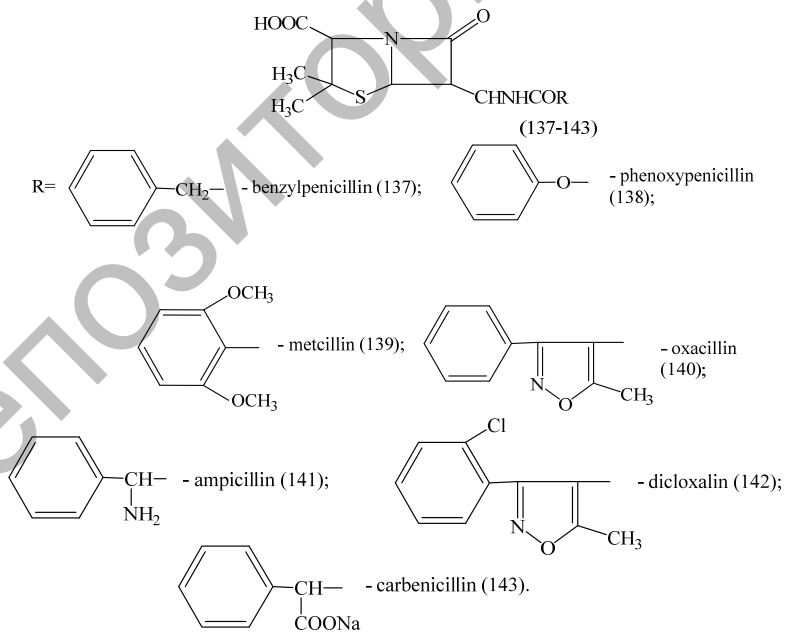
All penicillins (137-143) are acids and obtained from mold cultures in the form of sodium or calcium salts. Penicillins are very unstable. They are easily destroyed by heating, with the action of acids, alkalis, oxidants, enzymes, salts of heavy metals, and sunlight. Benzylpenicillin is the most stable one (137). It is superior in its bacteriostatic properties to other penicillins, and therefore, it is the most valuable one [69].



(136)

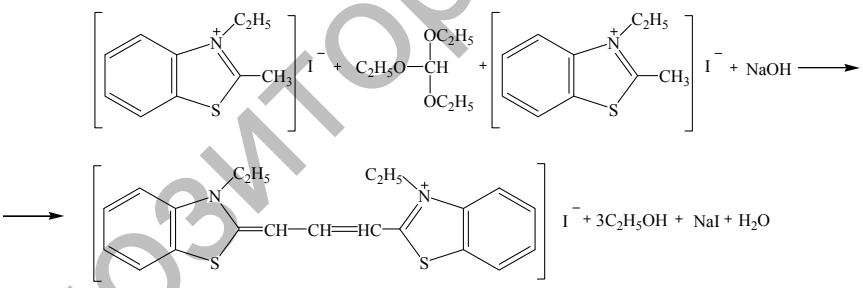
A fragment of the thiazole ring in the form of β-[thiazolyl-2]-β-alanine is included in the antibiotic bottromycin, which was isolated from the culture of *Streptomyces bottropensis* [70].

Condensed thiazole derivatives include the compounds of the benzothiazole series. Benzothiazoles are not widely used in biochemistry and pharmacology according to available literature.



But they proved to be important compounds in the production of cyanic dyes. Cyanic dyes of the benzothiazole series (144) are dyes-sensitizers, often used in color and infrared photography. The action of such photosensitizers is that they activate the photosensitive layer on the film or plate, making it more sensitive to irradiation. Benzothiazolium dyes, being introduced into the emulsion of the film, not only increase its sensitivity, but also absorb the incident light with a certain wavelength, give the film a yellow or red color. Recently they have almost replaced dyes-sensitizers of quinoline series, the effect of which in this respect is less effective. The replacement of hydrogen of the average methine group by methylene gives a color from green to red (panchrom). An increase in the number of methine groups up to 11 makes it possible to take pictures almost in the dark (infrared photography) [71].

Recently, condensed heterocyclic systems with a nodal nitrogen atom, containing a thiazole ring, also attract the attention of researchers. Thiazolo[3,4-a] pyridine derivatives suitable for the preparation of polymethine dyes undoubtedly occupy a special place among the simplest compounds of this type [72].



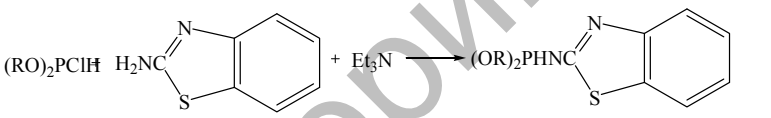
(144)

The authors of [73] synthesized 2-(α-chlorobenzyl)pyridines from 2-(α-hydroxybenzyl)-pyridines and thioacetamides. When these reagents are fused, the salts of 3-methyl-1-arylthiazolo[3,4-a] pyridiniumperchlorates are formed, which form cyanines with electrophilic reagents. It was found that the thiazolopyridinium cycle had a high electron donor and a large effective length in the resulting dyes.

A variety of derivatives of 2-aminothiazole is used as the starting objects for the synthesis of various dyes. Thus, monomeric dyes have been synthesized by diazotization of 2-amino-4-(4-vinylphenyl)thiazole in concentrated orthophosphoric acid and the combination of the resulting diazo compounds with phenol and N, N-dimethylaniline, which are used as copolymers in the preparation of structural-crystalline polystyrenes [74].

In [75] authors obtained disperse azo dyes, using 2-aminothiazole as diazo-constituents, 3-aminoisothiazole, 5-amino-1,2,4-thiadiazole, and 2-amino-1,3,4-thiadiazole.

Phosphorylated benzothiazoles with significant pesticidal properties among condensed thiazole derivatives are of particular interest. In particular, the reaction of 2-aminobenzothiazole with dialkylphosphoric acid chlorides in the presence of triethylamine yielded N-(2-aminobenzothiazolyl amidodialkylphosphites (145-147) exhibiting fungicidal and herbicidal properties [76, P. 815].

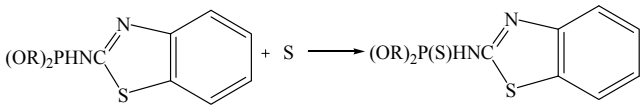


(145-147)

R=C_2H_5 (145); *i*-C_3H_7 (146); C_4H_9 (147).

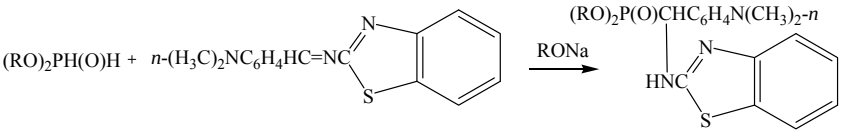
These compounds (145-147) reacted with sulfur to form the corresponding N-(2-aminobenzothiazolyl)amidodialkylthiophosphates (148-150) [76, P. 816].

Another type of phosphorylated 2-aminobenzothiazoles (151, 152) was obtained by the interaction of dialkylphosphoric acids in the presence of sodium alcoholates with a Schiff base synthesized in turn from 2-aminobenzothiazole and *p*-N,N-dimethylaminobenzaldehyde [76, P. 817].



(145-147) (148-150)

R=C_2H_5 (148); *i*-C_3H_7 (149); C_4H_9 (150).



R=CH_3 (151); C_2H_5 (152).

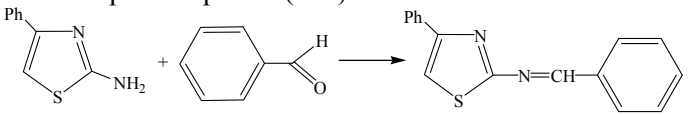
(151, 152)

Analysis of available literature data shows that the introduction of a sulfur atom and a phosphorus-containing fragment into the molecule of the heterocyclic amine, for example, as a residue of dialkylphosphorous acids, causes these compounds to exhibit pesticidal properties. Thus, the authors of [77] proposed phosphorylated and thiophosphorylated 2-aminotriazolines and 2-aminothiazoles, for example, O-phenyl-N-thiazolidine-2-ylidene-amidomethylthiophosphonate, as effective insecticides for controling the Colorado potato beetle and other soil-borne pests.

The compounds of general formula $(RO)_2PSSX$, where X=4-*n*-R^1-phenyl-5-phenylacetamidothiazol-2-yl and 4-*p*-R^1-phenyl-5-phenyl-thiazole-2-yl have the pesticidal activity, and R^1=H; CH_3; Cl; OCH_3 [78].

The preparation of fungicides and herbicides is also accompanied by the introduction of 2-aminothiazoles of the substituted benzoyl group into the molecule [79]. Compounds of the formula SCR=C(*tert*-Bu)N=CNR^1C(X) NR^2R^3 (R = H, Cl, R^1, R^2, R^3 or alkyl; X = O, S and *tert*-BuC=CRSC (NHR^1)=N (R = H, Cl, R^1 = H, alkyl, alkenyl, Ph) have fungicidal activity [80].

The Schiff bases obtained on the basis of the derivatives of 2-aminothiazole are compounds possessing a whole complex of practically useful properties. Thus, the authors [81] synthesized the corresponding derivatives of $SC(R^1)$=C(R)N=CN=CHX (R=Ph, 4-ClC_6H_4) by the reaction of substituted 2-aminothiazoles with various aldehydes (PhCHO, PhCH = CHCHO or 2-HOC_6H_4CHO) or 4-MeC_6H_4, R^1=H, Cl, Br, X=Ph, PhCH=CH, 2-HOC_6H_4), among which there are substances inhibiting the development *of Helminthosporium oryzae*, for example compound (153).

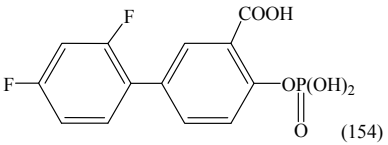


(153)

Another group of authors [82] showed the possibility of using (153) as complexones. In addition, the compound (153) and its derivatives serve as convenient synthons for the preparation of various heterocycles, as well as for the cyclization of terpenes.

However, the introduction of various compounds of the phosphorus-containing structural fragment into the molecules causes the presence of not only pesticidal properties, but also predetermines the possibility of the synthesis of many pharmacologically active substances. The therapeutic effect of phosphorus-containing drugs is known to be associated with a variety of cell functions. Phosphorus-containing drugs have the most diverse structure and can contain such molecular fragments as P-C, P-O-C, C-N-P, P-H bonds in their structure. In some preparations, the basic bond can be a phosphorus-containing functional group that determines bioactivity, while in others it can only exert a definite influence on the overall pharmacological effect [83].

Thus, the relationship between the structure of drugs and their pharmacological activity can be traced to the chemical modification of known antiviral drugs with organophosphorus compounds. As the analysis of literature data shows, the introduction of a phosphorus-containing structural fragment into the molecules of medicinal substances leads to the preservation or enhancement of the activity of the compounds, the reduction of their ulcerogenic effect, and a number of other side effects in all cases. In particular, compounds (154, 155) exhibit anti-inflammatory, antipyretic and analgesic activities, both in intragastric and intraperitoneal administration, with low toxicity and a much weaker ulcerogenic effect compared to their analogues with diflunisal and butadione preparations. Phosphate (156), a derivative of paracetamol, in the form of water-soluble salts of lysine, glycine and adenosine is recommended as an analgesic and antipyretic agent [84].



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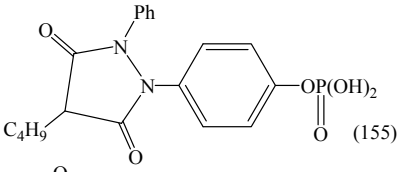

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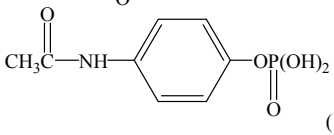


(156)

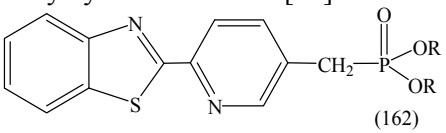
A series of acylphosphonates of the type (157-160), where [RC(=O)] is the carboxylic acid residue, has anti-inflammatory activity, as shown in the model of reduction in paw edema in rats. In contrast to the precursors (acetylsalicylic, indolylacetic, 4-iso-butylphenylacetic, 2-(4-iso-butylphenyl)-propionic, 4-allyloxy-3-chloro-phenylacetic and other acids), their phosphorus-containing analogues practically do not cause gastrointestinal tract irritation when administered orally. Compounds (157-160) are soluble in lipids and thus penetrate well through cell membranes. These substances are recommended for external use in the form of ointments, suspensions of solutions to protect against sun and ultraviolet burns or to reduce pain effects after UV irradiation [85].

$RC(=O)P(=O)(OR)_2$

(157-161)

R=CH_3 (157); C_2H_5 (158); *i*-Pr (159); Pr (160); C_4H_9 (161).

Derivatives of 2- (benzothiazolyl)-5-picolinylphosphonic acid (162) (hydrobromide, hydrochloride, phosphate, sulfate, methanesulfonate and others) known as low-toxicity analgesics possess the strongest anti-inflammatory properties. Compounds of general formula (162) are more active than butane-diones for the anti-inflammatory activity by almost 2 times [86].

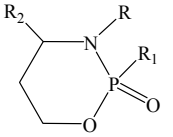


(162)

As is known, the application of phosphorus organic compounds in medical practice began with the introduction of substances with

anticholinesterase activity. Organophosphorous compounds are successfully used for the treatment of glaucoma, malignant neoplasms of paralysis and a number of other diseases [87-90].

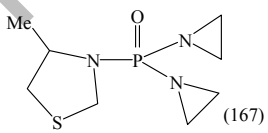
One of the first antitumor organophosphorus preparations used in medical practice was cyclophosphamide (163), which had a wide spectrum of chemotherapeutic effects. It is able to inhibit the growth of a large number of tumors of different nature. Its analogues, which are isophosphamide (164), trophosphamide (165), suphosphamide (166), which have a specific effect on cyclophosphamide-resistant neoplasms [91-94], are also available.



(163-166)

(163) R= R_2= H, R_1 = $N(CH_2CH_2Cl)_2$;
(164) R= $ClCH_2CH_2$, R_1= $NHCH_2CH_2Cl$ R_2= H;
(165) R= $ClCH_2CH_2$, R_1= $N(CH_2CH_2Cl)_2$, R_2= H;
(166) R= H, R_1= $NHCH_2CH_2OSO_2CH_3$, R_2= H.

The antitumor drug imiphos (167), which is widely used at present in clinical practice, contains a phosphorylated thiazolidine fragment in its structure [95].



(167)

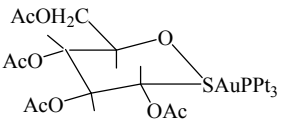
Organophosphorus complexones occupy a special place among organophosphorus medicines, the metabolism of which in living organisms is given great attention. It is well known that diphosphonates have found wide application in medical practice as regulators of calcium metabolism in the body due to their complexing properties [96-99].

Publications on the effectiveness of the application of diphosphonic acid derivatives in the treatment of rheumatoid arthritis and osteoporosis have been appeared in recent years. The derivatives of methylenebisphosphonic acid and their salts are offered as anti-

arthritic agents. Substances are moderately toxic, used both intravenously and orally. They are highly selective for inhibition of bone resorption, good absorption and do not have side effects. Diphosphonic acids are also proposed as components of active compositions with many drugs, which enhances their effectiveness and reduces the side effects of the drugs. Thus, the activity of acetylsalicylic acid and other derivatives of salicylic acid is enhanced when used in combination with hydroxyethylene diphosphonic acid (HEDP), dichloromethylene diphosphonic acid (DCMDP) and their salts [100-105].

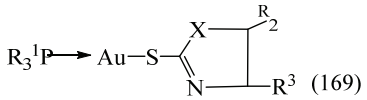
Good results were obtained when using the composition of the disodium salt of HEDP or DCMDP with steroidal anti-inflammatory drugs (prednisolone, cortisone, hydrocortisone) [106]. The use of diphosphonates in combination with prednisolone is more effective in treating rheumatoid arthritis than with each component separately. In addition, lower doses of steroids are required to achieve a therapeutic effect, the frequency of their administration decreases, and the side effects manifested in the treatment with steroids (bone mineralization, bone erosion) decrease. These phosphonates are recommended for the treatment of rheumatoid arthritis in compositions with gold salts. For example, an aqueous solution for intramuscular injection contains 500 mg of DCMDP disodium salt and 50 mg of gold thiomalate. Side effects such as kidney damage and bone erosion are minimized in the clinical use of this composition [107, 108].

Trivalent phosphorus compounds complexes (phosphines, phosphites) with gold salts are known to have physiological activity (antiarthritic, antitumor). For example, the thioglucose derivative of auranofin (168) is used in the medicine as an antiarthritic drug [109].

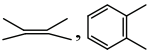


(168)

Complexes of phosphines and phosphites with heterocyclic sulphides of gold (I) of general formula (169) are proposed for the treatment of arthritis [110].



(169)

R^1=alkyl C_1-C_3, alkyl-O, Ph, PhO, R^2 and R^3=H,  ,

X=O, S, NH, NMe

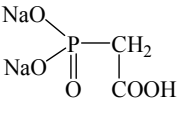
Aminoalkanephosphonic acids and their derivatives are also recommended for use in compositions for the treatment of rheumatoid arthritis, osteoparitis and Wilson's disease. Phosphatidylinositol analogues are specific selective inhibitors of phospholipase C, which has been carefully studied, and the percentage inhibition for all synthesized compounds was determined [111].

Among the organic derivatives of phosphoric acids, PALA (170), which is a peptide derivative of phosphonic acid with a P-C bond [112], can be of great practical importance.

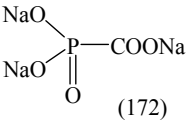
(170)

Other potential antiplastic drugs, phosphorylated amino acids, were also obtained [113].

Undoubtedly, interesting classes of organic phosphorous compounds are antiviral drugs, many of which have been extensively studied. These are drugs such as phosphonet (disodium phosphonoacetic acid) (171) and phospharnet (trisodium salt of phosphonoformic acid) (172), which suppress the replication of the DNA of herpesvirus types 1 and 2 [114].

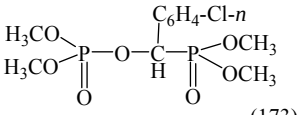


(171)



(172)

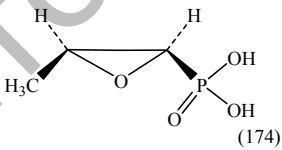
Phosphonates that simultaneously contain the P-C and P-O-C bonds regulate lipid metabolism and cholesterol in the blood, for example (173) [115].



(173)

Organophosphorus antibacterial drugs include synthetic drugs and antibiotics. Synthetic preparations based on phosphonates are limitedly used in medical practice, which is due to their low antimicrobial activity and a rather narrow spectrum of action. Peptide derivatives of phosphonic acid are active against both gram-positive and gram-negative bacteria [116].

More effective antibacterial drugs are organophosphorus antibiotics. The antibiotic phosphonomycin (174), which is an analogue of the natural amino acid ciliatine (2-aminoethylphosphonic acid), is the most known among organophosphorus antibiotics. Phosphonomycin (174) is an optically active phosphonate with an epoxy group at the α-position of the molecule. This antibiotic has a low toxicity and is used to treat infectious diseases of the urinary tract, sepsis, meningitis, endocarditis, and lung abscess. Phosphonomycin having a bactericidal action inhibits enzymes of biosynthesis as shown by biochemical studies and thereby delays the synthesis of the bacterial cell wall [117].



(174)

Thus, a number of substances among the organophosphorus compounds that possess anti-inflammatory, analgesic, anti-arthritic, diuretic, antitumor, antibacterial properties have been found in recent years. They are found among various classes of organophosphorus compounds (mono-, diphosphonic acids, phosphonium salts, phosphine oxides). They are not inferior to the known analogous preparations for pharmacological activity in a number of cases and are advantageously distinguished from them by the absence of side effects, as well as by their lower toxicity. Therefore, the search for new drugs in a number of different organophosphorus compounds seems promising [118].

Chapter 2

SYNTHESIS, REACTIVITY AND BIOLOGICAL ACTIVITY OF PHOSPHORYLATED DERIVATIVES OF 2-AMINOTIAZOLE

2.1 Synthesis, structure and reactivity of amidophosphorous acid *tert*-butyl esters

The presence of nitrogen and sulfur atoms in organic compounds molecules causes their high physiological activity often leading to a decrease in toxicity [119]. Derivatives of 2-aminothiazole possessing the most diverse physiological effects, namely bronchodilator [120], antiviral [121], anti-inflammatory [122], antitumor [123], and other have become effective drugs. In addition, the compounds of the thiazole series are widely used in engineering and agriculture [124, 125].

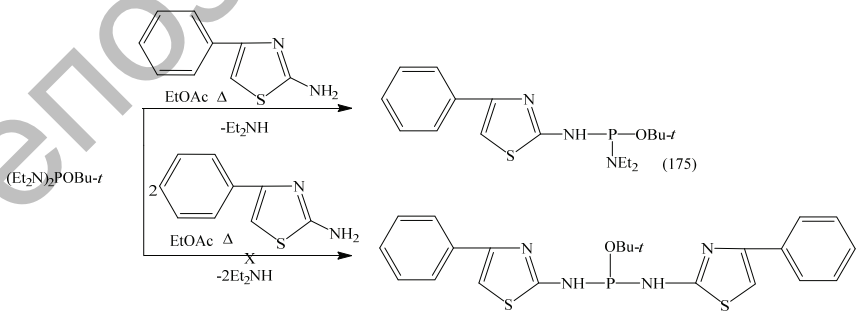
Phosphorylated thiazoles are of considerable theoretical and practical interest, remaining, nevertheless, little studied area of research. Attempts to synthesize phosphorus-containing derivatives of thiazole and its homologues were made at various times. In particular, introduction of 2-aminothiazole into direct condensation with aromatic aldehydes and dialkyl phosphites in the presence of alkali metal alkoxides failed, which is obviously due to the low basicity of 2-aminothiazole (pKa 5.39). Phosphonomethylation of 2-aminothiazole was achieved by the reaction of dialkyl phosphites with benzaldehyde diacetal in the presence of boron trifluoride etherate. The possibility of equilibrium between amino and imino structures was established and a significant shift in the equilibrium toward the amino-form was shown [52].

The analysis of literature data shows that there is practically no information on the interaction of trivalent phosphorus compounds with 2-amino-4-phenylthiazole or its derivatives. Undoubtedly, the fundamental difference in the reactivity of the compounds of trivalent phosphorus makes the result of the interaction not obvious. However, 2-amino-4-phenylthiazole derivatives containing a trivalent phosphorus atom can be oxidized to pentavalent phosphorus

derivatives, which makes them unique synthons for further chemical transformations.

It is known that esteramides of phosphorous acid are of particular interest in the series of trivalent phosphorus compounds. They easily exchange amido group under the influence of alcohols, amines and phenols. Such a method is very convenient for obtaining amidophosphites that are difficult to obtain in direct synthesis [126, 127]. The reaction of transamidation of tetraethyl-diamido-*tert*-butylphosphite with 2-amino-4-phenylthiazole resulting in the formation of diethylamido-(4-phenylthiazolyl-2-amido)-*tert*-butylphosphite (175) was investigated. The reaction was carried out by heating equimolar amounts of tetraethyl-diamido-*tert*-butyl phosphite and 2-amino-4-phenylthiazole in ethyl acetate with simultaneous distilling off the diethylamine identified as hydrochloride. The amount of diethylamine released indicates the completeness of the reaction. The formed diethylamido-(4-phenylthiazolyl-2-amido)-*tert*-butylphosphite (175) purified by recrystallization from benzene is a white crystalline substance soluble in polar and nonpolar organic solvents and water.

Only one mole of diethylamine was detected during the transamidation of tetraethyldiamido-*tert*-butyl phosphite with two moles of 2-amino-4-phenylthiazole under the same conditions. Amidophosphite (175) was isolated and identified when one more mole of phosphite was added to the reaction medium. Thus, two residues of 2-amino-4-phenylthiazole cannot be introduced to the P (III) atom apparently due to steric hindrance [128, 129].



In the IR spectrum of compound (175) there are absorption bands in the region of 1441 and 1598 cm^{-1} referred to the C=C bond vibrations, there is an absorption band at 1483 cm^{-1} corresponding to the vibrations of the endocyclic C=N bond, the vibrations of the N-H bond resonate in the characteristic region of 3435 cm^{-1}, while the P-O-C bond absorption is detected at 1071 cm^{-1}.

The protons of the phenyl ring appear as a multiplet in the range of 7.22-7.40 ppm, the proton singlet of the *tert*-butyl group is found at 1.40 ppm in the ^1H NMR spectrum of compound (175) measured in DMSO-d_6 solution. The triplet of methyl protons with a spin-spin coupling constant $^3J_{HH}$=7 Hz is located at 1.16 ppm. The multiplet of methylene protons is found in the region with a center at 2.59 ppm. The proton signal of the N-H group resonates as a singlet in the 7.80 ppm region, and the proton signal of the C5 of thiazole ring is detected as a singlet in the characteristic region of 7.05 ppm.

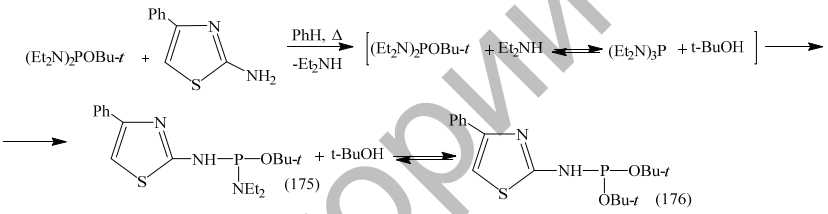
A systematic study of the reactivity and structural features of phosphorylated heterocyclic amines has shown that the structures of phosphorylated and thiophosphorylated 2-aminothiazoles and 2-aminothiazolines are predominantly in the imino form. However, a significant shift of the amine-imine tautomeric equilibrium toward the amino-form was observed in the case of phosphonoalkylated thiazole derivatives [47, 52].

Analysis of IR and NMR spectroscopy data allows assigning an amino structure to diethylamido(4-phenylthiazolyl-2-amido)-*tert*-butylphosphite (175). The basis for this is the signal of the proton of the thiazole ring at C5, which is found in the region of 7.05 ppm typical for it, and also the stretching vibrations of the C=N endocyclic bond in the region of 1483 cm^{-1}, which differ significantly from the vibrations of the exocyclic C=N resonating at 20-40 cm^{-1} higher. In addition, the existence of amino-derivatives of heterocyclic compounds in the amine or imine form depends on the basicity of the exocyclic nitrogen atom [130]. The presence of a phenyl radical in the 4-position of 2-aminothiazole reduces the basicity of the amino group significantly and causes a shift of the tautomeric balance towards the amino form.

As a continuation of the research, benzene was used as a solvent in order to vary the conditions for carrying out the reamidation of tetraethyldiamido-*tert*-butylphosphite with 2-amino-4-phenylthiazole.

The choice of the solvent was determined by the inertness of the reagents to the solvent chosen. However, it turned out that the process proceeds unambiguously in benzene, and leads to the formation of a mixture of reaction products (175, 176).

Obviously, diethylamine, a by-product of the reamidation reaction, is capable of reacting with the original tetraethyl-diamido-*tert*-butyl phosphite to form hexaethyl triamidophosphite and *tert*-butanol. The *tert*-butanol released in turn reacts with the product (175), which leads to the formation of the compound (176). This reaction direction can be explained by the poorer solubility of 2-amino-4-phenylthiazole in benzene than in ethyl acetate, which reduces the probability of collision of tetraethyl-diamido-*tert*-butyl phosphite molecules and 2-amino-4-phenylthiazole and an increase in the probability of side reactions of reamidation and alcoholysis.



2.2 Interaction of esteramides of phosphorous acid with electrophiles

Esteramides of phosphorous acids are typical ambident systems. They have two nucleophilic centers with respect to the electrophilic compounds due to the presence of the P-N group in the molecule, which are the phosphorus atom and the nitrogen atom.

One of the important issues arising from the vast experimental material is the identification of factors that affect on selectivity in the ambiguous system P-E (where E is O, S, N). Although the experimental data do not exhaust the solution of the problem in many aspects, some regularities were revealed quite definitely.

It is known that if the nucleophilic center is a phosphorus atom, then the reaction proceeds through the intermediate formation of a quasiphosphonium complex and always leads to derivatives of a tetracoordinated phosphorus atom. The specificity of the phosphorus

atom that is the presence of both unshared pair of electrons and vacant d-orbitals determines the possibility of this kind of rearrangement.

If E appears as the nucleophile in the P-E system, when interacting with the electrophilic unsaturated carbon atom, the reaction proceeds according to the scheme for the replacement of the amide group of the esteramides of phosphorous acid without changing the valence of the phosphorus atom.

Indeed, knowledge of the general regularities of the reactivity of the ambiguous systems of compounds of the trivalent phosphorus atom can greatly facilitate the theoretical analysis of possible conversion schemes in the reacting system, and indicate the structure of the final products of the reaction correctly. Therefore, attracting special attention of researchers to the assessment of ambiguity as a real property of the derivatives of the trivalent phosphorus atom becomes urgent and necessary. The investigation of *tert*-butyl esters of amidophosphorous acids containing a complex heterocyclic fragment in their structure under the conditions of the A.Ye. Arbuzov reaction is expected to be very interesting and promising. Data on their reactivity along with data on the mechanisms and directions of reactions of linear and cyclic *tert*-butyl esters of amidophosphorous acids with electrophilic reagents can help in the creation of a unified scheme that uniquely establishes the reaction center of polyfunctional systems.

On the other hand, the P (III) acid esters, being very reactive compounds, are of interest as synthons in the synthesis of new preparatively and technologically convenient methods for the preparation of organophosphorus compounds with predetermined practical properties. In this respect, studies of the reactions of *tert*-butyl esters having a high reactivity with carboxylic acid halides, phenylthioisocyanate and other compounds containing mixed functional groups are most promising.

Despite the variety of aspects that cause interest in chosen direction of research, these reactions, important in theoretical, preparative and applied respects, have been studied mainly on the example of linear and cyclic ester amides of phosphorous acids, and there is practically no information on synthesis and chemical modifications of the P (III) acids esters containing heterocycles in their structure.

Undoubtedly, the study of the behavior of the amidophosphite (175) synthesized under the conditions of the A.Ye. Arbuzov reaction with a wide range of electrophilic reagents, as well as the development of the synthesis methods for new polyfunctional compounds possessing a set of useful properties based on newly obtained compounds are very appropriate.

2.2.1 Reactions of esteramides of phosphorous acid with carboxylic acid halides

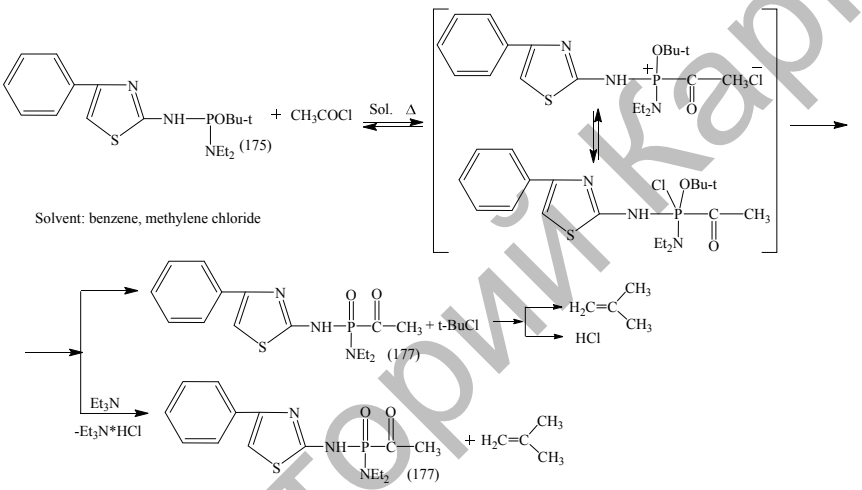
The reactions of the P (III) acids esteramides with carboxylic acid halides proceed in a complicated and ambiguous way. The direction of the course of these reactions depends significantly on the structure of the initial compounds and on the conditions of the process [131-133].

A number of authors carried out special studies to determine the causes of the effect of the structure, the conditions of the process (temperature, solvent, catalysts) on the direction of these reactions. Thus, M.A. Pudovik and co-workers have shown that the cyclic ester amides of P (III) acids interact with acetyl chloride, mainly by the scheme of amide group substitution for the chlorine atom of acetyl chloride, and the acyclic esteramides by the Arbuzov reaction scheme with the formation of the corresponding acetylphosphonates [134-136].

The reaction of diethylamido-(4-phenylthiazolyl-2-amido)-*tert*-butylphosphite (175) with acetyl and benzoyl chlorides in various conditions was investigated to evaluate the possibility of influencing the direction of the reactions of esteramides of phosphorous acids containing a heterocyclic fragment in their structure with some electrophiles. It was shown that the reaction of amidophosphite (175) with acetyl chloride, both in benzene and in methylene chloride, proceeded regioselectively with the participation of a trivalent phosphorus atom to form the corresponding diethylamido-(4-phenylthiazolyl-2-amido)-acetylphosphonate (177). Control over the course of the reaction was carried out by thin layer chromatography and measurement of the amount of isobutylene released [137].

Obviously, the reaction mechanism involves a nucleophilic attack of the phosphorus atom with the formation of an intermediate

quasiphosphonium compound of a pentacovalent or ionic form depending on the nature of the solvent. The rapid decomposition of "quasiphosphonium" leads to the isolation of isobutylene measured by the method of displacement of water and identified as a dibromo derivative. Indirect evidence of the proposed reaction mechanism is the isolation of an equimolar amount of the hydrochloride precipitate during the reaction in the presence of triethylamine [138].



It was also found that the reaction proceeded at a higher process velocity and ended within 10-15 minutes in the methylene chloride medium. More polar solvents contribute to the formation of the ionic form of a quasiphosphonium compound, which is ultimately responsible for the course of the A.Ye. Arbuzov reaction [139].

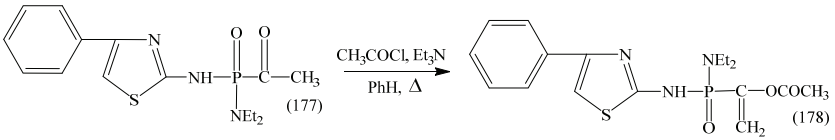
Absorption bands are present in the region of 1462, 1599 cm^{-1} in the IR spectrum of compound (177), which corresponds to stretching vibrations of C=C. The absorption band in the region of 1623 cm^{-1} indicates the presence of a C=O group. The displacement of the region of stretching vibrations of the carbonyl group in this frequency range is probably due to the masking of the frequency range by deformation vibrations of the NH group (1550-1590 cm^{-1}). The vibrations of the endocyclic C=N bond resonate in the region of 1502 cm^{-1}, and an absorption band corresponding to the valence vibrations of the

secondary amino group appears in the region of 3375 cm^{-1}. The absorption band disappears in the 1071 cm^{-1} region, which is characteristic for the P-O-C bond, and an absorption band attributed to the P=O bond vibrations in the 1203 cm^{-1} region appears in the IR spectrum.

The proton of the phenyl ring corresponds to a multiplet in the range of 7.22-7.50 ppm of the ^{1}H NMR spectrum of compound (177). The protons of the acetyl group resonate in the characteristic region of 2.20 ppm. A triplet of methyl protons was detected at 1.20 ppm. The multiplet of methylene protons is found in the region with a center at 2.55 ppm. The singlet signal of the proton of the N-H group appears in the region of 7.50 ppm, and the proton signal of the C5 thiazole ring resonates in the characteristic region of 7.00 ppm.

The presence of an acetoxy group in the structure of diethylamido-(4-phenylthiazolyl-2-amido)-acetylphosphonate (177) predetermines the possibility of reactions that are associated with the process of enolization. It is known that the reactions of ethyl(tetraethyl-diamido)phosphite with acetyl chloride proceed with the significant formation of tetraethyl-diimido-α-acetoxyvinyl-phosphonate [140], which is explained by the interaction of the tetraethyl-diamidoacetylphosphonate formed at the beginning of the reaction with the acyl halide according to the scheme proposed for the reaction of dialkylacylphosphonates with trimethylchlorosilane, dialkylchlorophosphites and acetyl chloride [141].

There was carried out the interaction of amidophosphite (175) with acetyl chloride in the 1:2 ratio, and also in the presence of two moles of dry triethylamine to confirm this possibility. As a result, it was shown that the phosphonate (177) formed in the first stage reacted with the enol form with the next molecule of acetyl chloride to form the corresponding vinyl acetyl phosphonate (178). The structure of the synthesized compound (178) is proved by the data of IR and ^{1}H NMR spectroscopy.



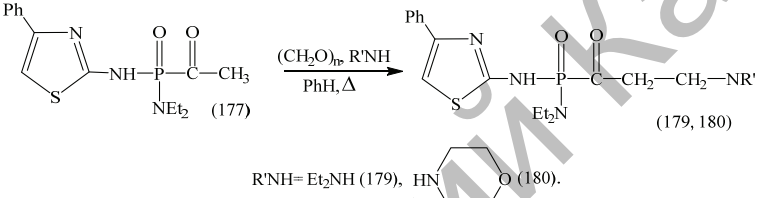
The absorption band in the region of 1458, 1584 cm^{-1} in the IR spectrum of compound (178) corresponds to stretching vibrations of C=C. The absorption band in the region of 1644 cm^{-1} is attributed to the vibrations of the C=O group. The vibrations of the endocyclic C=N bond resonate in the region of 1486 cm^{-1}, and an absorption band corresponding to the stretching vibrations of the NH bond appears in the region of 3167 cm^{-1}. Vibrations of P=O and C-S bonds are detected in the characteristic regions of 1205 cm^{-1} and 695 cm^{-1}, respectively.

The multiplet in the range of 7.22-7.48 ppm in the ^1H NMR spectrum of compound (178) is related to the resonance of protons of the aromatic ring. The protons of the $OCOCH_3$ group appear in the characteristic region of 2.18 ppm. A triplet of methyl protons was detected at 1.15 ppm. The multiplet of methylene protons appears in the region of 2.59 ppm. The proton signal of the NH group in the form of a singlet is found in the region of 11.80 ppm. The singlet signal of the proton in the region of 7.60 ppm is related to the proton resonance at C5 of the thiazole ring. The proton signals of the $C=CH_2$- structural fragment are found at 4.10 and 4.60 ppm, respectively.

Another confirmation of the structure of ketophosphonate (177) suggesting the possibility of the existence of an enol form is a kind of condensation reaction of the aldol type. The interaction of ketophosphonate (177) with diethylamine, morpholine under the conditions of the Mannich reaction was carried out to confirm this fact. As a result, it was shown that the ketophosphonate (177) reacted with paraform and diethylamine or morpholine while boiling in dry benzene with an equimolar amount of water and phosphonates (179, 180).

Absorption bands are present in the region of 1443, 1444, 1532, 1559 cm^{-1} in the IR spectra of compounds (179, 180), which correspond to stretching vibrations of C=C. The absorption bands in the 700-703 cm^{-1} region indicate the presence of a C-S bond. The stretching vibrations of the endocyclic C= N bond appear in the region of 1486-1487 cm^{-1}, and an absorption band corresponding to the stretching vibrations of the secondary amino group appears in the region of 3283-3390 cm^{-1}. The absorption band in the region of 1184 and 1204 cm^{-1} is attributed to the P=O bond vibrations.

The proton of the phenyl ring corresponds to a multiplet in the range of 7.25-7.48 ppm in the ^{1}H NMR spectra of compounds (179, 180). Triplet at 0.85 ppm is attributed to the vibrations of methyl protons. The protons of the CH_2-CH_2 fragment for compound (179) resonate in their characteristic region of 2.50 and 2.69 ppm, while protons of the morpholine residue are found at 2.37 and 3.67 ppm for compound (180). The multiplet of methylene protons is found in the region with a center at 2.59 ppm. The proton signal of the NH group in the form of a singlet resonates in the region of 7.89 ppm, and the proton signal of the C5 of thiazole ring is also identified as a singlet in the characteristic region of 7.00 ppm.

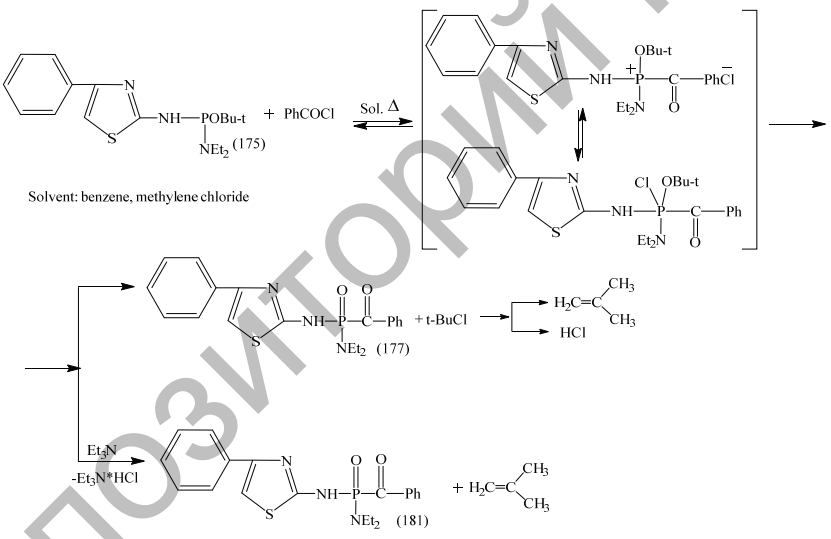


It is known that the electrophilicity of a carbonyl carbon atom affects the direction of the reaction, and the relative rate of P-acylation increases with increasing electrophilicity [142]. The available literature data on the influence of the nature of the acylating agent, the nature of the solvent and the temperature are contradictory and even mutually exclusive [143]. In particular, the studies of the Kazan school of chemists contradict Hudson's data on the stereochemical suppression of the Arbuzov reaction in a series of cyclic amidophosphites [144].

In order to confirm this situation as well as to obtain new data on some regularities of the reactions of *tert*-butyl esters of amidophosphorous acid of a heterocyclic structure, diethylamido-(4-phenylthiazolyl-2-amido)-*tert*-butylphosphite (175) was investigated in the reactions with benzoyl chloride under various conditions. It was shown that the reaction proceeded only at the phosphorus atom when heated in both polar and nonpolar aprotic solvents. Control of the reaction by thin-layer chromatography also showed that the reaction proceeded unambiguously with the formation of only the Arbuzov

reaction product. The amount of isobutylene released was equimolar [145].

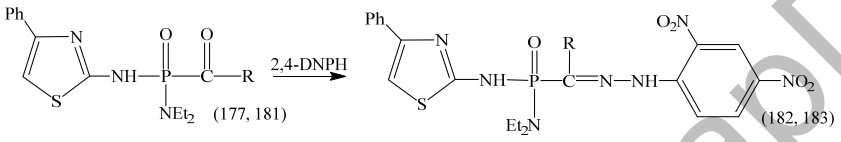
The product of the reaction diethylamido-(4-phenylthiazolyl-2-amido)benzoylphosphonate (181) purified by recrystallization from ethyl alcohol is a white crystalline substance. The IR spectrum of (181) contains absorption bands in the region of 1476 and 1598 cm^{-1} corresponding to the C=C bond vibrations, the vibrations of the NH bond resonate at 3372 cm^{-1}. The band of absorption of the endocyclic C=N bond appears in the characteristic region of 1502 cm^{-1}, a strong absorption band due to the valence vibrations of the C=O group, resonates at 1632 cm^{-1}, and there is an absorption band due to the vibrations of the P=O-group in the 1186 cm^{-1} region. The C-S bond vibrations appear in the characteristic region of 689 cm^{-1}.



The protons of the aromatic ring appear as a multiplet in the regions of 7.42-7.54 ppm and 7.45-7.81 ppm in the ^1H NMR spectrum of compound (181). Triplet at 1.07 ppm corresponds to the vibrations of methyl protons. A multiplet of methylene protons is found in the region of 2.55 ppm. The proton signal at C5 of the thiazole ring is detected as a singlet in the characteristic region of 7.25 ppm. The

proton of the secondary amino group in the form of a singlet resonates in the region of 7.8 ppm.

Chemical confirmation of the structure of phosphonates (177, 181) is the isolation of colored precipitates of hydrazones (182, 183) under the action of 2,4-dinitrophenylhydrazine.



There are absorption bands in the region of 1457, 1598 cm^{-1} in the IR spectrum of compound (182) corresponding to the stretching vibrations of the C=C bond. The absorption band in the region of 1615 cm^{-1} is attributed to the vibrations of the exocyclic C=N bond. The vibrations of the endocyclic C=N bond are identified in the region of 1519 cm^{-1}. An absorption band corresponding to the stretching vibrations of the NH bond appears in the region of 3284 cm^{-1}. The vibrations of P=O and C-S bonds are detected in the characteristic regions of 1206 cm^{-1} and 630 cm^{-1}, respectively.

The results obtained [146] completely confirm the previously established experimental data in the reactions of tetraethyl-diamido-*tert*-butyl phosphite with acid halides performed under a variety of conditions. The presence of the *tert*-butoxyl group in the diethylamido-(4-phenylthiazolyl-2-amido)-*tert*-butyl phosphite (175) structure makes it possible, on the one hand, to control the direction of the reaction by isolating isobutylene and measuring its quantity, which may indicate the direction of the process, and on the other hand, to model the structure of the intermediate product by the influence of external factors.

2.2.2 Interaction of esteramides of phosphorous acid with isocyanates

Reactions of P (III) acids esters with isocyanates are studied sufficiently well. It is known that partial esters of phosphorous acids in the presence of basic catalysts are readily attached to esters of

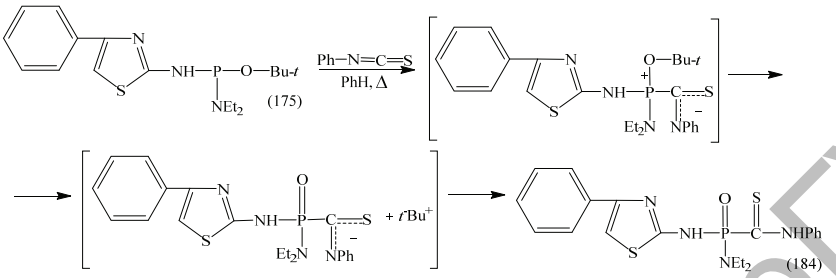
isocyanic acid to form substituted dialkylphosphonoformic amides [147].

Using the example of cyclic esteramides of P (III) acids, Hudson showed that the reaction with phenyl isocyanate proceeded according to the P-N bond introduction scheme with the formation of the corresponding products, while maintaining coordination of the phosphorus atom [148].

The authors of [149] found that *tert*-butyldiethylphosphite, di-*tert*-butylethylphosphite and tri-*tert*-butylphosphite reacted with phenyl isothiocyanate at room temperature to form diethyl phenylthiocarbamoyl-, ethyl(*tert*-butyl)phenylthiocarbamoyl- and di-*tert*-butyl-phenylthiocarbamoylphosphonates. However, the mechanism and structure of the individual products formed are still debatable in spite of the great history and constant interest in these reactions.

The reaction of diethylamido-(4-phenylthiazolyl-2-amido)-*tert*-butylphosphite (175) with phenyl isothiocyanate was studied in order to obtain new data on the mechanisms of reactions of the P (III) acids esters with isocyanates and the synthesis of organophosphorus compounds with biological activity. As a result, it was shown that the reaction resulted in the formation of the corresponding diethylamido-(4-phenylthiazolyl-2-amido)-N-dimethylthiocarbamoyl phosphonate (184), a stable substance that is highly soluble in organic solvents and water.

Absorption bands are present in the region of 1562 cm^{-1} and 1164 cm^{-1} in the IR spectrum of compound (184), which correspond to the stretching vibrations of C=C and C=S bonds, respectively. The vibrations of the endocyclic C=N bond are identified in the region of 1578 cm^{-1}, and an absorption band corresponding to the stretching vibrations of the secondary amino group is found in the region of 3373 cm^{-1}. The absorption band in the region of 1309 cm^{-1} is attributed to the P=O bond stretching vibrations.



The multiplet in the region of 7.15-7.48 ppm and 7.80-7.95 in the ^{1}H NMR spectrum of compound (184) is assigned to the resonance of protons of the aromatic ring. A triplet of methyl protons is detected at 1.15 ppm. The multiplet of methylene protons is identified in the region of 2.55 ppm. The proton signal of the NH group in the form of a singlet is found in the region of 4.00 ppm. The singlet signal of the proton in the region of 6.80 ppm is related to the proton resonance at C5 of the thiazole ring.

The formation of the compound of the phosphonate structure in this reaction indicates the course of the process through an intermediate product with the P-C bond, which evidently decomposes rapidly via the S_N1 mechanism with the elimination of trimethylcarbocation as it is typical for quasiphosphonium compounds containing a *tert*-butoxy group on the phosphorus atom. Trimethylcarbocation further protonates the phosphorus-containing part of the molecule resulting in the final product of the reaction and converting to isobutylene.

Investigation of the reactions of *tert*-butyl esters of amidophosphoric acids with phenyl isothiocyanate showed that they proceeded quite easily and selectively, under mild conditions, even with complex polyfunctional systems such as compound (175).

In general, it should be noted that the description of the reaction mechanisms of the amidophosphorous acid *tert*-butyl ester with various electrophiles is within the framework of the classical theory. The process proceeds through the formation of an intermediate quasiphosphonium compound and results in the formation of the products with the phosphonate structure.

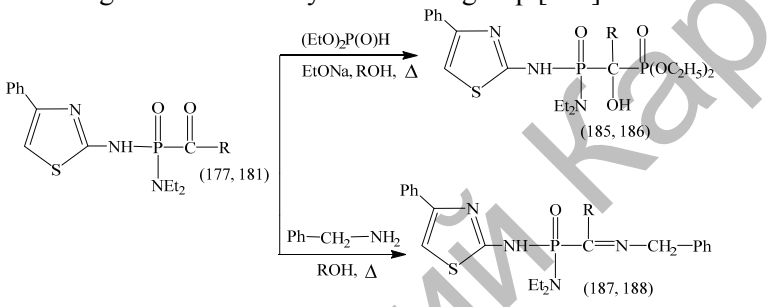
2.3 Synthesis, structure and chemical transformations of α-ketophosphonic acids esters and their derivatives

α-Ketophosphonic acids esters are a class of highly reactive organophosphorus compounds. Despite the lability of P-C bond, α-ketophosphonic acids esters have proved to be interesting key compounds for a number of syntheses based on the use of increased activity of the carbonyl group, in particular, for the production of α-aminophosphonic acids and phosphorylcarbenes [150].

The decomposition of esters of α-ketophosphonic acids under the influence of such a weak nucleophile as water is one of the first chemical transformations observed for these compounds [151].

The reactions of α-ketophosphonic acids esters with nucleophiles are successfully classified by the authors of reference [127], who proposed the scheme of reactions of acetylphosphonate with compounds of the XH (or XNa) type and diazoalkanes. The authors indicate that the action of proton-containing compounds on acetylphosphonate results in a cleavage of the P-C bond with the formation of a derivative of acetic acid and a dialkylphosphite. If the nucleophilic reagent is aprotic, the cleavage of the P-C bond is accompanied by migration of the phosphorus moiety. Numerous experimental facts confirm the general nature of the reactions in these directions, including a series of works by Japanese researchers devoted to the study of the reaction of α-ketophosphonic acids esters with thiazolium and benzimidazolium salts. A 2-substituted 1,4-thiazine derivative from benzoylphosphonate and thiamine in the presence of bases was obtained by the authors of [152]. Later, the reaction was extended to various N-substituted thiazolium salts and 1,3,4-oxadiazolium salts with intermediate isomerization products isolated in some cases. It is assumed that the nucleophilic center of the thiazolium is attached to the carbon atom of carbonyl of α-ketophosphonic acids esters. Then isomerization occurs in phosphate, which is hydrolyzed to form enol under treatment with an alkali. At the same time, the cycle is expanded by introducing a new carbon atom to form the 1,4-thiazine derivative. Reactions of esters of α-ketophosphonic acids with the benzimidazolium salts gave adducts that did not form quinoxaline derivatives during alkaline hydrolysis.

Diethylamido-(4-phenylthiazolyl-2-amido)-acetylphosphonate (177) and diethylamido-(4-phenylthiazolyl-2-amido)-benzoylphosphonate (181) were introduced into the reaction with benzylamine and dialkylphosphites under the conditions of the Abramov's reaction in order to study their synthetic potential. As a result, the reactions proceeded according to the classical scheme with high yields of the target products (185, 186) and (187, 188), which indicated a significant reactivity of the keto group [153].



R= CH_3- (185, 187); Ph- (186, 188).

There are absorption bands in the regions of 1441 and 1462, 1532 and 1596 cm^{-1} in the IR spectra of compounds (185, 186) that correspond to the stretching vibrations of C=C. The absorption bands in the regions of 1482 and 1502 cm^{-1} are attributed to the vibrations of the endocyclic C=N bond. Absorption bands corresponding to the stretching vibrations of the secondary amino group are detected in regions of 3354, 3375 cm^{-1}. Troughs of P=O and C-S bonds are found in the characteristic regions of 1306, 1302 cm^{-1} and 657, 705 cm^{-1}, respectively. Broad absorption bands corresponding to the vibrations of the hydroxyl group appear in the 3437 and 3516 cm^{-1} regions. The P-O-C bond vibrations resonate in the region of 1022 cm^{-1}.

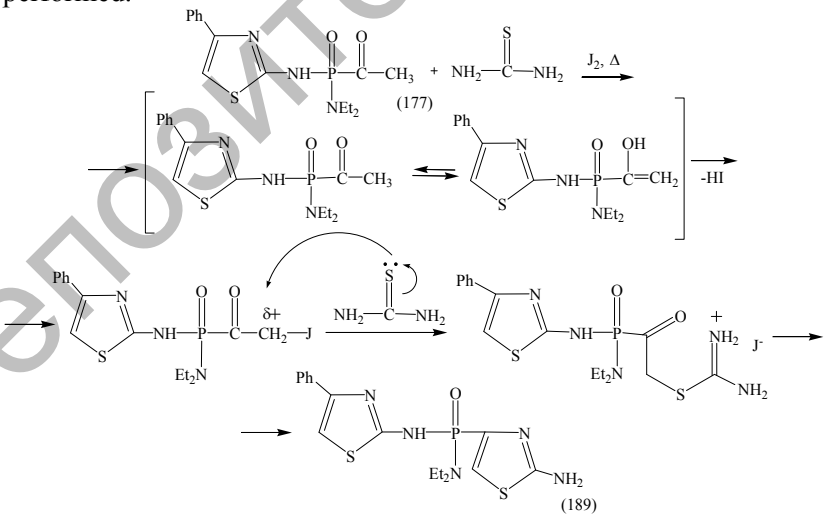
There are absorption bands in the regions of 1457 and 1470, 1532 and 1578 cm^{-1} of the IR spectra of compounds (187, 188) that correspond to the stretching vibrations of the C=C bond. The absorption bands in regions of 1519 and 1522 cm^{-1} correspond to the vibrations of the exocyclic C=N bond. The vibrations of the endocyclic C=N bond resonate in the region of 1615 and 1578 cm^{-1}. The absorption bands of stretching vibrations of the NH bond appear

in the regions of 3384 and 3351 cm^{-1}. The vibrations of P=O and C-S bonds resonate in the characteristic regions of 1213 cm^{-1} and 693 cm^{-1}, respectively.

Continuing investigation of the synthetic possibilities of the resulting ketophosphonates (177, 181), the synthesis of new derivatives of 2-aminothiazole, which are becoming increasingly important in pharmaceutical production, biochemistry and technology, has been studied. It is known that one of the most common methods for the synthesis of thiazoles is the Hantzsch reaction consisting in the interaction of α-halocarbonyl compounds with amides, thioamides, thiourea and other compounds containing the N-C=S fragment. Another method is the Dodson-King method.

The authors of [59] succeeded in synthesizing 4-diethylphosphono-2-aminothiazole by reacting diethylbromoacetyl phosphonate with thiourea. However, this process can proceed according to the simplified Dodson-King scheme as a result of the interaction of diethylacetylphosphonate, thiourea and iodine in the 1:2:1 ratio, respectively.

Taking into account the well-known literature data and the high reactivity of the ketophosphonate synthesized (177), an attempt to close the thiazole ring under classical experimental conditions was performed.



(189)

As a result of many hours heating of acetylphosphonate (177) with thiourea in the presence of crystalline iodine and treatment of the reaction mixture in the usual manner, the corresponding phosphoryl thiazole (189) was isolated [154]. Crystalline iodine was used as a reagent in the synthesis of phosphorylthiazole (189). The structure of synthesized ketophosphonate (177) suggests the possibility of the existence of an enol form. The reaction proceeds according to the classical mechanism involving the halogenation of the enol form of ketophosphonate 177 and the nucleophilic attack of the electrophilic center that is the carbon atom bonded to the halogen atom by the sulfur atom, to form an acyclic intermediate and its subsequent cyclization to the desired product, phosphorylthiazole (189).

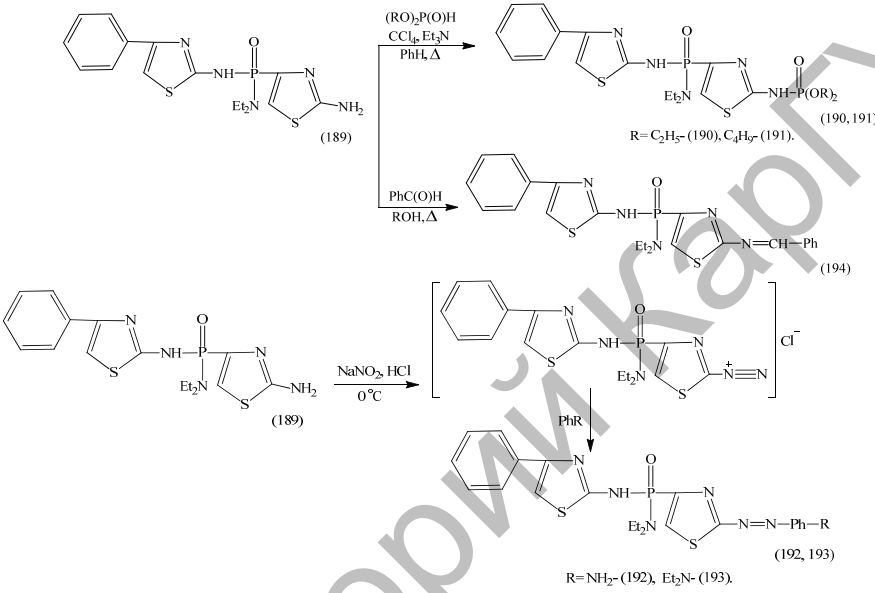
Absorption bands are present in the region of 1518 cm^{-1} and 1623 cm^{-1} in the IR spectrum of compound (189), which correspond to stretching vibrations of the C=C bond. The vibrations of the C-S bond are identified in the region of 668 cm^{-1}. The absorption band in the region of 1484 cm^{-1} is attributed to the vibrations of the endocyclic C=N bond. An absorption band corresponding to the stretching vibrations of the secondary amino group appears in the region of 3317 cm^{-1}, while there is a characteristic absorption band of the primary amino group in the form of two peaks in the region of 3436 cm^{-1}. The absorption band in the region of 1198 cm^{-1} is attributed to the P=O bond vibrations.

The protons of the aromatic ring appear as a multiplet in the region of 7.15-7.48 ppm in the ^1H NMR spectrum of compound (189). A multiplet of methylene protons is detected with a center in the region of 2.55 ppm. Triplet at 1.07 ppm corresponds to the vibrations of methyl protons. The proton signal at C5 of the thiazole ring is identified as a singlet in the region of 5.65 ppm. The proton of the secondary amino group in the form of a singlet resonates in the region of 10.05 ppm.

The structure of phosphoryl thiazole (189) is also proved chemically. The presence of a free amino group suggests the possibility of carrying out a number of chemical transformations and obtaining interesting and very valuable products for fine organic synthesis.

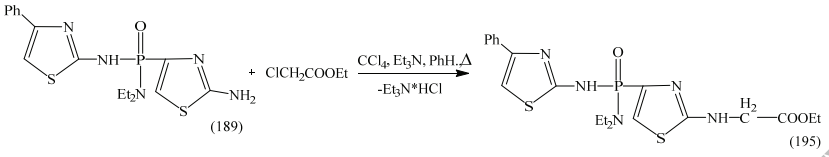
In particular, the interaction of phosphoryl thiazole (189) with dialkylphosphites in a carbon tetrachloride medium in the presence of

triethylamine has been investigated and the formation of the corresponding products of the Todd-Atherton reaction (190, 191) has been shown.



There are absorption bands in the 1441 and 1459, 1548, and 1596 cm^{-1} regions corresponding to C=C stretching vibrations in the IR spectra of compounds (190, 191). The absorption bands in the region of 1484 and 1506 cm^{-1} are related to the vibrations of the endocyclic C=N bond. Absorption bands corresponding to the stretching vibrations of the secondary amino group appear in the regions of 3386 and 3375 cm^{-1}. Stretching vibrations of the P=O and C-S bonds appear in the characteristic regions of 1208-1306 cm^{-1} and 631-703 cm^{-1}, respectively. Wide absorption bands corresponding to the vibrations of the hydroxyl group appear in the regions of 3326 and 3516 cm^{-1}. The vibrations of the P-O-C bond resonate in the region of 1021 cm^{-1}.

Along with the synthesis of phosphonates (190, 191), azo dyes (192, 193), Schiff bases (194) and ester (195) were obtained, which in turn are interesting key compounds in a number of different chemical transformations [155].



There is an absorption band in the region of 1486 cm^{-1} in the IR spectrum of compound (192) corresponding to the vibrations of the endocyclic C=N bond and an absorption band in the region of 1615 cm^{-1} referred to as the stretching vibrations of the exocyclic C=N bond. Troughs of C=C bonds appear in the region of 1530 cm^{-1}. The absorption band at 1309 cm^{-1} corresponds to the vibrations of the P=O group, the C-S bond characterizes the absorption band in the region of 700 cm^{-1}. The absorption band of stretching vibrations of the NH bond is detected in the region of 3439 cm^{-1}. The characteristic band in the region of 2362 cm^{-1} confirms the presence of the N=N bond.

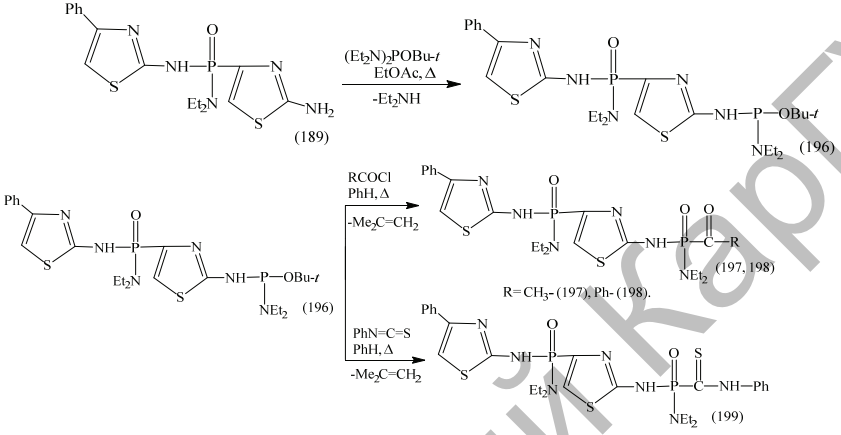
There are absorption bands in the region of 1444, 1529 cm^{-1} related to the stretching vibrations of the C=C bond in the IR spectrum of compound (194). The absorption bands in the region of 1621 cm^{-1} correspond to the troughs of the endocyclic C=N bond. The vibrations of the exocyclic C=N bond appear in the region of 1691 cm^{-1}, and the absorption band in the region of 696 cm^{-1} corresponds to the vibrations of the C-S bond. The absorption band of stretching vibrations of the NH bond is found in the region of 3440 cm^{-1}. P=O vibrations resonate in the characteristic region of 1205 cm^{-1}.

The IR spectrum of compound (195) contains absorption bands in the regions corresponding to the stretching vibrations of the following bonds, namely 1599 (C=C), 1483 (C=N), 689 (C-S), 3436 (NH-), 1307 (P=O), 1754 (COOEt) cm^{-1}.

The presence of a free amino group in the structure of phosphoryl thiazole (189) leads to the possibility of secondary reamidation and the formation of amidophosphite (196), which has a wide synthetic potential.

The reactions of amidophosphite (196) with electrophilic reagents resulting in the formation of Arbuzov reaction products (197-199) were investigated. It was shown that the process proceeded in accordance with the classical scheme of the reaction mechanism established and completely correlates with the above experimental

data on the direction and mechanism of the reactions of *tert*-butyl esters of amidophosphorous acid of heterocyclic structure with various electrophilic reagents [156].



There are absorption bands in the region of 1442 cm^{-1} and 1532 cm^{-1} in the IR spectrum of compound (196), which correspond to stretching vibrations of the C=C bond. The troughs of the C-S bond are found in the region of 658 cm^{-1}. The absorption band in the region of 1483 cm^{-1} is related to the vibrations of the endocyclic C=N bond. The absorption band corresponding to the stretching vibrations of the secondary amino group appears in the region of 3436 cm^{-1}. The trough of P=O bond is found in the region of 1201 cm^{-1}. The absorption band corresponding to vibrations of the P-O-C bond is found in the characteristic region of 1023 cm^{-1}.

The protons of the phenyl ring appear as a multiplet in the region of 7.30-7.50 ppm, the singlet of protons of the *tert*-butyl group is found in the region of 2.15 ppm in the ^1H NMR spectrum of compound (196) measured in a DMSO-d_6 solution. The triplet of methyl protons is located at 1.20 ppm. The methylene proton multiplet is detected in a region with a center of 2.59 ppm. The signal of the proton of the N-H group is found as a singlet in the region of 7.75 ppm, and the signal of the proton C5 of the thiazole ring appears as a singlet in the characteristic region of 7.2 ppm.

The IR spectrum of compound (197) contains absorption bands in the region of 1439 cm^{-1} and 1578 cm^{-1}, which characterize the

stretching vibrations of the C=C bond. The troughs of the C-S bond are found in the region of 654 cm^{-1}. The absorption band in the region of 1502 cm^{-1} corresponds to the vibrations of the endocyclic C=N bond. The absorption band in the region of 3372 cm^{-1} is attributed to the stretching vibrations of the NH group. Vibrations of the P=O bond appear in the characteristic region of 1305 cm^{-1}. The absorption band corresponding to the vibrations of the C=O bond is detected in the characteristic region of 1630 cm^{-1}.

Continuing a systematic search in the field of tasks assigned, the possibility of using ketophosphonates (177, 181) as basic structures for the synthesis of phosphorylated glycidic esters has been investigated.

Phosphorylated glycidic esters are known to be convenient synthons for introducing lipophilic phosphonolipid fragments into the structure of known and new potential drugs, which facilitate the transmembrane transport of biologically active substrates. Modification of the amino groups of neuroactive amino acids by phosphorylated glycidic esters leads to the appearance of pronounced psychotropic properties in these compounds [157]. The possibility of using phosphorylated epoxides for the direct synthesis of acyclic phosphonate nucleotide analogues is also noteworthy [158].

Thus, some phosphorylated glycidic esters were obtained by reacting dialkyl phosphites with α-chloroacetoacetic acid ethyl ester in the presence of triethylamine. The method for producing epoxy compounds by reacting acetyl and benzoyl phosphonates with diphenyldiazomethane at 80°C [159] is known.

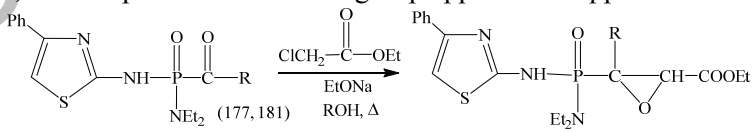
The authors of [160] carried out the synthesis of 3-dialkoxyphosphorylpropyl-glycidyl ester by homolytic phosphorylation of allylglycidyl ester with the corresponding dialkylphosphites in the presence of *tert*-butylbenzoyl peroxide as an initiator at a temperature of 140-170°C and at the molar ratio of reagents dialkyl phosphite: allyl glycidyl ester: peroxide 3.0-4.0:1.0:0.02-0.03.

The evaluation of the current state of this area indicates that the known method for producing glycidic esters, the Darzan-Claisen reaction, has not been used previously for the preparation of phosphorus-containing ethylene oxide-carboxylic acid esters.

The ketophosphonates (177, 181) synthesized in the condensation reaction with ethyl ester of monochloroacetic acid in the presence of sodium ethylate form the corresponding 2-phenyl-2-[diethylamido-N-(4'-phenylthiazolyl-2'-amido)phosphono]ethyl ester of epoxypropionic acid (200) and 2-methyl-2-[diethylamido-N-(4'-phenylthiazolyl-2'-amido)phosphono]ethyl ester of epoxypropionic acid (201) in 75 and 76%, respectively. Obviously, the reaction is complicated by the formation of alkoxyacetic ester. However, the method described above is a very technologically advanced and convenient preparative method for the synthesis of phosphorylated glycidic esters [161].

The IR spectra of compounds (200, 201) contain absorption bands in the region of 1442, 1461 and 1547, 1549 cm^{-1}, respectively, which characterize the stretching vibrations of the C=C bond. The presence of absorption bands in the region of 1749 cm^{-1} indicates the presence of a COOR group. The troughs of the endocyclic C=N bond resonate in the region of 1483 cm^{-1}, and there is an absorption band corresponding to the stretching vibrations of the secondary amino group in the region of 3435 cm^{-1} and absorption bands related to the vibrations of the P=O bond in the region of 1205 and 1307 cm^{-1} are detected, respectively.

The protons of the aromatic ring appear as a multiplet in the region of 7.25-7.40 and 7.45-7.55 ppm in the ^1H NMR spectra of compounds (200, 201) measured in DMSO-d_6 solution. The triplet of methyl protons is observed at 1.15 and 1.20 ppm. The methylene proton multiplet is found in a region with a center at 2.56 ppm. The signal of the proton of the NH group resonates as a singlet in the region of 7.8 ppm, and the signal of the proton at the C5 thiazole ring appears as a singlet in the characteristic region of 7.15 and 7.2 ppm, respectively. The proton of the oxirane cycle was found in the region of 3.85 ppm, the methyl protons in the oxirane cycle resonate at 1.2 ppm, and the protons of the ester group appear at 4.2 ppm.



R= CH_3- (200); Ph-(201).

The interest in epoxy compounds is undoubtedly connected with the possibility of their transformation into aldehydes and ketones containing one carbon atom more than the original carbonyl compounds. This transformation occurs as a result of the usual alkaline hydrolysis and subsequent decarboxylation of glycidic acid with the formation of the aldehyde being accompanied by a rearrangement.

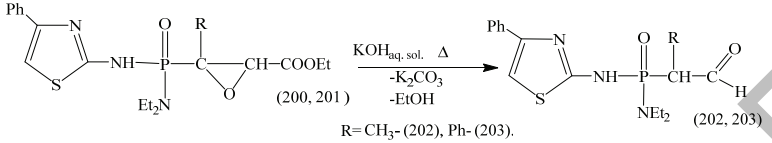
There is known a simple procedure for converting glycidic ester to the corresponding acid. The glycidic ester is treated with a solution of sodium ethylate in absolute ethanol at a molar ratio of reagents, after which exactly one equivalent of water is added; finally, the sodium salt of glycidic acid is precipitated by diluting the mixture with dry ether. In most cases, glycidic acids are very easily converted to aldehydes and ketones by heating them to the decomposition temperature.

However, it was observed that the formation of the corresponding phosphorylated aldehydes (202, 203) became possible under the established experimental conditions as a result of the alkaline hydrolysis reaction of the epoxy compounds synthesized (200, 201) and did not require additional and intermediate stages of isolation and processing that simplified the scheme for obtaining the latter [162, 163].

There is an absorption band in the region of 1632 cm^{-1} indicating the presence of a C(O)H group in the IR spectrum of compound (203). The absorption bands in the region of 1440, 1564 cm^{-1} correspond to the stretching vibrations of C=C. The vibrations of the endocyclic C=N bond resonate in the region of 1502 cm^{-1}, and there is an absorption band corresponding to the stretching vibrations of the secondary amino group in the region of 3373 cm^{-1} and the absorption band in the region of 1308 cm^{-1} is attributed to the vibrations of the P=O bond. The absorption band characterizing the C-S bond is found in the region of 688 cm^{-1}.

The proton signal at the C5 thiazole ring appears as a singlet in the region of 6.10 ppm in the ^1H NMR spectrum of compound (203) measured in a DMSO-d_6 solution. The protons of the phenyl radical resonate as a multiplet in the range of 7.15-7.60 ppm. The triplet of methyl protons is observed at 1.00 ppm. The methylene proton multiplet is found in a region with a center at 2.75 ppm. The signal of

the proton of the NH group is observed as a singlet in the region of 4.00 ppm, and the proton of the aldehyde group is detected in the region of 7.78 ppm.



R= CH_3- (202), Ph- (203).

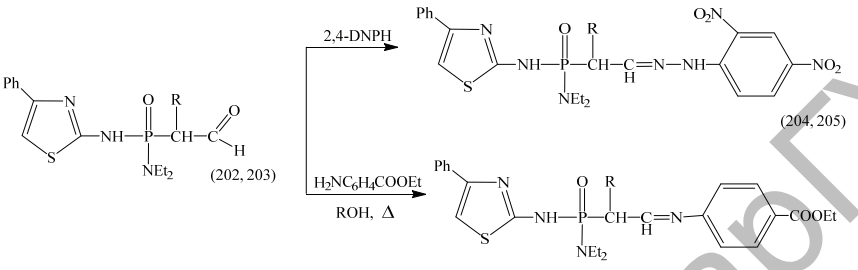
Chemical confirmation of the structure of the phosphorylated aldehydes synthesized (202, 203) is the release of colored precipitates of hydrazones (204, 205) under the action of 2,4-dinitrophenylhydrazine, as well as the formation of compounds (206, 207) as a result of the interaction of phosphorylated aldehydes (202, 203) with ethyl *p*-aminobenzoic acid ester.

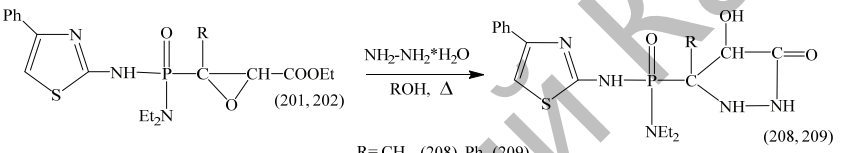
In addition to the transition to aldehydes and ketones, glycidic esters are capable of a variety of other transformations that are no less valuable for fine organic synthesis. In particular, the reaction of the interaction of epoxy compounds (200, 201) with amines, namely hydrazine hydrate has been investigated. Such a choice of a reagent is determined by the possibility of obtaining pyrazolidones on the basis of the phosphorylated thiazolyl-containing glycidic esters (200, 201) synthesized. For example, it is known that the reaction of an amide and β, β-dimethylglycidic acid ethyl ester with phenylhydrazine produces 1-phenyl-3,3-dimethyl-4-oxypyrazolidone-5.

The corresponding 4-R-4-[diethylamido-(4'-phenylthiazolyl-2'-amido)phosphono]-5-hydroxypyrazolidones (208, 209), where R=CH_3-, Ph-, respectively, were isolated and characterized as a result of many hours of heating (10 hours) of glycidic esters (200, 201) with hydrazine hydrate at a temperature of 170-180°C.

There are absorption bands in the region of 1441, 1532 cm^{-1} in the IR spectrum of compound (208), which correspond to the stretching vibrations of C=C. The absorption band in the region of 1598 cm^{-1} indicates the presence of C=O-group. The troughs of the endocyclic C=N bond resonate in the region of 1483 cm^{-1}, and there is an absorption band corresponding to the stretching vibrations of the secondary amino group in the region of 3435 cm^{-1} and an absorption

band in the region of 1307 cm^{-1} is related to the vibrations of the P=O bond.





The protons of the aromatic ring appear as a multiplet in the range of 7.23-7.40 ppm in the ^{1}H NMR spectrum of compound (208) measured in a DMSO-d_6 solution. The triplet of methyl protons is located at 1.15 ppm. The methylene proton multiplet is found in a region with a center at 2.55 ppm. The signal of the proton of the NH group resonates as a singlet in the region of 7.80 ppm, and the signal of the proton C5 of the thiazole ring appears as a singlet in the characteristic region of 7.2 ppm.

In general, it should be noted that the ketophosphonates synthesized (177, 181) and their derivatives, in particular phosphorylated aldehydes (202, 203) can be used as intermediates for obtaining various classes of organophosphorus compounds due to their high reactivity and solving general theoretical questions of organic chemistry.

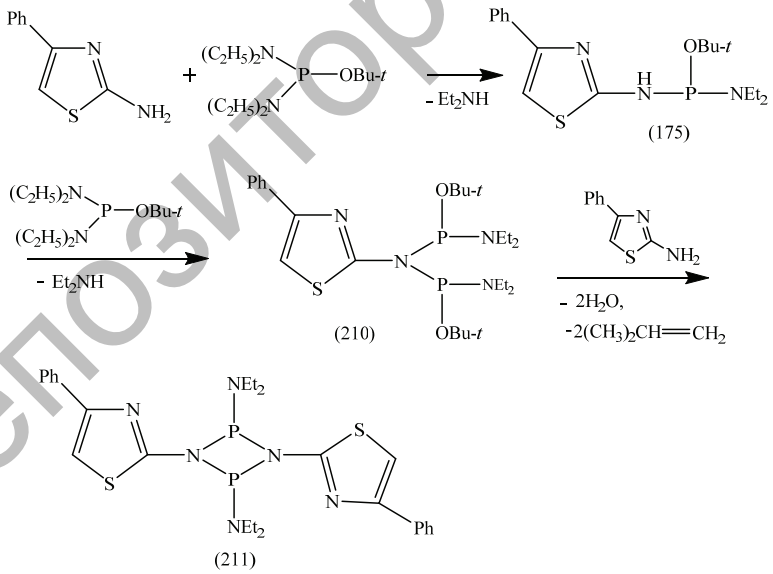
2.4 New approach to the investigation of the 2-amino-4-phenylthiazole phosphorylation reaction

The development and chemical modification of new derivatives of 2-aminothiazoles is interesting in applied and theoretical terms. The

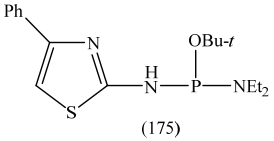
possibility of the amidophosphite transamination reaction under the action of 2-amino-4-phenylthiazole [128, 129] has been previously studied.

It has been shown that the reaction in the ratio of reagents 1:1 in the ethyl acetate medium occurs; but an attempt to reamidate two amido groups of amidophosphite did not resulted in the formation of the target product, which was obviously associated with steric hindrances in coordinating two residues of 2-amino-4-phenylthiazole at the P (III) atom.

In continuation of these studies, we attempted to phosphorylate 2-amino-4-phenylthiazole with two moles of diamidophosphite [164]. Introduction of two aminothiazole residues to the phosphorus atom would provide an interesting compound, both in theoretical and practical terms. Benzene was chosen as the solvent due to its inertness with respect to the reagents. The reaction was carried out with simultaneous distillation of the diethylamine released in a mixture with benzene. We believe that the reaction proceeds according to the following scheme:

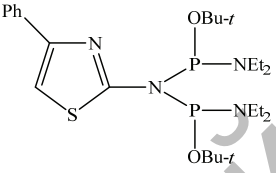


The reactions were monitored by mass spectrometry. The results of analyzes of mass spectra indicate that a product (175) with a molecular weight of 351 is formed at the first stage of the reaction, which corresponds to the structure:



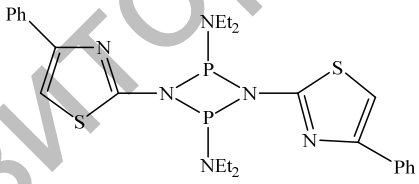
(175)

The peak of molecular weight 527 corresponds to the structure (210):



(210)

As a result of the reaction, the final product of the phosphorylation reaction, 1,3-bis(4-phenylthiazole-2-yl)-2,4-bis(N, N-diethyl-amino)-1,3-diazo-2,4-diphosphetidine (211) was isolated. The structure of 211 is proved by X-ray structural analysis. The molecular weight is equal to 554.



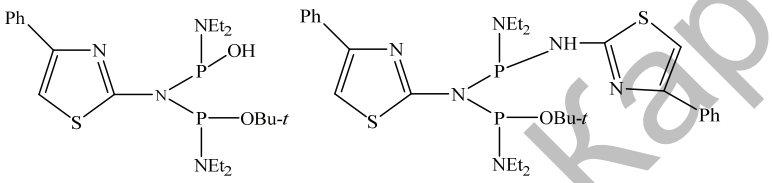
(211)

The study of the reaction by the method of mass spectrometry made it possible to detect intermediate substances and to present the mechanism of the formation of phosphetidine (211) through the stages of formation of a number of intermediate products.

It was noted that the reaction was accompanied by the release of isobutylene, which was identified by the water displacement method, and was also recorded by the HPLC method, the amount of isobutylene gas evolved was not determined.

The formation of isobutylene is explained by the ease of the second stage of the Arbuzov reaction with the detachment of a stable

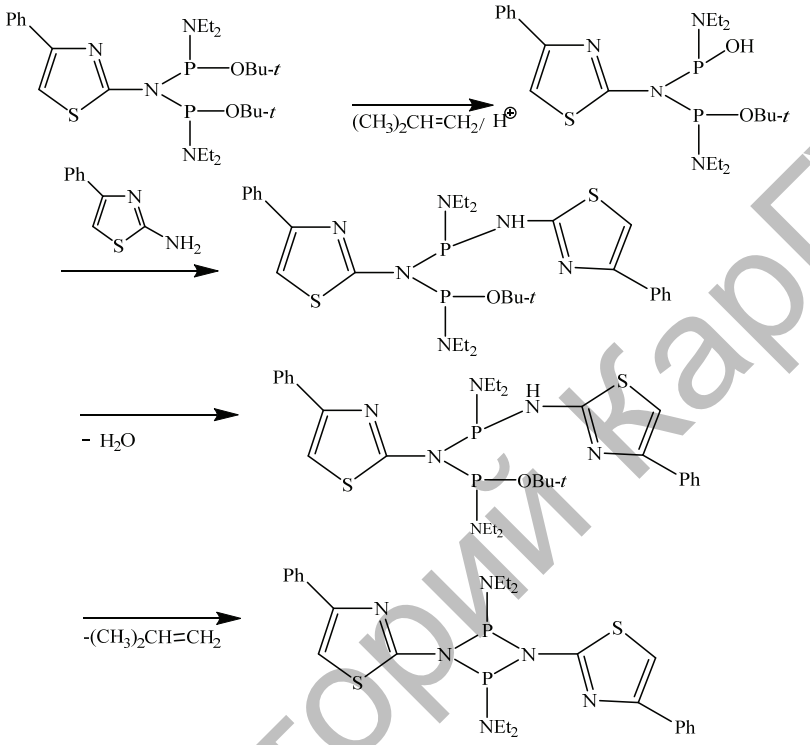
carbocation $(CH_3)_3C^+$, which is stabilized by the separation of a proton and the formation of isobutylene. The study of mass spectra shows the probability of formation of a water molecule, since peaks corresponding to the presence of low molecular weight substances (isobutylene, water) are clearly visible in the mass spectrum. The result of such reasoning can be the detection of peaks in the mass spectrum, which, obviously, correspond to the following structures:



Thus, intermediate structures formed have been proved by the data of the mass spectra, as a result, the formation of the final product can be described by the scheme below.

It was completely unexpected for us to isolate the final phosphorylated product, which was attributed to a four-membered phosphetane structure containing two P (III) phosphorus atoms and two nitrogen atoms according to X-ray analysis, mass and NMR spectra. Water and *tert*-butanol were determined as by-products of the reaction, which also confirms the proposed reaction pattern.

A peculiar moment of the reaction is the release of isobutylene, which usually results in the formation of a stable phosphoryl group. Such a reaction is characteristic of the full esters of phosphorous acid and amidoesters. In the case of the presence of a *tert*-butoxyl group, it is known that the second stage of the Arbuzov reaction scheme proceeds much faster and leads to the formation of the corresponding phosphonates or amidophosphates. However, the release of isobutylene was detected, but the formation of compounds of the phosphonate and amidophosphate structure was not observed.



(211)

This behavior is obviously due to the fact that under the reaction conditions the concentration of the reaction mixture is observed with constant distillation of diethylamine released, which brings the reaction centers closer together, and therefore the hydrogen atom of the amino group protonates the oxygen atom of the *tert*-butyl group, which explains the formation and release of the water molecule. The structure of the compound obtained (211) is reliably proved by the X-ray diffraction analysis data presented in Figure 1.

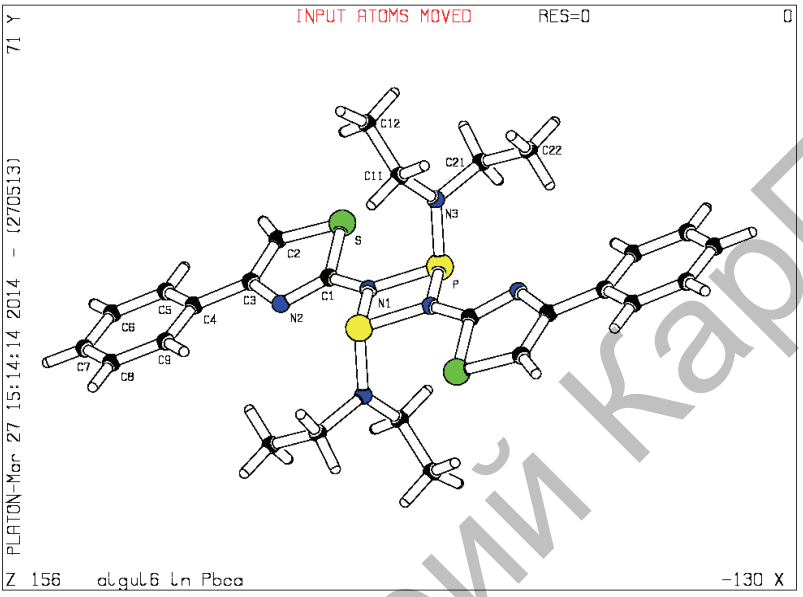


Figure 1. X-ray diffraction analysis of 1,3-bis(4-phenyl-thiazole-2-yl)-2,4-bis(N, N-diethyl-amino)-1,3-diazo-2,4-diphosphetidine (211)

Tables 1 and 2 show the data on the bond lengths of the compound synthesized (211), their geometry (spatial position), and data of computer calculation for eight assumed spatial positions.

Table 1

Bonds lengths of (211) and their geometry

Coden	N-subst.	P-N (mean)	Angle	N-C	P-arr.
MOVMUF	*t*-Bu	1.729	22.74	1.487	Cis
NAXZAN01	*t*-Bu	1.725	18.50	1.485	Cis
QIDNAS	*t*-Bu	1.729	21.38	1.484	Cis
PIPBPZ	*t*-Bu	1.735	27.69	1.483	Cis
TAJSII	*t*-Bu	1.724	29.59	1.481	Cis
ESULOT	*t*-Bu	1.718	21.29	1.480	Cis
NAXZAN	*t*-Bu	1.734	18.61	1.479	Cis
ESUMAG	*t*-Bu	1.720	17.30	1.479	Cis
FEMBIJ	*t*-Bu	1.727	18.02	1.478	Cis

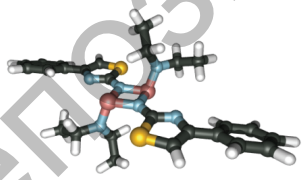
ESULUZ	*t*-Bu	1.714	11.73	1.477	Cis
GIQJUM	-	1.730	27.81	1.460	Cis
NUCZAM	Me	1.712	0.00	1.430	Trans
GIXKUT	-	1.740	0.02	1.406	Trans
DOGLOA	Ph	1.711	0.00	1.405	Trans
BAYTOK[a]	Ph	1.718	10.97	1.394	Cis
SUKVOJ	-	1.783	0.00	1.361	Trans
compound 1	-	1.743(3)	0.00	1.364(4)	Trans

Table 2

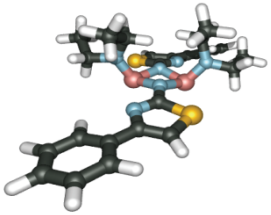
Computer calculation of various positions of (211)

REFCODE	**E_{TOT} [h]**	**NICS(0)**	**E_{rep} [h]**
1 (AI63)	-2816.12944240	-5.7790	4727.3032818556
AI63-CIS	-2816.12359144	-8.7360	4712.5283370202
DOGLOA	-2290.06454571	-4.6950	5335.3015442764
DOGLOA-CIS	-2290.05003464	-8.3361	5324.1835692228
ESULOT	-1995.11335295	-10.0784	4389.4657990480
ESULOT-TRANS	-1995.10496558	-3.7446	4320.6453956046
NUCZAM	-2470.27131437	-5.2710	4368.0535755184
NUCZAM-CIS	-2470.26874061	-10.6990	4355.3437140196

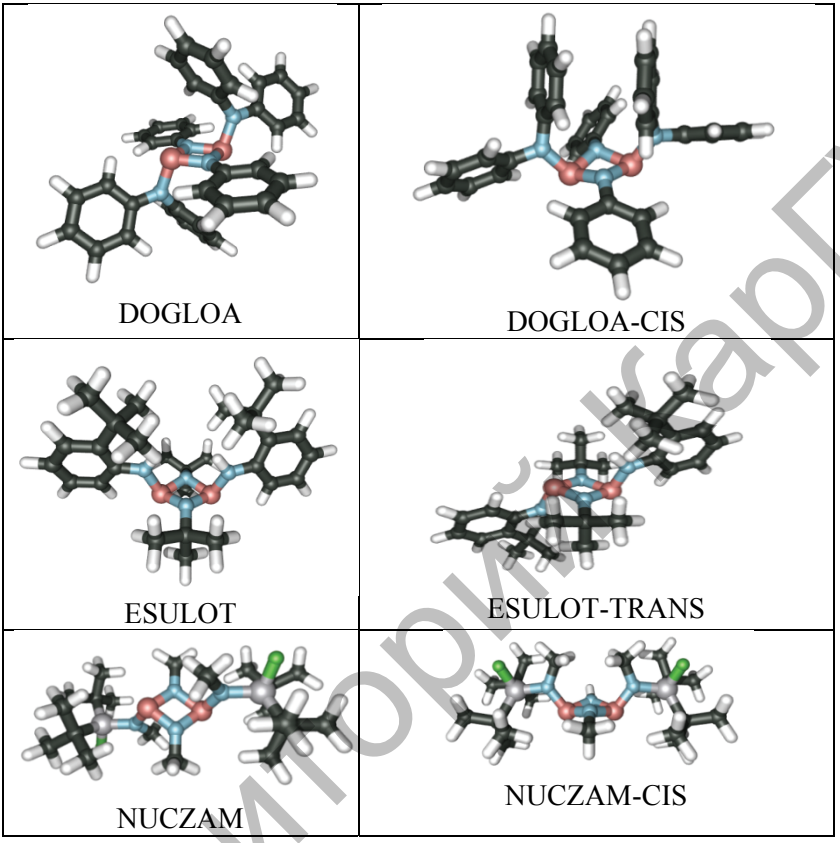
The resulting phosphetidine (211) has an unusual structure and can be in several structural forms.



1 (AI63)



AI63-CIS



The synthesized compound of unusual structure is an oil-like compound that crystallizes upon prolonged standing. The structure of the compound is also confirmed by the complex of physico-chemical constants, spectral data and mass spectrum.

Thus, ambiguous results were obtained as a result of the 2-amino-4-phenylthiazole transamidation reaction by tetraethyldiamido-*tert*-butylphosphite. It was shown that the reaction direction depended on the conditions of the reaction and the ratio of reagents [165].

2.5 Synthesis and investigation of organophosphorus complexones based on 2-aminothiazole and its derivatives

The progress of many areas of science and technology is largely associated with the development of chemistry of coordination compounds with polydentate ligands, among which complexones occupy one of the leading places. The chemistry of complexones opens up practically inexhaustible possibilities for modifying the properties of cations, which creates great potential prospects for their widespread use. However, the insufficient range of these compounds limits their application [166].

The development of new technology sets new challenges for science. A number of key problems of industry, medicine and agriculture can be successfully solved from the standpoint of the use of highly effective complexing agents. The need to create a wide range of complexones with a large range of complexing properties in a wide range of pH values remains a promising area of research to the present day [167].

The term “complexones” was proposed in 1945 by Herold Schwarzenbach (1904-1978), a professor at the University of Zurich, for organic ligands of the group of polyamino polyacetic acids containing iminodiacetate fragments bonded to various aliphatic and aromatic radicals. Subsequently, a large number of similar compounds were synthesized, including other acid groups instead of acetate, namely alkylphosphonic, alkylarsonic and alkylsulfonic and phosphorus (III), sulfur (II), selenium (II), and tellurium (II) instead of nitrogen (III).

Modern synthetic chemistry of chelating agents is based on two main areas, namely carboxyalkylating and alkylphosphorylation of amines; the introduction of complexone fragments in a molecule containing mobile hydrogen atoms or halogen. The wide possibilities of modifying the structure of molecules of complexones have opened up great prospects for creating compounds with a predetermined set of properties for solving both theoretical and practical problems of coordination chemistry.

Currently, methods for producing complexones are being improved due to the fact that they have found wide application in various fields of science and technology [168, 169]. For example, the

complex-water-chemical regime implemented by the method of partial or full stabilization of natural make-up and network water with additives of chelating agents and (or) complexonates has been widely used in heat supply and hot water systems.

When treating water with complexones, it is possible to exclude the stage of water softening (inhibition of scale formation) or the stage of aggressive gases removal (inhibition of corrosion). Sometimes these two stages are excluded, in this case they speak of water stabilization (scale formation inhibition and corrosion) [170]. Along with complexones of the polyamine polycarboxylic acid class, complexones containing phosphonic groups, $PO(OH)_2$, are becoming increasingly common for solving the problems of thermal power engineering. The phosphonate ion has the shape of a distorted tetrahedron and possesses a higher dedentation compared to the carboxylate ion having a flat configuration. These complexones are characterized by high reactivity; interact with a large number of cations in a wide range of pH forming strong complexes. A feature of phosphorus-containing chelating agents is the ability to influence the crystallization of calcium carbonate. They interfere with crystal growth and prevent the formation of carbonate scale at concentrations significantly lower than stoichiometric ones [171], which makes them promising as scale inhibitors in water circulation systems.

The widespread application of complexones in various areas of science and technology led to a great deal of attention to the development of methods for their preparation. The 50s of the XIX century, when the role of complexones as the most promising class of organic ligands became apparent can be considered as the beginning of the development of synthetic chemistry of complexones. Very interesting results can be expected from the synthetic chemistry of sulfur-containing complexones with thioalkyl-acid (carboxylic, phosphonic) groups that has been developing in recent years. A number of ligands containing a phosphorus (III) atom as the main center instead of the traditional nitrogen atom have been developed. Particular attention is paid to the preparation of esterified derivatives of chelating agents. The chemistry of carboxyl and phosphorus-containing polycomplexes has evolved.

Modern synthetic chemistry of chelating agents is based on two main areas:

- carboxyalkylation and alkylphosphorylation of amines;
- introduction of complexone fragments in a molecule containing mobile hydrogen atoms or halogen.

Complexones are used in the oil and cement industry (prevention of scaling in pipes, slowing the setting of concrete), in medicine, in agriculture (prevention of chlorosis and anemia, the introduction of iron and other metals into the soil, food of animals in the form of complexonates or vice versa, for their removal from the soil or from a living organism) [172].

Application of complexones in analytical chemistry, oil and gas industry

The practical application of chelating agents in the oil and gas industry is based on their unique ability to effectively inhibit the growth of crystals. Only active centers of crystals are blocked, therefore a low consumption of complexone is required, which is a prerequisite for the development of new economical and environmentally friendly technologies. The traditional field of application of chelating agents in the oil and gas industry is preventing scaling, as well as inhibiting the formation of FeS in the preparation and transportation of iron and hydrogen sulfide-containing oils.

The industrial production of many complexones and the reduction of their price allow us to consider them as a substitute for corrosion inhibitors. Instead of passivating the metal surface, neutralization of active corrosion centers is achieved not only on the metal surface due to complexones, but also in the aggressive environment surrounding it [173].

As a result of the high salinity of formation water, salt deposits are formed well in the oil and gas, which sharply reduce oil recovery, and sometimes completely stop it. There have been created complexones, which are active inhibitors of salt formation and are well combined with formation waters without clogging the pores of the formation rock. The proposed inhibitors are characterized by high metal consumption and activity at low concentrations with respect to substances forming precipitates (5 g of the preparation per 1 m^3 of water). Such substochiometric interaction of complexones with metal cations determines their ability to inhibit crystal growth and exhibit the effect of a gliding reaction.

According to the chemical composition, salt deposits are diverse, but mainly they are calcium carbonate, magnesium sulfate, and barium sulfate. An effective way to control mineral deposits is the use of chemicals that prevent the crystallization of poorly soluble salts. Phosphorus-containing complexones are the most effective of them. Their use allows us to almost completely prevent the formation of scaling.

Salt deposits in the oil fields are controlled by three groups of methods, namely technological, physical, and chemical. The most effective and long-lasting protection of equipment against scaling is carried out by chemical methods using scaling inhibitors that prevent crystallization of poorly soluble salts.

The ability of complexones to form stable water-soluble complexes with iron (III) and thereby prevent the occurrence of iron sulfide precipitate allows for the joint production, transportation and preparation of multi-grade oils [174].

Complexones are widely used in analytical chemistry. Their application in titrimetric (volumetric) analysis is the most important, where a large section of analytical chemistry has emerged and successfully developed on the basis of complexones known as "complexonometry" or "chelatometry". Complexes are also effectively used in photometric, polarographic, chromatographic and other physico-chemical methods of analysis, in gravimetric analysis. Complexones are used for masking interfering ions, dissolving poorly soluble compounds, changing the system redox potentials and for many other purposes [175].

The application of complexones in medicine and agriculture

One of the links of chemicalization remains a balanced supply of plants with all the necessary elements, which guarantees high yields. Trace elements are especially important. Their lack in soil or being in an inaccessible form leads to lower yields, disease and plant death. In addition, the content of beneficial elements in the soil decreases when harvesting and it must be constantly replenished. The possibility of modifying the structure of complexones, and, consequently, the properties of the complexones formed by them, the availability of these compounds and their production on an industrial scale open up broad prospects for the creation and use of complexones and complexonates of metals for the chemicalization of agriculture.

Complexonates of metals are used due to their valuable properties for the introduction of microelements into plants. They are practically non-toxic, sufficiently soluble in water, resistant, slightly adsorbed by the soil, due to which they can be kept in the soil solution for a long time. The application of the complexes themselves makes it possible to extract trace elements from the soil that are in inaccessible form. The application of chelating agents for the modification of mineral fertilizers is of particular note, i.e. to translate trace elements contained in fertilizers in a form inaccessible to plants into digestible biologically active complexonates [176].

The introduction of chelating agents into solid mineral fertilizers at one of the technological stages of production is a promising method. The introduction of complexones improves the nutrition of plants, affects the structure and physico-chemical parameters, slows down the degradation of phosphates, and improves the uniformity of particle size distribution. It is known that the addition of chelating agents allows optimizing the technology for producing liquid complex fertilizers and significantly increase their shelf life.

The application of fertilizers containing small amounts of copper, zinc, molybdenum and boron in the form of complexonates, which significantly reduce the formation of pathological shoots in potatoes, is known. The introduction of nickel, iron, copper, manganese and other chelates into the soil increases the content of trace elements in leguminous plants, favorably affects the quality of cotton fiber, stimulates the germination of cotton and increases its yield [177].

Complexones occupy an important place in the development of drugs and diagnostics. Their abilities to penetrate cell membranes, manifest the functions of biocatalysts, imitate the functions of certain enzymes, etc. were established. Mineral metabolism regulators, bactericidal and antiviral preparations, anti-allergic substances, diagnostic preparations, etc. have been manufactured on the basis of complexones.

According to their application in medical practice and the effect it provides, chelating agents can be classified as follows:

- antidotes;
- mineral metabolism regulators;
- bactericidal and antiviral drugs;
- medicines used in oncological diseases;

- antiallergic substances;
- diagnostic drugs.

Polyamino polycarboxylic, polyamino polyphosphonic, diphosphonic acids, their sodium, potassium salts and their complexonates are used as the basis for these preparations.

The elimination of incorporated toxic or radioactive metals from the body, especially when water-soluble non-metabolized and secreted chelates are formed, is one of the most extensive and sufficiently studied areas of application of complexones in medicine [178].

Properties of organophosphorus complexones

Research in the field of complexones [179] leads to the conclusion that the most important tasks of coordination chemistry in general and the chemistry of complexones, in particular, are the issues of chelate stability and selectivity of chelation. The development of highly selective reagents is associated with great difficulties, since such substances must selectively chelate cations that are very close to each other in physical and chemical properties, size, spatial configuration, and a tendency to complex formation [180]. Chemistry of phosphorousorganic complexones [181] is among new, emerging trends in the field of complexones leading to the solution of the issues under discussion.

Organophosphorous complexones possess a number of specific properties that significantly distinguish them from carboxyl analogues and allow us to resolve some issues of chelation selectivity. The development of the field of organophosphorus complexones became possible only after the development of methods for the synthesis of aminoalkylphosphonic acids, to the group of which they belong. The main regularities of the complexation of phosphorylated ligands were revealed by Kabachnik M.I. and Dyatlova N.M. on the example of compounds, in the structure of which PO_3H_2 and PO_2H_2 groups were fragmentarily included [182, 183].

When interacting with transition metals, phosphorus-containing complexones form strong hydrogen and polynuclear complexes, which is not typical for carboxyl-containing prototypes. Copper compounds are especially strong among the normal complexes. For example, the stability constant of a complex with ethylenediamineisopropylphosphonic acid exceeds that with ethylenediamine diacetic acid by 7 orders of value. An exceptional

case is the large difference in the stability of the copper and other transition metal complexes [184].

Stable complexes with phosphorylated polyamines also form lightly hydrolyzing elements, namely iron, indium, gallium, titanium, and chromium. The strength of their hydrogen complexes is remarkable, in some cases it is superior to the strength of normal complexes of the corresponding aminopolycarboxylic acids, and the extremely low solubility of polynuclear compounds [185].

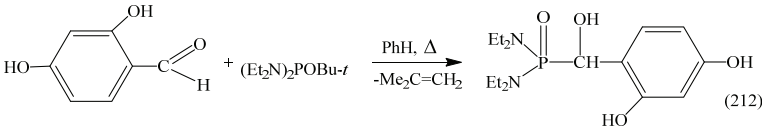
The potential ability of aminoalkylphosphonic acids to exhibit increased denatability due to the oxygen of the phosphonic groups favors the complex formation with rare-earth elements, for which, as is known, a high coordination number and a high affinity for oxygen are characteristic. Alkylene polyamino polyalkyl phosphonic acids form high-strength mononuclear hydrogen and normal as well as polynuclear complexes [186].

2.5.1 Methods of synthesis, reactivity and complexing properties of 2-aminothiazole derivatives

One of the most interesting and promising areas of research in the chemistry of organophosphorus complexones is the reaction of derivatives of trivalent phosphorus acids with various electrophilic reagents. The reactions of esteramides of P (III) acids with carbonyl compounds have been studied quite fully and it has been established that they proceed ambiguously depending on the structure of the starting compounds [187].

The study of the reactions of tetraethyl diamido-*tert*-butyl phosphite with 2,4-dioxybenzaldehyde, which has an electrophilic carbon atom of the carbonyl group and a high mobility of hydrogen atoms of hydroxyl groups, is of undoubted interest. It has been shown that the reaction proceeds in a non-polar solvent at its boiling point and is accompanied by abundant release of isobutylene.

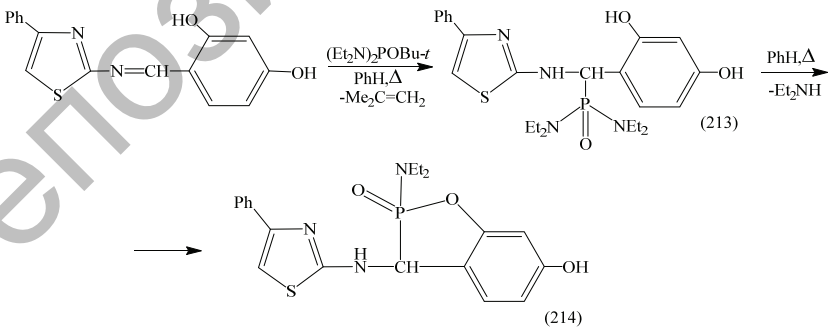
Obviously, the phosphonate (212) obtained, having a high basicity of the oxygen atom of the phosphoryl group, P=O and the mobility of hydroxyl hydrogen atoms is capable of complexing with various metal cations.



The IR spectrum of compound (212) contains absorption bands in the region of 1467, 1620 cm^{-1}, which corresponds to the stretching vibrations of C=C. The absorption band in the region of 3400 cm^{-1} indicates the presence of the OH group. The stretching vibrations of the P=O bond are observed in the region of 1211 cm^{-1}.

The protons of the phenyl ring appear as a multiplet in the range of 6.13-6.85 ppm in the ^{1}H NMR spectrum of compound (212). The protons of the hydroxyl groups of the phenyl radical are located at 5.06 ppm. The methylene proton multiplet is found in a region with a center at 2.59 ppm. The signal of the proton of the OH group at the methine carbon atom resonates as a singlet in the region of 2.00 ppm. The methine proton resonates in a region centered at 4.50 ppm.

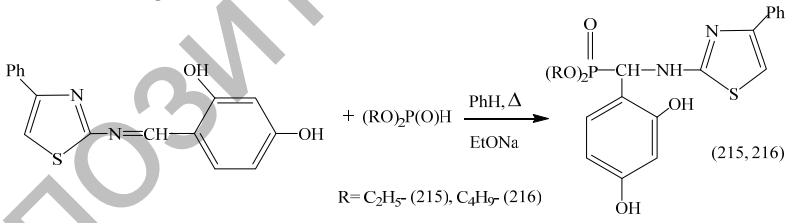
In continuation of the research, it was advisable to study the interaction of tetraethyldiamido-*tert*-butyl phosphite with a Schiff base obtained on the basis of 2-amino-4-phenylthiazole. As a result, it was found that the reaction proceeded in a non-polar aprotic solvent accompanied by the release of an equimolar amount of isobutylene and diethylamine. The release of diethylamine suggests that the phosphonate (213) formed in the first stage can be further converted to the product (214) [188].



The IR spectrum of compound (213) contains absorption bands in the region of 1444, 1520 cm^{-1}, which corresponds to stretching vibrations of C=C. The absorption band in the region of 3392 cm^{-1} indicates the presence of the OH group. The vibrations of the C=N endocyclic bond resonate in the region of 1483 cm^{-1}, and there is an absorption band in the region of 3200 cm^{-1}, corresponding to the stretching vibrations of the secondary amino group and an absorption band in the region of 1225 cm^{-1} is related to the vibrations of the P=O bond.

Phosphonates (215, 216) were synthesized by addition of dialkyl phosphites to the Schiff base in the presence of sodium alcoholate catalysts. The low yields of phosphonates (213, 214) obtained by this reaction are obviously explained by the low resistance of Schiff bases to the action of sodium alkoxides [52, p. 526].

There are absorption bands in the regions of 1442, 1610 cm^{-1}, which correspond to the stretching vibrations of C=C in the IR spectra of compounds (215, 216). The vibrations of the endocyclic bond C=N resonate in the region of 1485 and 1490 cm^{-1}, and there is an absorption band in the region of 3200 cm^{-1} corresponding to the stretching vibrations of the secondary amino group and an absorption band characteristic of the P=O vibrations appears in the region of 1302 cm^{-1}. Troughs related to the signal of the hydroxyl group are found in the region of 3460 and 3562 cm^{-1}.



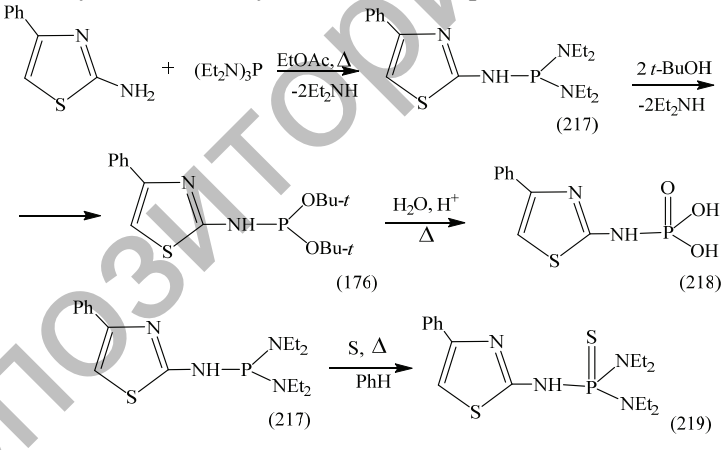
The search for organophosphorous complexones on the basis of 2-amino-4-phenylthiazole was relevant. Thus, phosphonic acid (218) was obtained by transamidation of triamidophosphite with 2-amino-4-phenylthiazole followed by treatment with *tert*-butanol and acid hydrolysis of the resulting compounds [189].

The synthetic capabilities of the amidophosphite obtained (217) are also determined by the possibility of converting it into pentavalent

phosphorus derivatives, which was confirmed by the example of the reaction of compound (217) with sulfur in a benzene suspension to form the product (219).

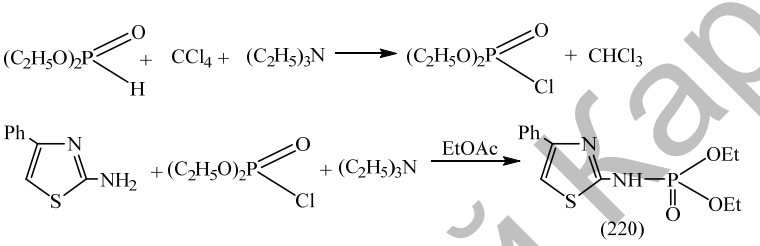
The IR spectrum of compound (219) contains absorption bands in the region of 1442, 1590 cm^{-1}, which corresponds to stretching vibrations of C=C. The absorption band in the region of 730 cm^{-1} indicates the presence of the P=S bond. The troughs of the endocyclic C=N bond resonate in the region of 1485 cm^{-1}, and an absorption band found in the region of 3320 cm^{-1} corresponds to the stretching vibrations of the secondary amino group, and an absorption band in the region of 1302 cm^{-1} is related to the vibrations of the P=O bond.

The compounds synthesized (212-219), according to the structure, have a complexing ability due to the presence of a phosphonic group, as well as nitrogen atoms and a hydroxyl group. In addition, compounds (212-219) potentially possess pharmacological activity, namely antiparasitic, antiasthmatic, antiallergic, psychotropic, antiepileptic according to the data of computer bioprognosis and, undoubtedly, can be widely used in medical practice.



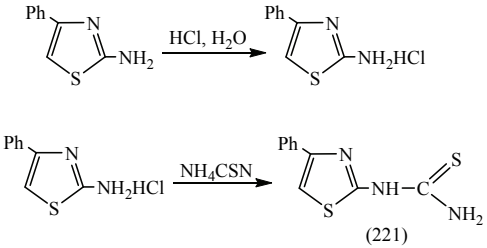
The reaction of O-alkylphenylphosphonite with the corresponding aminoheterocycles in carbon tetrachloride in the presence of triethylamine (Todd-Atherton reaction) is another common method for the synthesis of phosphorylated (thiophosphorylated) heterocyclic amines.

It seemed to us to be possible to carry out the reaction of the latter with diethylphosphite due to the presence of the reactive amino group in 2 amino-4-phenylthiazole. The process proceeded under the conditions of the classic Todd-Atherton reaction, where, diethylphosphorous acid chloride formed in the first stage, and, the amine is directly phosphorylated in the second stage followed by release of triethylamine hydrochloride.



The reaction was carried out in a medium of carbon tetrachloride at boiling. The reaction was monitored by thin layer chromatography. The resulting compound diethyl ester of 4-phenyl-2-amidothiazolyl phosphoric acid (220) is a white crystalline compound soluble in water and in organic solvents. Characteristic absorption bands in the region of 1517 cm^{-1} and 1598 cm^{-1} were found in the IR spectrum, which relate to vibrations of C=C bonds, there is an absorption band at 1482 cm^{-1}, corresponding to vibrations of the endocyclic C=N bond, vibrations of the NH bond resonate in the characteristic region 3435 cm^{-1}, and the P=O bond absorption appears at 1201 cm^{-1}.

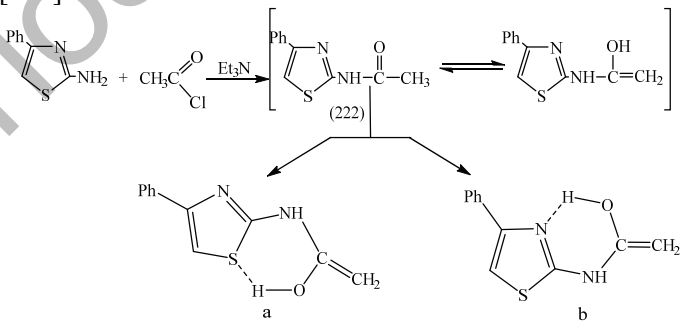
Despite the fact that the chemical properties of compounds of the thiazole series are well studied, the synthetic potential of 2-amino-4-phenylthiazole is not fully disclosed. Chemical modification of 2-amino-4-phenylthiazole can be carried out with the participation of the free amino group, which has a sufficiently high nucleophilicity. Using this feature of the structure, allows us to get a variety of derivatives based on nucleophilic substitution reactions. For example, the interaction of 2-amino-4-phenylthiazole with ammonium rhodanide leads to the formation of a derivative (221) [190].



(221)

The resulting compound 4-phenyl-2-thiouridothiazole (221) is a white crystalline compound soluble in water and in organic solvents. There is a characteristic absorption band in the region of 1620 cm^{-1} in the IR spectrum of (221) related to the C=C bond vibrations, the vibrations of the free amino group resonate in the region of 3359 cm^{-1} in the form of two absorption bands. Compound (221) is a potentially biologically active compound to be interesting both from the standpoint of phosphorylation and as an object for complexometric studies.

Another derivative of 2-amino-4-phenylthiazole is 4-phenyl-2-amidothiazolyl acetate (222), which is obtained by the reaction of 2-amino-4-phenylthiazole with acetyl chloride in the presence of triethylamine. There is an acetyl group in the structure of thiazolylacetate, which is capable of easy enolization, and the presence of a bound amino group, obviously, due to the +M-effect, increases the electron density on the oxygen atom of the carbonyl group, which ultimately will contribute to an increase in enolization, and this in turn increases the complexing ability of the object under study [191].



However, when studying 4-phenyl-2-amidothiazolylacetate as a complexing agent, one should also bear in mind the ability of its structure, both ketone and enol forms, to form intramolecular hydrogen bonds.

The choice of objects for the study of complexation containing a phosphorus atom or representing various functional derivatives of 2-amino-4-phenylthiazole without a phosphorus atom is due to the fact that it is possible to combine phosphorylated and non-phosphorylated ligands to produce complex compounds with an extended range of properties.

Interest in organophosphorus compounds was determined by their diversity and a unique set of properties that make these compounds valuable objects of theoretical research and give them great practical significance. The most important use of organophosphorus compounds is the protection of agricultural plants and animals from pests and diseases.

Effective medicinal compounds are found among organophosphorus compounds. They include, in particular, anti-glaucoma agents, anticancer drugs, complexing agents are used for the prevention and treatment of beryllium and lead poisoning. Many organophosphorus compounds are flotation agents, extractants of heavy metals, additives to oils and fuels, plasticizers, stabilizers of high-molecular compounds. Phosphorus-containing polymers, the study of which is also given attention, are used in modern technology as thermostable and non-combustible materials, ion exchangers, glues, etc.

Continuing research on the preparation of new phosphorylated thiazole derivatives, thiazole containing a phosphorus component directly at the thiazole ring based on the classical method of formation of the thiazole cycle using the well-known Hantzsch reaction scheme was attemted to synthesize. The thiazole ring has previously been obtained from the reaction of thiourea and diethyl bromoacetyl phosphonate. Diethyl ketophosphonate is of great interest as the main synthon for obtaining 2-aminothiazole with a phosphorus component.

It is known that ketophosphonates are rather easily synthesized according to the scheme of the classical Arbuzov reaction using trialkylphosphites and acid halides. However, the disadvantage of this reaction is the use of a significant excess of the acid halide, as well as

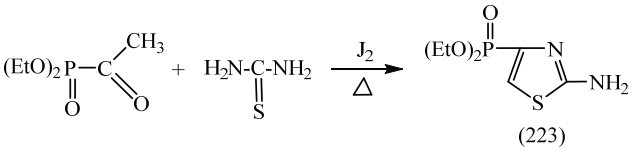
the need to remove the evolved alkyl halide from the reaction medium, which can also easily react and be competitive in Arbuzov reactions along with the acid halide. However, the yield of the target product was below 40%. In addition, the target product may contain impurities of the initial reagents.

It is known from the literature data that dialkylphosphites almost entirely exist in the phosphonate form $(RO)_2P(O)H$, in which the phosphorus atom does not have a lone pair of electrons. Therefore, dialkylphosphorous acids themselves are practically not reactive compared to trialkylphosphites. However, the corresponding anions quite easily replace the halogen atom in alkyl halides (the Michaelis-Becker reaction) resulting in phosphonate esters. Dialkyl phosphites can be used for carrying out reactions in the presence of tertiary amines or their readily available sodium salts. Since the latter are much more reactive than trialkylphosphites, they are very convenient for the synthesis of phosphonates containing a secondary alkyl radical. These properties of phosphoryl acids make it possible to carry out the process of obtaining diethyl ketophosphate through the sodium salt of diethyl phosphite, which should significantly affect the yield of the product.

The preparation of the sodium salt was carried out in a benzene medium, dripping diethyl phosphite to the benzene layer, which contained a portion of sodium. The interaction took place rapidly with the release of hydrogen. The end of the reaction was proved by the complete disappearance of sodium in the reaction medium.

Acetyl chloride was slowly added to the reaction mixture in the second stage of the reaction. The addition was carried out with slight cooling and with vigorous stirring. The reaction was accompanied by precipitation of salt. The end of the reaction was confirmed by thin-layer chromatography. The resulting ketophosphonate is a liquid with a low specific odor, boiling at a temperature of 60-61°C.

The optimal conditions for obtaining 4-(diethylphosphono)-2-aminothiazole (223) are the same as for the preparation of 4-phenyl-2-aminothiazole, however, double excess of thiourea should be used at least for a better yield.

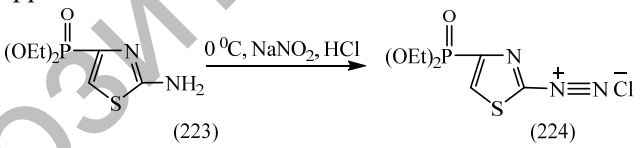


(223)

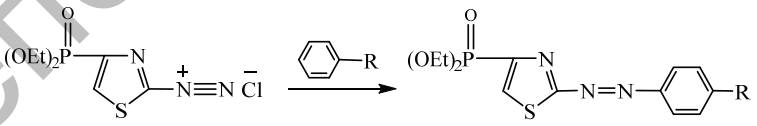
The resulting thiazole derivative (223) is a white crystalline compound soluble in water and in organic solvents. There are characteristic absorption bands in the region of 1040 cm^{-1} and 1206 cm^{-1} in the IR spectrum related to vibrations of P-O-C and P=O bonds, respectively. The vibrations of the free amino group resonate in the region of 3375 cm^{-1} in the form of two troughs.

The structure of 2-amino-4-(diethylphosphono)thiazole (223) is very interesting from the standpoint of the possibility of chemical functionalization. In particular, the presence of a free amino group in the second position, which is capable of easily forming diazonium salts, makes it possible to obtain azo dyes of various structures based on the synthesized salts.

Using this possibility, we managed to obtain 4-(diethylphosphono)-2-diazonium chloride (224) under very mild conditions, which was *in situ* reacted with various anilines and phenols. As a result of the experiments, the corresponding azo dyes were obtained, which had been of particular interest as objects of practical application.

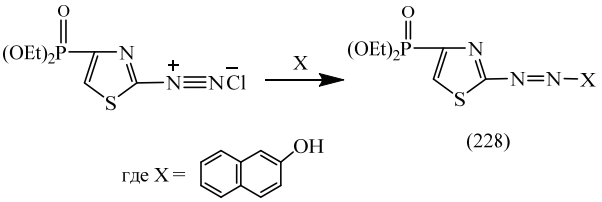


(223) (224)

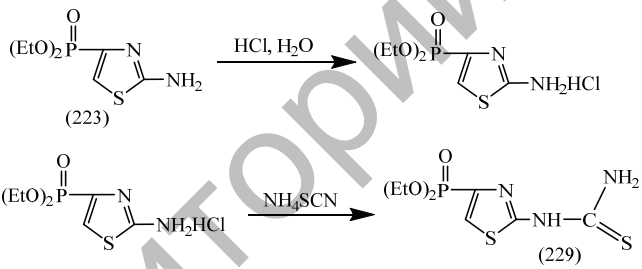


(225-227)

where R= NH_2-, NEt_2-, OH-



The reaction of diethylphosphonothiazole with ammonium rhodanide was carried out according to the scheme presented below in order to continue the investigation of the reactivity of 2 amino-4-diethylphosphonothiazole (223), as well as to obtain compounds possessing a complex of useful properties both complexing and biologically active ones. The resulting 2-thiourido-4-diethylphosphonothiazole (229) is a white crystalline compound soluble in water, alcohol, and other polar solvents.

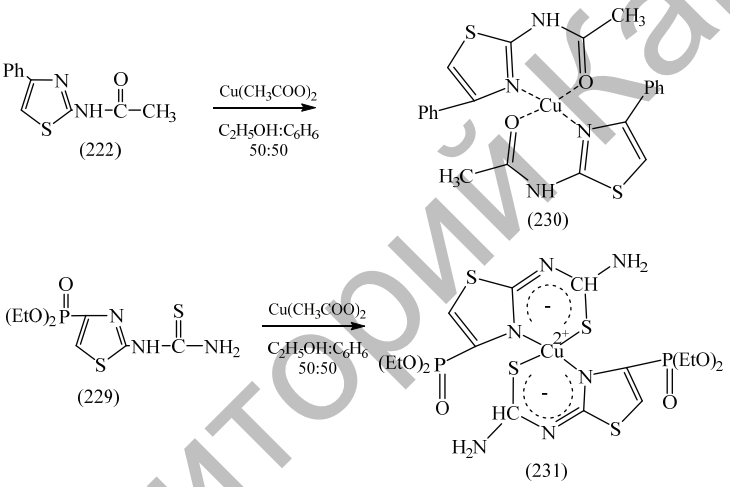


The structure of the resulting phosphorylated thiourea derivative suggests the potential ability to complex due to the presence of two amino groups and a polar thiocarbonyl group.

The chemistry of complexones opens up practically inexhaustible possibilities for modifying the properties of cations, which creates great potential prospects for their widespread use. Comprehensive studies of complexones and complexes based on them made it possible to identify fundamentally new areas of their application and solve a number of priority tasks of science and technology. Fundamental studies of the patterns of complex formation reactions involving complexones have opened up broad prospects for solving specific practical problems related to the control of processes occurring in complex multi-component systems.

Interaction with copper (II) acetate in various aqueous - organic media was carried out in order to study the complexing ability of compounds (222) and (229). Alcohols, acetone, dioxane, and dimethylformamide were used as solvents miscible with water. It was found that colored compounds of greenish-blue color were formed only in an aqueous-alcoholic medium. All further studies were performed using ethanol.

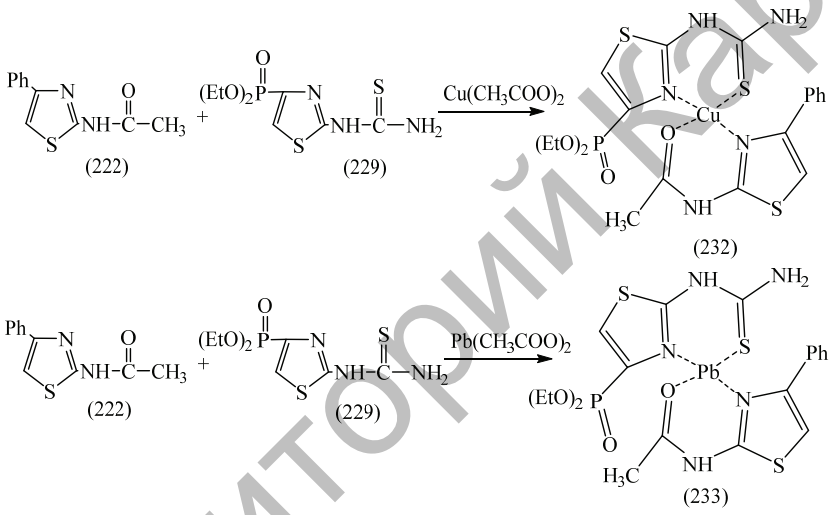
The study of the structure of the complexes obtained (230, 231) allows us to assume that they have the structure shown in the diagram.



Currently, much attention is paid to the complexes, which include two different ligands. Mixed complexes of organophosphorus elements with chelating agents are of particular interest. Compounds of this kind are stronger than complexes with one or two homogeneous ligands. This opens up wide possibilities for the effective use of polyligand agents for various technological operations.

Copper and lead complexes were synthesized to assess the complexing ability of 2-thiourido-4-diethylphosphonothiazole (229) and 4-phenyl-2-amidothiazolyl-acetate (222). The reaction was carried out by heating equimolar amounts of compounds (222), (229) and copper and lead acetate in a benzene-alcohol medium. The formation

of blue-green crystals was observed for complexes with copper ions and white crystals for complexes with lead ions in the heterophase system. Structural studies of the complexes obtained at this stage do not allow us to establish their structure reliably. Moreover, when studying the structures of the complexes formed, the tendency of the studied ligands to form intramolecular formation of hydrogen bonds should be taken into account. The proposed structures of the complexes obtained on the basis of (229) and (222) are shown below.

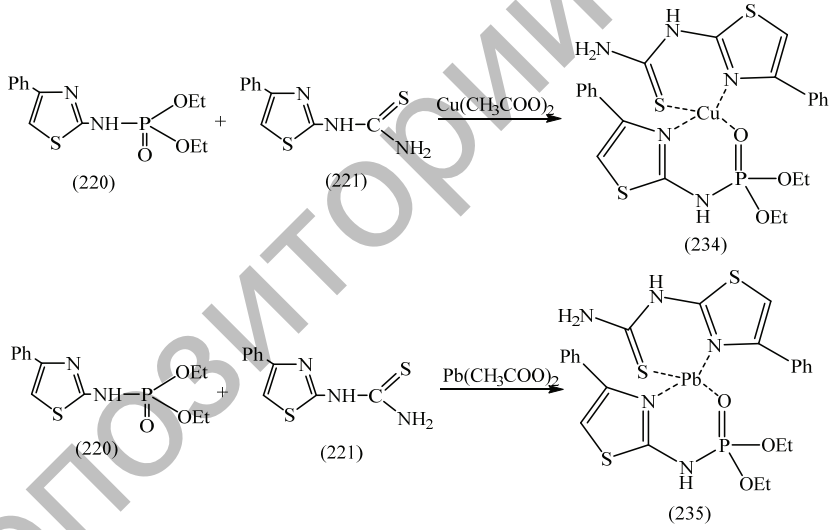


The reaction of the latter with compound (222) and copper acetate was carried out in order to investigate potential methods of coordination of (229) in mixed-ligand complexation reactions. In assessing the proposed structure of the complex synthesized, both ligands are capable of intramolecular formation of hydrogen bonds, and, therefore, the most likely way of coordination will be the following structure, in which two donor-acceptor bonds with copper ion are realized due to unshared electronic pairs of sulfur atoms.

Studies of the complex formation of various organic compounds with metal ions have now moved to a new level, for which the decisive characteristic is polyfunctionality or versatility of organic matter, including the relationship of reactivity with biological activity and thermodynamic stability with the degree of metal ion binding,

which provides and the practical application of these compounds. Therefore, it is necessary to take into account both structural and energy features of various systems in order to understand the deep-seated processes of a biological and ecological nature.

A reaction of the simultaneous interaction of (220) and (221) with copper and lead acetate was studied in order to assess their potential complexing ability to form strong mixed ligand complexes with a number of heavy metals. Evaluation of the spectral data allowed us to assume that 4-phenyl-2-amidothiazolylphosphoric acid diethyl ester (220) in combination with 4-phenyl-2-thiouridothiazole (221) can form strong complex compounds due to its ketone form, with the donor-acceptor character of bonds prevailing. At the same time, diethyl-4-phenyl-2-amido-thiazolylphosphoric acid (220) in combination with (221) can form complexes due to its enol form [192].



The coordination of the copper ion with the compound molecule (221) occurs due to the formation of a donor-acceptor bond at the exocyclic sulfur atom. The bond is formed by the oxygen atom of the phosphorus group in the case of the ligand of compound (220).

Mixed-ligand complexes synthesized (220), (221) with heavy metal ions are stronger than their single-ligand counterparts, since

they are stabilized not only by covalent bonds and electrostatic forces, but also by hydrophobic interaction.

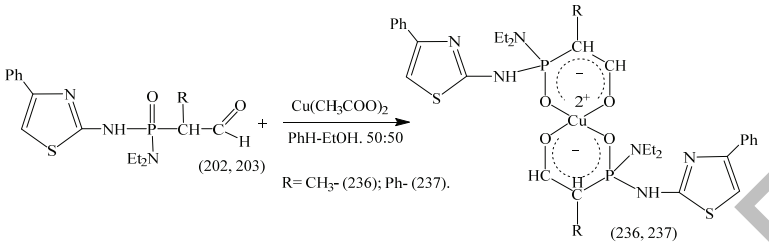
The study of the interaction of phosphorylated complexones with cations of different groups of the periodic table made it possible to identify a number of features in the behavior of these ligands. Particular attention should be paid to the ability of the compounds under study to form strong complexes with copper and lead.

2.5.2 Spectrophotometric analysis of organophosphorus complexones and metal complexonates based on 2-aminothiazole derivatives

The modern level of development of industry, technology, agriculture and medicine requires the use of highly sensitive methods of analysis, allowing determining the microquantities (up to 10-7%) of various substances. So far, optical methods of analysis based on the interaction of radiant energy with the analyte are used for these purposes.

Compounds of the β-diketone class are good complexing agents due to their ability to keto-enol tautomerism. The authors of [193] investigated the interaction of acetylacetone with molybdenum ions (V, VI), using a spectrophotometric analysis method and showed that a colored yellow compound was formed only with molybdenum in oxidation state +5 in an aqueous-alcoholic medium. The absorption spectrum of this complex has two maxima, namely in the UV (λ = 340 nm) and visible (λ = 470 nm) regions. The highest rate of formation of molybdenum acetylacetonate (V) corresponds to a 2500-fold excess of acetylacetone, the acid concentration is 1.8 mol/L. The authors explain the use of a large excess of acetylacetone by the fact that the overwhelming part of it does not participate in complexation, but plays the role of a solvent in the system under study.

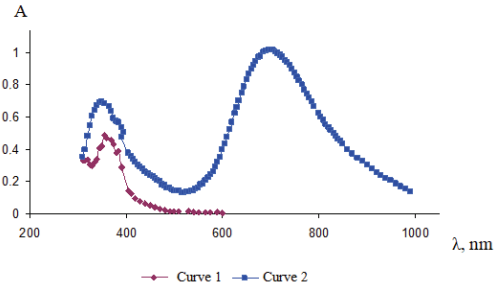
The synthesized phosphorylated aldehydes (202, 203) can be also used as effective complexing agents like compounds of the β-diketone class due to the ability of their structure to enolization.



Currently, one of the urgent tasks of modern analytical chemistry is to control the content of various chemical elements in natural and industrial facilities. Spectrophotometric determination of metals in the form of complex compounds with organic reagents by extraction methods has become widespread in practice. However, carrying out the extraction is labor intensive and demands using toxic solvents. In this regard, the development of new non-extraction methods for the determination of metals is of great interest.

The interaction of copper (II) ions with phosphorylated aldehydes synthesized (202, 203) was investigated in various aqueous-organic media. Alcohols, acetone, dioxane, and dimethylformamide were used as solvents miscible with water. It was found that colored compounds of greenish-blue color were formed only in an aqueous-alcoholic medium as a result of the experiments. All further studies were performed using ethanol.

There are two maxima, namely λ = 350 nm and 340 nm in the UV and λ = 705 nm and 700 nm in the visible region, respectively, in the absorption spectra of complexes (236, 237). There is one absorption maximum in the UV region at λ = 360 nm and 355 nm, respectively, in the absorption spectra of water-alcohol solutions of phosphorylated aldehydes (202, 203). The graphical dependence of the optical density of the compounds synthesized (202, 236) and (203, 237) on the wavelength is presented in Figures 2 and 3, respectively.

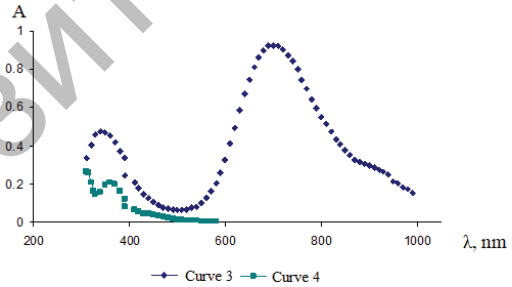


Curve 1 is the absorption spectrum of the compound (202); Curve 2 is the absorption spectrum of the compound (236)

Figure 2. Determination of the region of optimal light absorption by solutions of the compounds analyzed (202, 236)

The study of complexation in the established systems was extended in the visible region, since the reagent itself has a significant absorption in the UV portion of the spectrum.

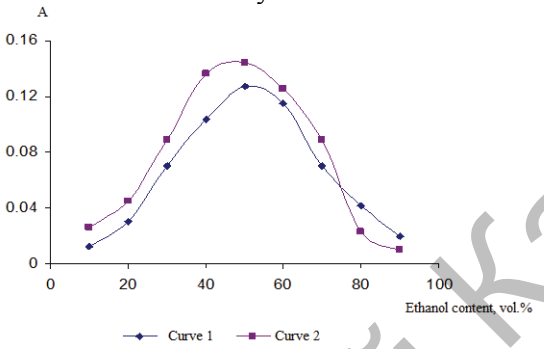
The influence of various factors on the complexation process, namely the percentage of organic solvent, the concentration of the reagent, and the acidity of the solution was studied to find the optimal conditions for the interaction of copper (II) ions with solutions of phosphorylated aldehydes synthesized (202, 203).



Curve 3 is the absorption spectrum of compound 203; Curve 4 is the absorption spectrum of compound 237

Figure 3. Determination of optimal light absorption by solutions of the compounds analyzed (203, 237)

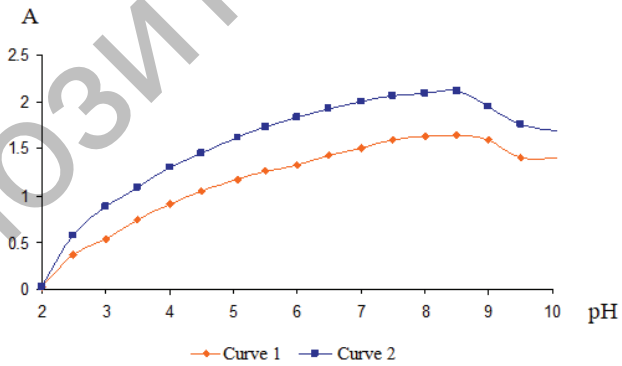
It is established that the dependence of optical density on ethanol content has the form of a curve with a maximum presented in Figure 4. As can be seen, the highest value of optical density is observed when the ethanol content is 50% by volume for both cases.



Curve 1 is the dependence for compound 236; Curve 2 is the dependence for compound 237.

Figure 4. Determination of optimal content of an organic solvent

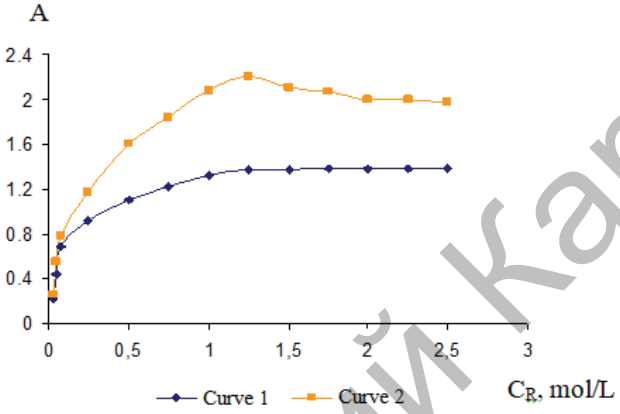
Figure 5 shows the effect of the acidity of the medium on the strength of the resulting complexes (236, 237). It follows from the obtained results that the greatest value of optical density is achieved in the region of pH 8-8.5.



Curve 1 is the dependence for compound 202; Curve 2 is the dependence for compound 203.

Figure 5. Determination of the optimal pH value of the solution

A study of the effect of the reagents (202, 203) concentration required for complete binding of the analyzed ion to the colored compound is shown in Figure 6. It is clear that it is 1.25 mol/L for compound (202), and it is 1.5 mol/L for (203).



Curve 1 is dependence for compound 202; Curve 2 is the dependence for compound 203.

Figure 6. Determination of the amount of reagent required for complete binding of the analyzed ion to the colored compound

Thus, as a result of our research, we determined the optimal conditions for the formation of the most durable complexes of phosphorylated aldehydes (202, 203) with ions of divalent copper, namely the content of ethanol is 50% by volume, 1500-2000-fold excess of reagents (202, 203), respectively, pH of 8-8.5 [194].

Continuing the study in the field of the task, the composition of the complexes synthesized (236, 237) was determined by the slope ratio method.

The slope ratio method (the Harvey-Menning method) is used to study various reactions, which result in one fairly strong M_mR_n complex: $mM + nR \leftrightarrow M_mR_n$.

The experience was put in two series. In the first series, the initial concentration of the reagent (202) C_R and C_{R1} (203) is kept constant and significantly greater than the concentration of the component M (where M is Cu^{2+}), which is taken different: $C_R > C_M$.

It can be assumed that the M component will be completely transferred to the M_mR_n complex due to the large excess of the reagent R (202, 203), whose concentration will be $1/m \times C_M$. Depending on the optical concentration of C_M concentration, the graphic insolubility obtained is presented in Figure 7.

$A_1=k_1C_M/m$ (where k_1 is a coefficient of proportionality) and determine the angular coefficient of this line: $tg\alpha_1= k_1/m$.

In the second series of experiments, the concentration of the component M(C_m) and the concentration of the reactant R, when compared to the analogous conditions are obtained by graphic inset: $A_2=k_2C_R/n$, and the angular coefficient of this line is $tg\alpha_2 = k_2/n$.

Applying the basic law of light absorption to the expressions of optical density A_1 and A_2, the decomposition equation: $A_1 = k_1C_M/m = tg\alpha_1 \times C_M = C_M\varepsilon l/m$ and $A_2=k_2C_R/n=tg\alpha_2 \times C_R=C_R\varepsilon l/n$. At the outset, $tg\alpha_1=\varepsilon l/m$ and $tg\alpha_2=\varepsilon l/n$.

Dividing one equality by another, the ratio of the angular coefficients was obtained, which is equal to the ratio of the stoichiometric coefficients in the formula of the complex M_mR_n in accordance with the expression (1):

$$tg\alpha_1/tg\alpha_2 = n/m \qquad (1)$$

The least squares method was used to calculate the angular coefficients characterizing the dependence of A_1 on C_M and A_2 on C_R in accordance with formulas (2-5), respectively. Data of the spectrophotometric study are presented in Tables 3 and 4, respectively.

Table 3

The values of the concentration of the reagent (202) and optical density

C^1_M mol/L	A_1	C^2_R mol/L	A_2
2.2×10^{-6}	0.103	0.43×10^{-5}	0.091
4.3×10^{-6}	0.215	0.86×10^{-5}	0.196
6.5×10^{-6}	0.316	1.30×10^{-5}	0.296
8.6×10^{-6}	0.407	1.71×10^{-5}	0.388
Note 1 At C_R=const; 2 At C_M=const.			

Table 4

Reagent concentration values (203) and optical density

C^1_M mol/L	A_1	C^2_{R1} mol/L	A_2
2.2×10^{-6}	0.110	0.43×10^{-5}	0.101
4.3×10^{-6}	0.220	0.86×10^{-5}	0.208
6.5×10^{-6}	0.358	1.30×10^{-5}	0.300
8.6×10^{-6}	0.424	1.71×10^{-5}	0.396
Note 1 At C_{R1}=const; 2 At C_M=const.			

$$tg\alpha = \frac{n\sum C_i A_i - C_i \sum A_i}{n\sum C_i^2 - (\sum C_i)^2} \qquad (2)$$

$$tg\alpha_1 = \frac{4\times0.67\times10^{-5} - 2.16\times10^{-5}\times1.04}{4\times1.39\times10^{-10} - 4.66\times10^{-10}} = 4.78\times10^4 \qquad (3)$$

$$tg\alpha_2 = \frac{4\times1.257\times10^{-5} - 4.30\times10^{-5}\times0.971}{4\times1.39\times10^{-10} - 4.66\times10^{-10}} = 2.34\times10^4 \qquad (4)$$

$$\frac{n}{m} = \frac{tg\alpha_1}{tg\alpha_2} = \frac{4.78\times10^4}{2.34\times10^4} = 2.04 \qquad (5)$$

Looking at the components M:R in the complexes (236, 237) equals 1:2, which corresponds to the indices represented in Figure 7 [195].

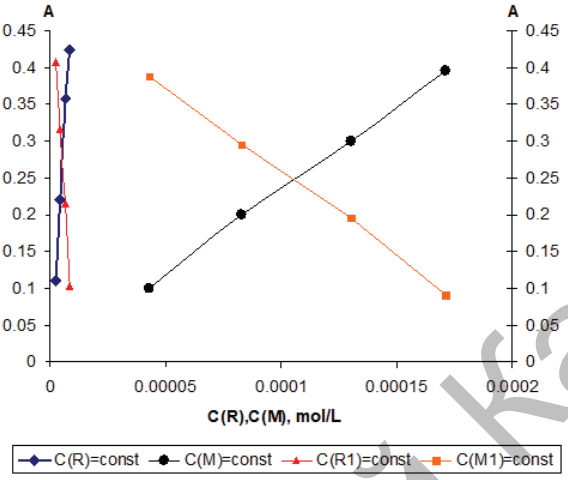


Figure 7. Graphic determination of the ratio of the stoichiometric coefficients m/n of the M_RR_M complexes (236, 237) by the slope ratio method

2.6 The biological activity of some compounds synthesized

Search and creation of a new drug is always associated with both high material costs and the risk of obtaining negative results due to the possible detection of side effects and toxicity. Computer prediction of the main and side effects of a pharmacological substance in the early stages of the study makes it possible to optimize the choice of the basic structures under study and reduce the total costs of research and development [196].

The computer program PASS C & T (Prediction of Activity Spectra for Substances Complex & Training) with a sufficiently high accuracy assesses the probability of a substance displaying various types of biological activity. The prediction is based on the structural formula of a chemical compound and is based on an analysis of the knowledge base, which includes structural formulas and data on the activities of known biologically active compounds. The PASS C & T version of the program predicts more than 900 types of biological activity, including the main and side pharmacological effects,

mechanisms of action, mutagenicity, carcinogenicity, teratogenicity and embryotoxicity. It was shown that the economic efficiency of using preliminary computer prediction of biological activity for planning the synthesis of compounds with the required properties was over 460%. The accuracy of the computer prediction is 300% higher than the experts' predictions [197].

Bioprognosis of basic and hypothetical compounds using the PASS C & T software was performed in order to optimize the choice of initial structures and the ways of their chemical modification. The results of the bioprognosis of compounds synthesized are presented in the Table 5.

As a comparative analysis of computer bioprognosis data shows, in some cases there is a relative increase in the probability of hypothetical compounds manifesting certain types of activity compared to those of the original compounds, and the introduction of various functional groups determines the presence of new biologically active properties. For example, diethylamido-(4-phenylthiazolyl-2-amido)-*tert*-butylphosphite (175) has anti-ulcer activity with a confidence coefficient of 0.752, whereas for 2-amino-4-phenylthiazole, this coefficient is 0.602.

In general, it should be noted that the thiazole fragment causes the compounds to have anti-fungal, anticoagulant, anti-thrombotic, fibrinolytic, anti-asthmatic, anti-ulcer properties, the compounds can also be used to treat Alzheimer's disease and as mucomembrane protectors.

Table 5

PASS C & T results of the computational prediction of biological activity of phosphorylated derivatives of aminothiazole

Compound No.	P_a	P_i	Estimated type of activity
175	0.971	0.002	Anti-inflammatory
	0.954	0.005	Antiallergic
	0.892	0.001	Antipsoriate
	0.872	0.042	Anticoagulant
	0.872	0.042	Antithrombolic
	0.872	0.042	Antifungal

177	0.998	0	Treatment of Amyotrophic Lateral Sclerosis
	0.757	0.027	Stimulator of bone tissue formation
	0.734	0.081	Anti-osteoporotic
	0.734	0.081	Antifungal
	0.699	0.076	Antiulcer
	0.695	0.077	Mucomembrane Protector
	0.538	0.025	Antiallergic
	0.502	0.001	Fibrinogen receptor antagonist
178	0.949	0.040	Antiseborrhoeic activity
	0.734	0.081	Antifungal
	0.743	0.058	Dermatological
	0.711	0.052	Antidote
	0.682	0.049	Treatment of Alzheimer's disease
	0.634	0.098	Anticoagulant
	0.634	0.099	Antitrombic
180	0.980	0.020	Anticoagulant
	0.695	0.020	Psychotropic
	0.532	0.061	Tubular Protector
	0.520	0.014	Anti-neoporotic
181	0.949	0.010	Antitrombic
	0.757	0.027	Antifungal
	0.741	0.036	Tubular Protector
	0.739	0.080	Antiparasitic
	0.695	0.070	Antidote
	0.695	0.056	Fibrinolytic
184	0.800	0.039	Antiparasitic
	0.742	0.031	Anticoagulant
	0.736	0.081	Fibrinolytic
	0.736	0.081	Antiallergic
	0.534	0.001	Antistatic
	0.523	0.027	Psychotropic
189	0.850	0.026	Tubular Protector
	0.850	0.026	Antidote
	0.790	0.014	Treatment of Alzheimer 's disease
	0.750	0.027	Antifungal
	0.630	0.098	Antitrombic
	0.630	0.098	Anticoagulant
	0.630	0.098	Fibrinolytic
200	0.822	0.061	Fibrinolytic
	0.822	0.061	Antitrombic

	0.784	0.076	Anticoagulant
	0.627	0.067	Tubular Protector
	0.545	0.013	Antiparasitic
201	0.833	0.057	Treatment of Alzheimer 's disease
	0.833	0.057	Fibrinolytic
	0.822	0.061	Antitrombic
	0.797	0.070	Anticoagulant
	0.659	0.036	Tubular Protector
	0.617	0.071	Agonist Dopamine D4
208	0.677	0.071	Treatment of Alzheimer 's disease
	0.617	0.071	Antiparasitic
	0.639	0.098	Tubular Protector
	0.634	0.098	Antitrombic
	0.634	0.098	Anticoagulant
	0.634	0.090	Antagonist of thrombocytes
	0.513	0.027	Antifungal
	0.502	0.023	Antiallergic
	0.500	0.078	Psychotropic
215	0.901	0.028	Antitrombic
	0.901	0.028	Antiallergic
	0.834	0.011	Antiparasitic
	0.844	0.027	Anti-Epileptic
	0.844	0.027	Treatment of Alzheimer 's disease
	0.650	0.027	Psychotropic
	0.572	0.018	Nootropic
	0.522	0.008	Treatment of prostate cancer
	0.522	0.008	Antifungal
216	0.867	0.010	Antiparasitic
	0.858	0.068	Tubular Protector
	0.853	0.050	Antitrombic
	0.844	0.027	Antifungal
	0.834	0.011	Antineoplastic
	0.809	0.009	Treatment of Alzheimer 's disease
	0.691	0.020	Antiallergic
	0.650	0.027	Psychotropic
	0.587	0.015	Antidote
	0.572	0.018	Nootropic
	0.522	0.008	Anti-Epileptic
217	0.924	0.003	Antiviral
	0.839	0.055	Fibrinolytic

	0.797	0.017	Antiparasitic
	0.793	0.013	Treatment of Alzheimer 's disease
	0.758	0.027	Antitrombic
	0.743	0.006	Antiallergic
	0.691	0.007	Cytostatic
	0.527	0.129	Fibrinolytic
	0.527	0.129	Anticoagulant

Note
1 P_a is the probability of the biological activity expression;
2 P_i is the probability of the absence of the biological activity.

A number of synthesized compounds passed the test for antilichen activity at the State Scientific Research Veterinary Station (Karaganda).

1-2% Solutions of diethylamido-(4-phenylthiazolyl-2-amido)-benzoylphosphonate, diethylamido-(4-phenylthiazolyl-2-amido)-vinyl acetylphosphonate and 2-amino-4-[diethylamino-(4-phenylthiazolyl-2)aminophosphoryl]thiazole were the objects of the study.

Fifty heads of young cattle of the experimental group were treated, 10 heads for each test compound, 10 – with the "Anti-Lishay" preparation (standard) and 10 heads is the control group with different degrees of damage. Processing took place in two stages and in several farms.

During commission examination, complete treatment of young cattle treated with "Anti-Lishay" (standard) was observed with the appearance of coat in the affected areas of the body.

In animals treated with solutions of compounds of diethylamido-(4-phenylthiazolyl-2-amido)-benzoylphosphonate, diethylamido-(4-phenylthiazolyl-2-amido)-vinyl acetylphosphonate and 2-amino-4-[diethylamino-(4-phenylthiazolyl-2)aminophosphoryl]thiazole, the formation of a crust was observed in the affected areas and a decrease in their number with partial appearance of the coat.

All tested compounds showed an average antilichen activity in the studied dosage forms with suppression of the disease relative to the standard by 58, 62 and 67%, respectively.

2.7 Quantum-chemical interpretation of some reactions of phosphorylated derivatives of 2-aminothiazole

As is known, the interpretation of directions and mechanisms of ambiguously occurring processes in organic chemistry is often difficult. In such cases, modern methods of computer chemistry are a valuable tool allowing calculating significant parameters of substances and processes such as enthalpy change, geometric parameters, charge distribution, and other.

Studying the interaction of phosphorous ester amides with a wide range of electrophilic and nucleophilic reagents, we often encounter the need for a quantum-chemical approach to interpreting certain features of the processes, and it is often necessary and sufficient to determine the thermodynamic parameters.

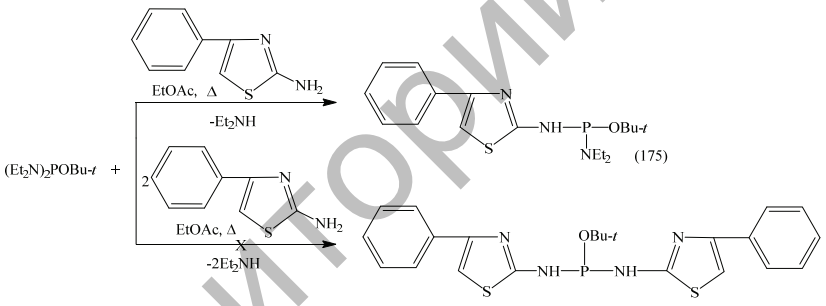
Comparison of data obtained using common semi-empirical methods of calculation with known experimental data makes it possible to recognize the calculation according to the PM3 method as the most suitable for the objects under consideration. The MOPAC program starting from version 6.0 contains the parameters for the three- and tetracoordinated phosphorus atoms and does not need special refinement. In some cases, a certain difficulty is the creation of a Z-matrix using the ChemOffice software package. As a rule, this is caused by a not quite correct transition from two-dimensional graphics to three-dimensional coordinates, so the HyperChem 7.0 package was used to generate the original matrix. In the same program package, preliminary optimization of the molecular structure of molecules by the Mm+ method was carried out. This procedure significantly reduces the time of subsequent calculations. After specifying the MOPAC directives and generating the source file, the correctness of the Z-matrix assignment was visually monitored using the RasWin program, which virtually eliminates incorrect atomic coordinates and bond parameters.

Data on energy parameters are given without zero fluctuations. The total energy value is the sum of the electron energy and the repulsion energy of the nuclei. The energy of atomization of elements was calculated and the experimental values of the heat of formation of elements were used to calculate the heat of formation $\Delta H^0_{f,\,298}$ [198]. The heat of reaction $\Delta H^0_{f,\,298}$ was taken as the difference in the values

of the total energy of the final and initial products of the reaction system.

The process of re-amidation with tetraethyl diamido-*tert*-butyl phosphite with 2-amino-4-phenyl thiazole was chosen to study the calculation method, which turned out to be an interesting example of the mutual influence of enthalpy and steric factors.

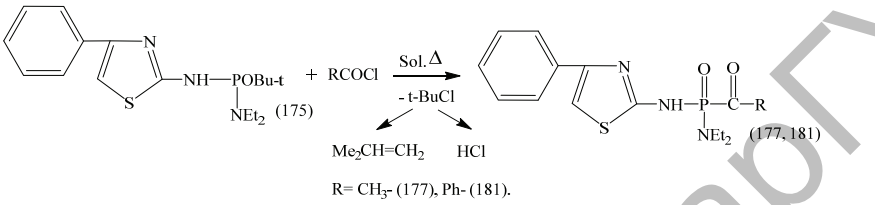
According to the calculation data, the change in enthalpy in the reaction for the formation of compound (175) is -8.20 kJ/mol, whereas this value is positive for the secondary reamidation product and is 307.28 kJ/mol. In addition, calculating the enthalpy of formation of the product of secondary reamidation, we had to resort to the GEO-OK directive, since the program was interrupted due to an excessive increase in the length of the links. Experimentally, the product of bisthiazolidation was also not possible to isolate even when the process was carried out under very harsh conditions.



Among the processes, proceeding with a change in the valence of the phosphorus atom, the classical and non-classical reactions of A.Ye. Arbuzov, in the series of *tert*-butylamidophosphites, are carried out especially easily. Taking into account the presence of several nucleophilic centers, it was interesting to model mathematically the reactions of compound (175) with acetic and benzoic acid chlorides resulting in the formation of ketophosphonates (177, 181).

According to the calculation data, the change in enthalpy in both processes is a positive value of about 104.00 kJ/mol, that is, the enthalpy factor impedes the process, but in practice both reactions proceed, and very actively. It seems justified to assume that the decisive role in this case is played by a significant increase in entropy

during the process, namely three molecules are formed from two, and two of them are gaseous substances at normal conditions (isobutylene and hydrogen chloride).



In continuation of the studies, the formation of glycidic esters (200, 201), phosphorylated aldehydes (202, 203) and 2-amino-4-[diethylamino-4-phenylthiazolyl-2)amino-phosphoryl]thiazole (189) were chosen as model systems for calculations. As follows from the calculated data, the heats of the reactions of the formation of glycidic esters (200, 201), phosphorylated aldehydes (202, 203) and 2-amino-4-[diethyl-amino-(4-phenylthiazolyl-2)aminophosphoryl]thiazole (189) are negative values, which indicates the occurrence of these processes with a significant energy gain.

Summarizing the above, it can be argued that the total energy of the system during all reactions tends to decrease its value, and the heats of reactions have negative values, which indicates the prospects for the reactions under study. Electronic and steric effects play a decisive role in the reactions of *tert*-butyldiamidophosphites with nucleophiles, whereas the entropy factor is decisive in the reactions with the formation of isobutylene.

2.8 Modification of nitrogen containing heterocyclic compounds

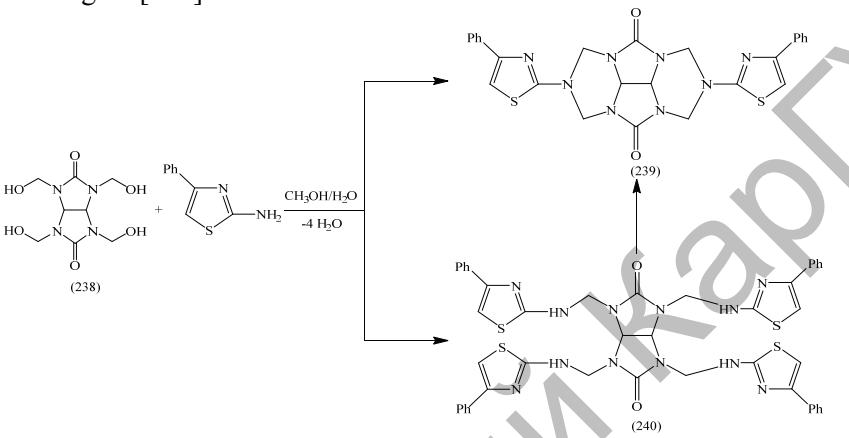
Heterocyclic compounds are an extensive class of organic molecules with an inexhaustible complex of practically useful properties. It has already been noted that thiazoles and their derivatives occupy a special place among them. Compounds of the thiazole series are of great importance for pharmaceutical production, biochemistry, technology, clinical and experimental medicine. In medicinal chemistry, thiazole derivatives are important compounds in view of a wide spectrum of biological activity. This class of heterocyclic compounds is used as anti-inflammatory, tuberculosis, antibacterial, antimicrobial, insecticidal, fungicidal pharmaceuticals, as well as local anesthetics and tranquilizers [199].

An urgent task of modern organic chemistry is to search for new methods for the directed synthesis of compounds with different biological activities. A wide range of compounds can be obtained through combinatorial chemistry. The introduction of the thiazole moiety into the structure of an organic compound makes it possible to obtain a wide range of compounds [200]. Various methods are used for the synthesis of organic compounds of various structures. One of such methods for the introduction of the thiazole ring is the functionalization of the existing active centers. The amino group can be easily transformed into the sulfamide, urea, carbdiamide, and other groups.

From this point of view, the possibility of chemical modification of glycoluril derivatives was investigated in order to obtain new azaheterocycles containing thiazole fragment. Considering the possibility of a synergistic effect when modifying glycoluril derivatives, which are of interest as synthons in the synthesis of biologically active substances, a thiazole ring was introduced as a pharmacophoric group. This modification was carried out using tetramethylolglycolyril (238) as a synthon, which contains reactive OH groups, and 2-amino-4-phenylthiazole, which can be condensed by a free amino group, as a reagent.

For this purpose, the condensation reaction of (238) with 2-amino-4-phenylthiazole as a representative of polyfunctional heterocyclic amines has been studied. As a result of research, we

found that the direction of the reaction of the interaction of the above-mentioned compounds depended primarily on the molar amounts of the reagent [201].



Thus, it is shown that 3,9-bis-[2-(4-phenyl)thiazolyl]-1,3,5,7,9,11-hexaazatetracyclo [5.5.2.$0^{3,14}$.$0^{9,13}$]tetradodecane-6,12-dione (239) is formed as the main product of azaheterocyclization with a yield of 64% when the reaction proceeds for 4 hours using a two-fold excess. When a fourfold excess of (238) is introduced into a similar reaction, the main condensation product is 2,4,6,8-tetramethylamino[2-(4-phenylthiazolyl]-2,4,6,8-tetraazabicyclo-[/3.3.0 /octane-3,7-dione] with a yield of 58%.

Low yields of previously unknown azaheterocycles (239) and (240) are mainly related to the fact that under the studied conditions side reactions of autocondensation products of (238) with 2-amino-4-phenylthiazole occur with the formation of a complex mixture of different molecular compounds of unknown structure (the presence of aminothiazole in these compounds the fragment has been reliably proven using NMR spectroscopy data) [202].

In addition, we have shown that (240) acyclicizes in 4 hours with a good yield (84%) to compound (239). This may indicate that synthesis of (239) most likely passes through formation as an intermediate product (240).

The structure of (239) is proved by spectral methods: IR spectrum (KBr), ν, cm^{-1}: 1706 (C=O), 1604 (C=C), 1476 (C=N). ^1H

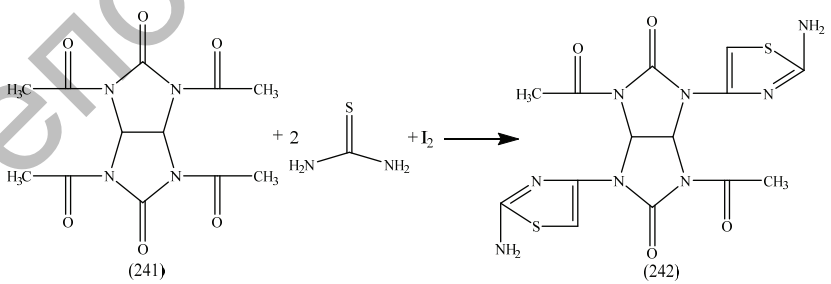
NMR spectrum (DMSO-d_6), δ, ppm: 3.34 d.d (8H, N-CH_2-NC(O), 4.74 s (4H, (O)CNCHNC(O)), 5.58 s (4H, H^5 thiazole), 7.71-7.25 m (20H, C_6H_5). ^{13}C NMR spectrum (DMSO-d_6), δ C, ppm: 62.985 (NCH_2NC(O)), 72.589 [(O)CNCHNC(O)], 127.675, 128.701, 129.004, 129.988 (C_{arom}), 116.543 (C^5 thiazole), 135.674 (C^2 thiazole), 152.756 (C^4 thiazole), 167.822 (C=O).

Spectral characteristics of (240): IR spectrum (KBr), ν, cm^{-1}: 3391 (N-H), 1684 (C=O), 1618 (C=C), 1474 (C=N). ^{1}H NMR Spectrum (DMSO-d_6), δ, ppm: 3.15 s (8H, $HNCH_2N$), 4.71 s (2H, (O)CNCHNC(O)), 5.51 s (4H, H^5 thiazole), 7.700-7.25 m (20H, C_6H_5), 8.59 broad s (4H, NH).

However, the introduction of the thiazole ring by its direct construction with glycoluril seemed to us more interesting and promising. You can use di- and tetraacetyl derivatives capable of creating a thiazole cycle according to the classical Hantzsch reaction scheme for this modification.

It is known that Hantzsch synthesis is one of the most commonly used methods for the preparation of compounds possessing a 2-aminothiazole ring. Various carbonyl compounds, thiourea and its derivatives enter into this reaction. It is necessary to carry out the reaction in the presence of molecular iodine in the case of using non-halogenated ketones.

In accordance with the above, the reaction of tetraacylated glycoluril (241) with thiourea in the presence of iodine was carried out, which resulted in the previously unknown thiazole derivative of glycoluril 2,6-di(2-amino-1,3-thiazolyl-4)-4.8-diacetyl-2,4,6,8-tetraaza-bicyclo [3.3.0.]octane-3,7-dione (242).



(241) (242)

The effect of the ratio of thiourea and iodine in the reaction mixture was investigated to optimize the reaction. In accordance with the literature data [203], two mole of thiourea for each mole of halogen must be present in the reaction mixture for the formation of a thiazole ring. It was found that the yield of the targeted product decreased when reducing the proportion of thiourea.

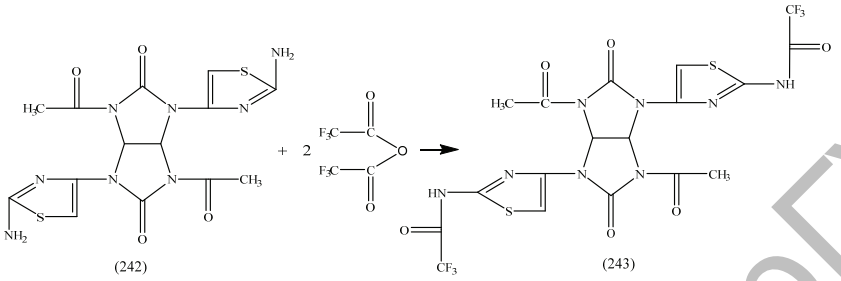
Thus, King and Raiden [204] reported that the formation of thiazole from acetophenones and thiourea was an oxidative process. Thus, the reaction passes through the interaction of iodine with the thiourea dimer. This fact partially explains the need to use two equivalents of thiourea. Various amounts of iodine were investigated in order to determine the most optimal concentration of iodine for the synthesis of the 2-aminothiazole moiety. It was found that a significant decrease in yield was observed when using less than one equivalent of iodine. Thus, it was found that two equivalents of thiourea and one equivalent of iodine formed one corresponding 2-aminothiazole fragment.

The hydroiodide 2,6-di(2-amino-1,3-thiazolyl-4)-4,8-diacetyl-2,4,6,8-tetraazabicyclo[3.3.0.]octane-3,7-dione obtained was transferred to the corresponding free amine by the action of ammonium hydroxide [205].

There are absorption bands at 1479, 1666, 1769, 3113, 3296 cm^{-1} related to vibrations of C=C, C=O, C=N, $COCH_3$, NH_2 bonds, respectively, in the IR spectrum of compound (242).

Four protons of the amine fragment give a signal in the region of 7.25 ppm, two protons of the thiazole fragment are detected as a singlet at 1.54 ppm, and six protons of the acyl group resonate with a signal at 2.54 ppm in the ^1H NMR spectrum.

The confirmation of the structure of the synthesized glycoluril derivative (242), as well as the solution of the question of further chemical modification, is the functionalization of the free amino group of the thiazole ring. For this purpose, the acylation of the amino group (242) with trifluoroacetic anhydride was carried out. As a result, N,N'-((4,8-diacetyl-2,4,6,8-tetraazabicyclo-[3.3.0.]octane-3,7-dione)-2,6-di(4-thiazoldiyl-2)-di(2,2,2-trifluoroacetamide) (243) was obtained [206].



(242) (243)

It has been found that the absorption bands characteristic for the stretching vibrations of the primary NH_2 groups are absent in the IR spectrum (243), and the signals characteristic of the amine proton are absent in the ^1H NMR spectra; but signals in the region of 8.14 ppm were detected corresponding to the proton of the two amide groups, two protons of the thiazole fragment are also found in the form of a singlet at 0.86 ppm, six protons of the acyl group resonate with a signal at 2.04 ppm.

CONCLUSION

A large number of scientific studies are devoted to the synthesis and investigation of reactivity, various kinds of biological activity of heterocyclic compounds. Derivatives of phosphorylated thiazoles are widely known as compounds of interest from the standpoint of the wide possibilities of studying high reactivity, as well as manifestation of a wide range of different types of biological activity.

It is known that the thiazole ring plays a significant role in many biochemical processes in a living organism, which causes great interest in the chemistry of these compounds from various points of view. The enzyme carboxylase, the antitumor drug "Imifos" and many others are known among the phosphorylated derivatives of 2-aminothiazole.

Organophosphorus compounds are also known for their biologically active properties. Thus, phosphonic acids are widely used in clinical practice as analgesic, antipyretic, and anti-arthritic drugs.

Undoubtedly, the combination in the structure of such valuable pharmacophore objects as the thiazole cycle and various organophosphorus fragments will be very valuable and promising in the synthesis of new drugs, as well as other practically useful objects including polydentate complexones with significant stability and efficiency of their application.

The monograph presents the following research results:

1. For the first time in the chemistry of thiazole, the synthesis of *tert*-butyl esters of amidophosphorous acid was carried out and their structure was established using IR and ^{1}H NMR spectroscopy.

2. The reactivity was studied and the mechanisms of reactions of synthesized *tert*-butyl esters of amidophosphorous acid with some electrophilic reagents were proposed.

3. Optimal synthesis routs have been developed and general and specific patterns of the chemical behavior of thiazolyl-containing phosphorylated glycidic esters, oxyphosphonates, phosphorylated aldehydes, 2-amino-4-[diethylamino-4-phenylthiazolyl-2)amino-phosphoryl]thiazole have been established.

4. A number of new organophosphorus complexones have been synthesized based on 2-amino-4-phenylthiazole and its functional derivatives. The complex-forming ability of the synthesized thiazolyl-

containing phosphorylated aldehydes was studied by the method of spectrophotometric analysis and the composition of the complexes has been determined.

5. New compounds obtained in the course of the study are model systems that are interesting from the point of view of studying their reactivity, regioselectivity of the process, which is a definite contribution to the development of the practice of fine organic synthesis, theoretical concepts and modern concepts in the field of organic chemistry and chemistry of organophosphorus compounds.

6. As a result of the research carried out, the ways of possible practical application of the compounds synthesized have been determined. Compounds with antilichen activity have been found.

Scientific studies presented in the monograph have been carried out at the Department of Organic Chemistry and Polymers of the Buketov Karaganda State University, at the Institute of Natural Resources of the National Research Tomsk Polytechnic University (Tomsk, Russia), at the Charles University in Prague (Czech Republic) as well as in the laboratory of chemistry of phosphorus and fluorine-organic compounds of the Jacobs University of Bremen (Bremen, Germany).

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CONTENTS

Scientific publication

Minayeva Ye.V., Salkeyeva L.K.

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Monograph

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