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### **Study of degree of basicity of 2-amino 4-phenylthiazole and 2-amino-4-oxothiazole by mineral acids protonation**

There was studied protonation of aminothiazoles of mineral acids of different strength in order to research the basicity of nitrogen atoms of free amino group and nitrogen of thiazole ring. The results obtained showed high ambidenty of 2-amino-4-phenylthiazole and 2-amino-4-oxothiazole associated with a high degree of delocalization of both the lone pair of electrons of the amino group and the thiazole ring nitrogen atom which creates opportunities for chemical modification of the aminoheterocycles with the free amino group and the ring nitrogen atom. Complexing ability of 2-amino-4-oxothiazole with cobalt (II) chloride caused by high degree of basicity of cyclic nitrogen atom was also studied.

*Key words:* aminoheterocycles, aminothiazoles, mineral acids, protonation, ambidenty, basicity, nucleophilicity, complexones.

It is known that interest to heterocyclic compounds is associated with a wide variety of biologically active properties characteristic for representatives of this class. In particular it does not cease the interest to azaheterocyclic compounds, including derivatives of thiazole, having great importance for the pharmaceutical industry, biochemistry, technology, clinical and experimental medicine. Thiazole derivatives possess antiviral, antiparasitic, antipyretic, antihemolytic, antihypertensive properties and are widely used in medical practice [1]. They are also used in engineering as effective components of the polymeric materials which increase their stability, possess the ability to inhibit the oxidation and corrosion processes, and exhibit complexing properties.

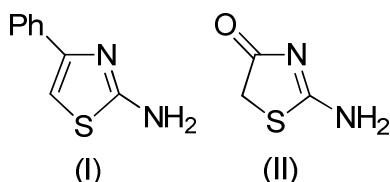
Among practically important thiazole derivatives mercaptothiazoles used as vulcanization accelerators in the rubber industry are well known [2].

Continuing investigations in the field of search and the synthesis of new interesting in practical terms thiazole derivatives, it seems interesting for us to continue researching the structural features of this class of compounds due to the dual reactivity. In this aspect as subjects of research we selected 2-aminothiazole derivatives known to have great importance for the pharmaceutical industry, biochemistry, technology, clinical and experimental medicine. A feature of these compounds is associated with the presence of the free amino group and a nitrogen atom of the heterocycle.

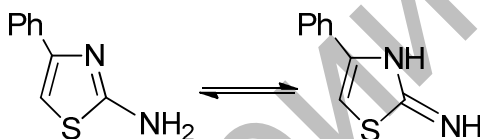
Among the best known amine derivatives of thiazole are 2- and 5-aminothiazoles which can exist in two tautomeric forms but with an evident predominance of the amino form that creates opportunities for their experimental studies aimed at the synthesis of compounds with practically useful properties.

2-Amino-4-phenylthiazole and 2-amino-4-oxothiazole were chosen as subjects of this study. These compounds are characterized by a number of structural features associated with the possibility of high delocalization of the lone pair of electrons (LPE) of the nitrogen atom of free amino group and the nitrogen atom of the heterocycle, and obviously allowance must be made for the presence of the exocyclic carbonyl group

in 2-amino-4-oxothiazole which is also capable to participate in the resonance. The presence of the phenyl substituent in the 4 position of the ring undoubtedly contributes to the distribution of the electron density in the molecule. The study of the influence of electronic and structural factors on the chemical behavior of the subjects investigated makes it possible to predict and control the behavior of such structures in the reactions of chemical modification. In this regard we consider that study of the processes of protonation may shed light on the behavior of the reaction centers under different conditions, as the usage of mineral acids of different strength may determine the most important nucleophilic center.



2-Aminothiazole is known to have sufficiently low basicity ( $pK_a$  5.39). The chemical structure of 2-amino-4-phenylthiazole suggests the possibility of chemical modification involving the free amino groups and electrophilic substitution reactions in the thiazole ring in the position 5. Some references confirm the ease of electrophilic substitution in position 5 and ease of nucleophilic substitution at the position 2 [3–5]. Nevertheless the presence of LPE at the extracycle nitrogen atom enhances the degree of aromaticity of the thiazole ring due to delocalization. This factor generally reduces the nucleophilic properties of the free amino group, but an increase in the basicity and nucleophilicity of the nitrogen atom of the ring is observed. All these factors taken together cause ambident behavior of 2-amino-4-phenylthiazole in reactions with electrophilic reagents, in particular the possibility of intramolecular proton transfer.



In this regard the study of the intramolecular proton transfer process using mineral acids of different strength will clarify determination of degree of the nucleophilicity of the nitrogen atoms and, consequently, the direction of the reactions with various electrophiles.

There are quite controversial opinions in the literature relative to the basicity of free amino group in the aminothiazole. So it is known that the lone pair of electrons of the nitrogen atom can easily enter into conjugation with thiazole ring which ultimately reduces the basicity of the amino group.

On the one hand the presence of LPE at the nitrogen atom of the thiazole ring can increase its nucleophilicity and hence reactivity in regard to different electrophiles, and on the other hand increases the basicity and nucleophilicity of the free amino group.

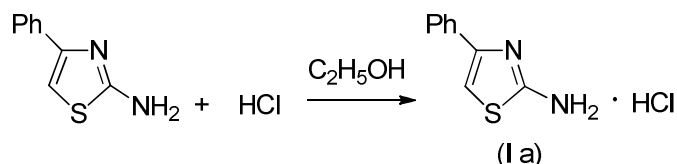
All of these factors together create conditions for ambident behavior of molecules of substituted 2-aminothiazoles in reactions with electrophilic reagents.

Thus research of direction of electrophiles attack, in particular the ability to form salts with one equivalent of a mineral acid, is highly informative regarding to basicity of exocyclic nitrogen atom of the amino group and the nitrogen atom of the thiazole ring.

Usage of mineral acids with different degrees of acidity can solve the problem to some extent. For this purpose concentrated hydrochloric acid ( $pK_a$  7.0), nitric ( $pK_a$  1.64) and sulfuric acids ( $pK_a$  3.0) were used.

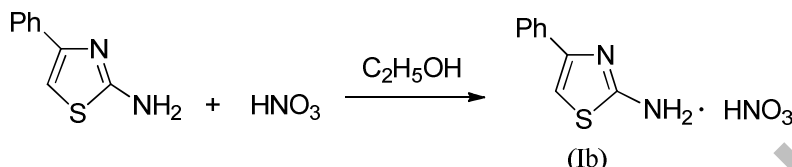
Study of protonation reactions of aminothiazole derivatives by mineral acids of different strength and structure of salts synthesized determines the strength of basicity and nucleophilicity of the free amino group and the ring nitrogen atom. Obviously during the research at least basicity and nucleophilicity of the free amino groups are changed symbatically.

The reaction of 2-amino-4-phenylthiazole (I) with hydrochloric acid was carried out in ethanol under heating for 2 hours, then upon cooling there was observed precipitating yellow crystals of thiazole hydrochloride (I), which a melting point exceeds significantly the melting point of the starting material and is 220 °C. Control of the reaction was monitored by TLC.

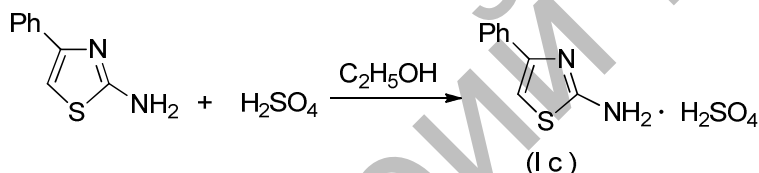


Investigation of (Ia) salt structure by IR and NMR spectroscopy indicates the presence of the bound amino group giving the evidence of the significant broadening of absorption bands in the 3300–3400  $\text{cm}^{-1}$ .

We used nitric acid as stronger acid, and the reaction is also carried out in ethanol under heating. Nitrate salt of blue color was separated upon reaction (m.p. 168 °C). (Ib) Salt structure was also confirmed by IR and NMR spectroscopy proving protonation at the nitrogen atom of free amino group.



To complete the study of protonating ability of sulfuric acid with respect to 2-amino-4-phenylthiazole was investigated. The reaction was carried out under similar conditions, as a result of which was salt of dark brown color obviously due to strong oxidation and carbonization of substance through the activated aromatic system was obtained. According data of spectral studies salt structure corresponds to the hydrosulfate of the aminothiazole (Ic) according to the following scheme:

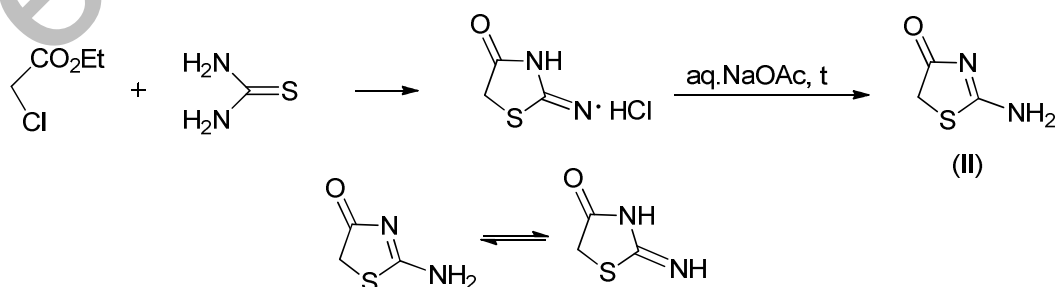


The results obtained testify to the high basicity of the free amino group which with forms the corresponding ammonium salts with one equivalent of strong mineral acids. The structure of salts obtained was proved by spectral methods.

As another subject of the study we selected 2-amino-4-oxothiazole which structure is distinguished by the presence of the exocyclic carbonyl group capable of additional polarization and delocalization due to the ring nitrogen atom and amino group. The presence of the C=O group can significantly affect the redistribution of the electronic density of the aminothiazole ring, because the polarization of the delocalized system in the direction of an oxygen atom can significantly decrease the basicity and thus nucleophilicity of the free amino group.

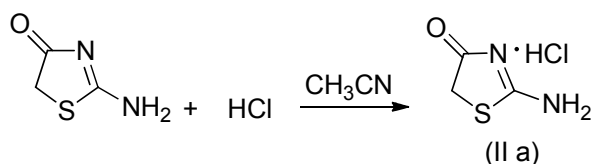
The starting 2-amino-4-oxothiazole was prepared according to a well-known procedure by interacting ethyl ester of monochloroacetic acid with thiourea in 95 % ethanol. After dissolving in 1.2 l hot boiled water crude hydrochloride obtained was treated with an aqueous solution of sodium acetate. Yield of the target product, m.p. 255–258 °C, was 79–82 %. The structure of compound obtained was confirmed by  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR spectra.

The reaction proceeds according to the following scheme:



Protonation of the 2-amino-4-oxothiazole by hydrochloric acid was carried out in acetonitrile while heating for several hours at the reflux temperature, following cooling of reaction mixture leads to precipitation of the desired salt (IIa).

The reaction proceeds according to the following scheme:

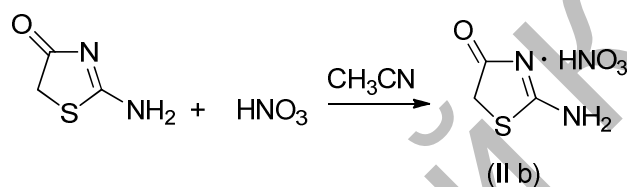


The results of spectral studies confirm the occurrence of protonation at the nitrogen atom of the thiazole cycle since IR-spectrum contains two absorption bands of free amino groups in the  $3300\text{ cm}^{-1}$ . The resulting salt is a crystalline yellow solid, m.p.  $200\text{ }^{\circ}\text{C}$ .

Undoubtedly the basicity of the free amino group is significantly reduced due to a significant resonance with the LPE of cyclic nitrogen atom, which in its turn is delocalized with  $\pi$  — electrons of the  $\text{C}=\text{O}$  bond.

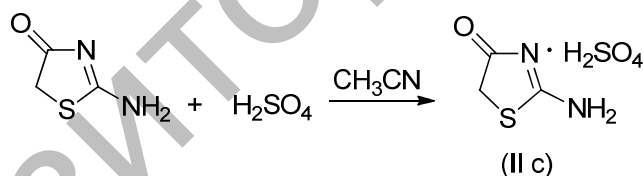
Thus the resonance with the participation of an electron pair of the free amino group has the greatest influence on the distribution of the electron density in the thiazole ring which is obviously due to its enhanced donor capacity.

To confirm these assumptions we used nitric acid as a stronger acid. The reaction was also carried out in acetonitrile under heating. After heating for 2 hours nitrate salt of blue color (IIb) was separated (m.p.  $153\text{ }^{\circ}\text{C}$ ).



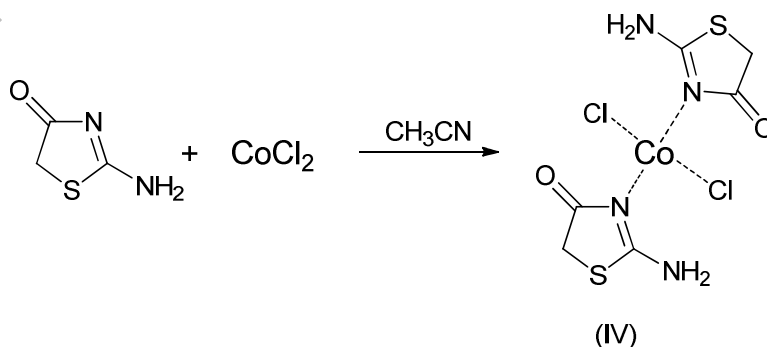
To complete the study we investigated the protonating ability of sulfuric acid with respect to 2-amino-4-oxothiazole. The reaction is carried out under the same conditions, thus compound obtained was colored in dark brown. Obviously coloring recess as in the case of aminothiazole (I) is caused by the strong oxidation and degradation due to activation of the thiazole ring as a result of coupling of free amino group with a conjugated system  $\text{C}=\text{N}-\text{C}=\text{O}$ .

We believe that the structure of the resulting salt (IIc) corresponds to the following scheme:



The findings of the research carried out show sufficient basicity of the cyclic nitrogen atom of 2-amino-4-hydroxythiazole due to conjugation of electrons of the amino group with a cyclic nitrogen atom, which in its turn is conjugated with the strongly polarized carbonyl group.

The structure of 2-amino-4 oxothiazole synthesized assumes its complexing ability which we showed at investigating its reaction with cobalt chloride with gentle heating for 24 hours in acetonitrile upto reflux.



The high degree of basicity of the cyclic nitrogen atom is eloquently confirmed by its ability to coordinate with the vacant d-orbitals of cobalt (II) chloride. Thus as a result of studies of complexing ability of 2-amino-4-oxothiazole chloride with cobalt (II), stable complex (IV) of blue colour was obtained, m.p.  $260\text{ }^{\circ}\text{C}$ .

The structure of the complex obtained was confirmed by X-ray diffraction, according to which the complexation of 2-amino-4-oxothiazole with cobalt (II) chloride proceeds on a cyclic nitrogen rather than the free amino group (see Fig.).

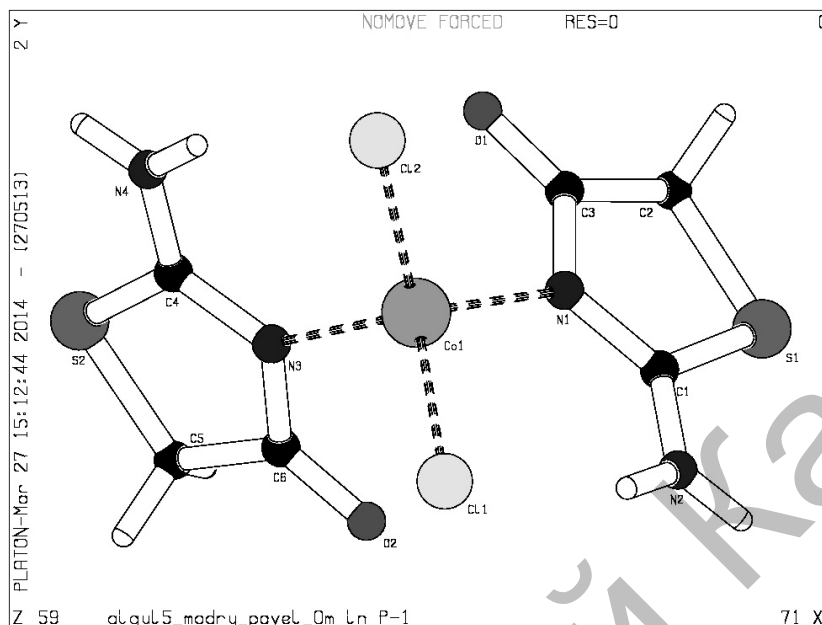


Figure. X-ray analysis of the complex of 2-amino-4-oxothiazole with cobalt (II) chloride

Moreover according to the computer bioprognostication data the complex obtained potentially possesses pharmacological activity such as antiparasitic, antiasthmatic, antiallergic, psychotropic, antiepileptic, and no doubt can be widely used in medical practice.

As a result of the study of protonation reaction of 2-amino-4-oxothiazole by mineral acids of different strength of acidity, it was found that the basicity of the nitrogen atom of the ring is much higher than basicity of the free amino group. X-ray diffraction proved the possibility of chelation of 2-amino-4-oxothiazole with cobalt (II) chloride, and the structure of the complex obtained was established indicating the higher basicity of the cyclic nitrogen atom of 2-amino-4-oxothiazole.

Thus the results obtained show a high ambidentivity of 2-amino-4-phenylthiazole and 2-amino-4-oxothiazole caused by the high degree of delocalization of both the lone pair of electrons of the amino group and the one of the ring nitrogen atom which creates great opportunities for chemical modification of such aminoheterocycles with participation of the free amino group and the ring nitrogen atom.

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### **Минералды қышқылдармен протондау арқылы 2-амино-4-фенилтиазолдың және 2-амино-4-оксотиазолдың негізділік деңгейін зерттеу**

Бос амин тобының азот атомы және тиазол сақинасының азот атомының негізділігін зерттеу мақсатымен аминотиазолдардың күші әр түрлі минералды қышқылдармен протондануы зерттелді. Алынған мәліметтер амин тобының бөлініспеген электрон жұбының және тиазол сақинасындағы азот атомының делокализациялану деңгейінің жоғарылығымен байланысқан, 2-амино-4-фенилтиазолдың және 2-амино-4-оксотиазолдың жоғары амбиденттігін көрсетті. Бұл осындай гетероциклдердің бос амин тобының және сақинадағы азот атомының қатысуымен химиялық түрленулерін жүргізуге кең мүмкіндіктер береді. Сонымен қатар циклдегі азот атомының жоғары негізділігімен байланысты 2-амино-4-оксотиазолдың кобальт (II) хлоридімен комплекс түзу қабілеті зерттелді.

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### **Исследование степени основности 2-амино 4-фенилтиазола и 2-амино-4-оксотиазола путем протонирования минеральными кислотами**

Изучено протонирование аминотиазолов минеральными кислотами различной силы с целью исследования основности атомов азота свободной аминогруппы и азота тиазольного цикла. Полученные результаты показали высокую амбидентность 2-амино-4-фенилтиазола и 2-амино-4-оксотиазола, связанную с высокой степенью делокализации неподеленной пары электронов как аминогруппы, так и атома азота тиазольного кольца, что создает широкие возможности химической модификации подобных аминогетероциклов с участием свободной аминогруппы и атома азота кольца. Также была изучена комплексобразующая способность 2-амино-4-оксотиазола с хлоридом кобальта (II), обусловленная высокой степенью основности циклического атома азота.