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**INTRAMOLECULAR HETEROCYCLIZATION OF HYDRAZIDE  
N-ANABASINIL ACETIC ACID DERRIVATIVES****S. D. Fazylov<sup>1</sup>, O. A. Nurkenov<sup>1</sup>, Zh. B. Satpayeva<sup>1</sup>, A. K. Svidersky<sup>2</sup>,  
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**Key words:** anabasine, hydrazide, 1,3,4-oxadiazole, thiosemicarbazide, 1,2,4-triazole-3-thione.

**Abstract.** The results of studying the reaction of hydrazide N-anabasinil acetic acid with orthoformic ether and various isothiocyanates are given. There were studied influence of various factors (temperature, reaction time and the ratio of reactants) to possible formation mechanisms of 1,2,4-triazole-3-thionic and allyl(phenyl)thiosemicarbazides derivatives of hydrazide N-anabasinil acetic acid. It was found that by acidifying the aqueous alkaline solutions of allyl(phenyl)thiosemicarbazides derivatives of hydrazide N-anabasinil acetic acid, they readily undergo intramolecular heteroring with creation of 4-allyl(phenyl)-5-anabasinomethyl-1,2,4-triazole-3-thiones. The obtained compounds are very promising in terms of studying the antibacterial properties. Composition and structure of the new obtained compounds are proved by elemental analysis and <sup>1</sup>H NMR spectroscopy.

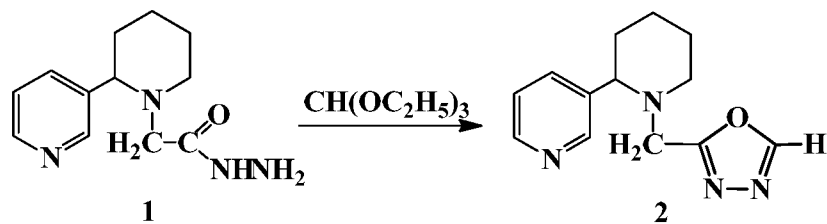
Promising model compounds in the search for new biologically active compounds are derivatives of hydrazine [1]. Hydrazine and its derivatives have been known since the early twentieth century as easily accessible physiologically active substances broad spectrum having antimicrobial, anti-tuberculosis, antiviral, anti-tumor and other types of activity at a relatively low toxicity. [2] Organic derivatives of hydrazine are studied in different schools of organic chemistry. Known to date information on the methods of synthesis of compounds based on hydrazides suggests the possibility of getting on their basis of biologically active substances and practically useful.

Hydrazides – are a reactive nucleophilic agents and which are able to react with various electrophilic reagents to form a large number of various substances. Thus, they react with carboxylic acids, acid chlorides, anhydrides, esters, alkyl halides (aryl), aldehydes and ketones to easily align with the unsaturated compounds to form various nitrogen-containing heterocycles [3, 4].

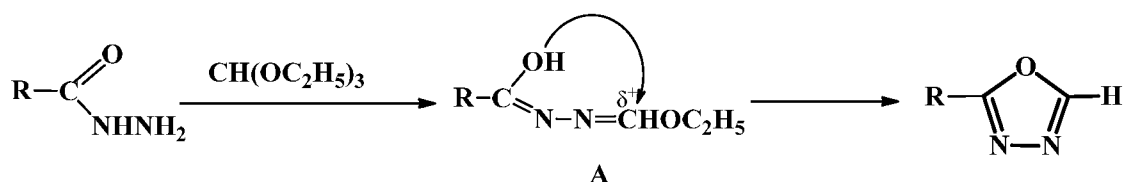
Anabasine fragment is known, still attracts the attention of synthetic chemists involved in the synthesis and the search for new insecticides and antibacterial agents [5]. Among the various derivatives of anabasine the compounds with high aphicidal [6], antimicrobial [7], antitrichofitoze [8] and other properties had been found. Combining in a single molecule hydrazide and anabasine fragments may lead to increased or the appearance of a new kind of bioactive actions.

In order to further modify the hydrazide N- anabasinil acetic acid (1), as well as attempts to produce on its basis 1,3,4-oxadiazole was held with its condensing orthoformic ester. The starting hydrazide N-anabasinil acetic acid (I) was prepared as described [9]. Orthoformic ester is widely used in organic chemistry for the synthesis of various heterocyclic systems [10]. In particular, in [11] work described the using of orthoformic ester in the synthesis of 1,3,4-oxadiazoles from the carboxylic acid hydrazides.

The formation of 2-substituted 1,3,4-oxadiazole (2) occurs by reacting the hydrazide N-anabasinil acetic acid (1) with a threefold amount of orthoformic ester by refluxing the reaction mixture during 25 hours according to the following scheme:



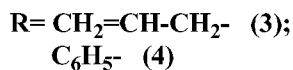
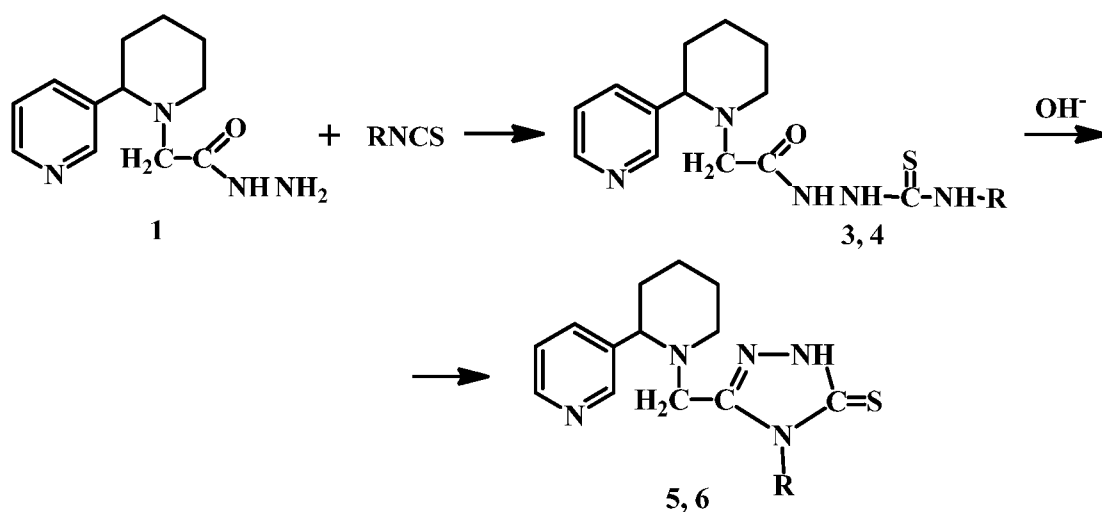
It is shown that the formation of 2-substituted 1,3,4-oxadiazole (2) is probably proceeds through the formation of intermediate (A) when attached to the ester reactant  $\beta$ -atom hydrazo-group, cleavage of two molecules of ethyl alcohol and passing hydrogen atom from  $\alpha$ -nitrogen the same group on the carbonyl oxygen. This reaction center intermediate for further transformation is positively charged carbon atom in the azo-methine group. Thus, the carbonyl carbon atom of the intermediate (A) is preferable to attack the center of the reaction of nucleophilic reagent - the oxygen atom of the hydroxyl group and subsequent cyclization of the passage to form a five-membered product (2).



The compound 2-(anabasinil)methyl-1,3,4-oxadiazole (2) is a milky powder substance soluble in various solvents.

The composition and structure of 2-(anabasinil)methyl-1,3,4-oxadiazole (2) were confirmed by elemental analysis, IR- and  $^1\text{H}$  NMR-spectroscopy.

In continuation of research by the modification hydrazide of N-anabasinil acetic acid (1) we have performed the synthesis of allyl(phenyl)thiosemicarbazide derivatives (3, 4), by reacting the hydrazide of N-anabasinil acetic acid (1) with allyl(phenyl)isothiocyanates in ethanol yields with 55% and 74%. Cyclization of thiosemicarbazide derivatives (3, 4) was carried out in an aqueous alkaline medium by heating the reaction to 80-85°C. In the presence of an alkali N-allyl (phenyl)thiosemicarbazides of N-anabasinil acetic acid (3, 4) further by acidifying we have formed 4-allyl(phenyl)-5-anabasinemethyl-1,2,4-triazole-3-thiones (5, 6).



The synthesized compounds (5, 6) are white crystalline solids, soluble in many polar and nonpolar organic solvents.

The composition and structure of the synthesized compounds (5, 6) were confirmed by IR- and  $^1\text{H}$  NMR-spectroscopy.

In the  $^1\text{H}$  NMR-spectrum of compound (4) all protons match the expected values of the chemical shifts. NH-protons of thiosemicarbazide fragment appear like widened and narrow singlet at 9.8 ppm, 4.10 ppm and 13.72 ppm. Protons of anabasine fragment appear in the expected regions of the spectrum. The analysis of the  $^1\text{H}$  NMR-spectrum of 4-phenyl-5-anabasine methyl-1,2,4-triazole-3-thione (6) shows that the protons of the piperidine and pyridine rings are shown in their characteristic spectral region. Methylene protons  $\text{H}^6$ ,  $\text{H}^7$ ,  $\text{H}^8$  of the piperidine ring are shown in the multiplet at 1.20-1.65 ppm. Methine proton  $\text{H}^5$  triplet appears not in its typical area of about 3.02 ppm, and in a stronger field at 2.96 ppm. Pyridine ring protons  $\text{H}^1$  and  $\text{H}^3$  are shown like doublet at 8.36 ppm and 7.28 ppm, the protons  $\text{H}^2$  and  $\text{H}^4$ , respectively doublet-doublet and a singlet at 7.07 ppm and 8.14 ppm. Protons of the phenyl ring resonate in a weak field at 7.54-7.56 ppm, as a multiplet complex. Thioamide N-H proton of triazole ring is shown in a rather narrow singlet downfield region of the spectrum at 13.73 ppm.

The main physico-chemical characteristics and the elemental analysis of the synthesized compounds (2-6) are shown in Table.

Physico-chemical constants, elemental analysis of the synthesized compounds (2-6)

Comp.	Yield, %	$T_{\text{mp.}}$ , °C	Found, %			Empirical Formula	Calculated, %		
			C	H	N		C	H	C
2	34	180-181	64,22	6,85	23,10	$\text{C}_{13}\text{H}_{16}\text{N}_4\text{O}$	63,91	6,60	22,93
3	55	146	57,91	7,25	21,35	$\text{C}_{16}\text{H}_{23}\text{N}_5\text{OS}$	57,63	6,95	21,00
4	74	100-102	61,98	6,55	19,19	$\text{C}_{19}\text{H}_{23}\text{N}_5\text{OS}$	61,76	6,27	18,95
5	85	111-113	61,20	6,98	22,48	$\text{C}_{16}\text{H}_{21}\text{N}_5\text{S}$	60,92	6,71	22,20
6	40	135-136	65,19	6,28	20,12	$\text{C}_{19}\text{H}_{21}\text{N}_5\text{S}$	64,93	6,02	19,93

Thus, we have obtained on base of hydrazide N-anabasinil acetic acid some 1,3,4-oxadiazole and 1,2,4-triazole-3-thiones in very promising biologically activity.

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## Н-АНАБАЗИНИЛСІРКЕ ҚЫШҚЫЛЫ ГИДРАЗІДТІ ТУЫНДЫЛАРЫНЫҢ ІШКІМОЛЕКУЛАЛЫҚ ГЕТЕРОЦИКЛИЗАЦИЯСЫ

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**Тірек сөздер:** анабазин, гидразид, 1,3,4-оксадиазол, тиосемикарбазид, 1,2,4-триазол-3-тион.

**Аннотация.** Мақалада N-анабазинилсірке қышқылы гидразидінің ортоқұмырска эфирі мен әртүрлі изотиоцианаттармен әрекеттесу реакцияларын зерттеу нәтижелері келтірілген. N-Анабазинилсірке қышқылы гидразидінің 1,2,4-триазол-3-тионды және аллил(фенил)тиосемикарбазидті туындыларының түзілуі мүмкін механизмдеріне әр түрлі факторлардың (температура, реакция уақыты мен реагенттер қатынасының) әсерлері зерттелген. N-анабазинилсірке қышқылының аллил(фенил)тиосемикарбазидті туындыларының ерітінділерін қышқылдатқанда, олар ішкі молекулалық циклденуге оңай түсіп, 4-аллил(фенил)-5-анабазинометил-1,2,4-триазол-3-тиондар түзетіні анықталды. Алынған жаңа заттар бактерияларға қарсы қасиеттерді зерттеуде қызығушылық тудыруы мүмкін. Алынған заттардың құрамы мен құрылысы элементті анализ бен ЯМР<sup>1</sup>H-спектроскопия әдістері арқылы дәлелденді.

## ВНУТРИМОЛЕКУЛЯРНАЯ ГЕТЕРОЦИКЛИЗАЦИЯ ПРОИЗВОДНЫХ ГИДРАЗИДА N-АНАБАЗИНИЛУКСУСНОЙ КИСЛОТЫ

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**Ключевые слова:** анабазин, гидразид, 1,3,4-оксадиазол, тиосемикарбазид, 1,2,4-триазол-3-тион.

**Аннотация.** Приведены результаты исследования реакции взаимодействия гидразида N-анабазинилуксусной кислоты с ортомуравьиным эфиром и различными изотиоцианатами. Изучено влияние различных факторов (температуры, времени реакции и соотношения реагентов) на возможные механизмы образования 1,2,4-триазол-3-тионового и аллил(фенил)тиосемикарбазидного производных гидразида N-анабазинилуксусной кислоты. Установлено, что при подкислении водно-щелочных растворов аллил(фенил)тиосемикарбазидных производных N-анабазинилуксусной кислоты, они легко подвергаются внутримолекулярной гетероциклизации с образованием 4-аллил(фенил)-5-анабазинометил-1,2,4-триазол-3-тионов. Полученные вещества являются весьма перспективными в плане изучения антибактериальных свойств. Состав и строение полученных новых соединений доказаны элементным анализом и ЯМР<sup>1</sup>H-спектроскопией.

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