N E W S
OF THE NATIONAL ACADEMY OF SCIENCES OF THE REPUBLIC OF KAZAKHSTAN
SERIES CHEMISTRY AND TECHNOLOGY
ISSN 2224-5286 **https://doi.org/10.32014/2020.2518-1491.5**
Volume 1, Number 439 (2020), 37 – 46

UDC 547.94; 548.737

O.A. Nurkenov[1,4], Zh.S. Nurmaganbetov[1,2], T.M. Seilkhanov[3], S.D. Fazylov[1], V.M. Manasheva[4], A.R. Zhasymbekova[4], A.S. Serikbolov[4]

[1]Institute of Organic Synthesis and Coal Chemistry the Republic of Kazakhstan, Karaganda;
[2]Karaganda Medical University, Kazakhstan;
[3]Sh. Ualikhanov Kokshetau State University, Kazakhstan;
[4]Karaganda State Technical University, Kazakhstan
nurkenov_oral@mail.ru, nzhangeldy@mail.ru, tseilkhanov@mail.ru, iosu8990@mail.ru, manasheva-venera@mail.ru, aigera-93-93@mail.ru, aidar1996@mail.ru

SYNTHESIS AND STRUCTURED N-ACYL AND THIOUREA DERIVATIVES CITIZINE AND ANABAZINE

Abstract. This work presents the results of studies on the chemical transformation of the alkaloids molecules cytisine and anabazine to obtain their N-cinnamoyl derivatives, as well as possible ways for their further modification. The optimal conditions for the preparation of N-cinnamoylcytisine and N-cinnamoylanabazine in the acylation reactions of alkaloids with cinnamoyl chloride are considered. Hydrazinolysis of the resulting N-cinnamoylcytisine and N-cinnamoylanabazine was carried out. It was shown that the interaction of acrylamide derivatives of alkaloids with hydrazine hydrate in ethanol leads to the formation of the corresponding pyrazole derivatives resulting from the intramolecular cyclocondensation of hydrazones of N-cinnamoyl derivatives. By the interaction of cinnamoylisothiocyanate with the above alkaloids, new thiourea derivatives are synthesized. The structures of the synthesized compounds were studied by ^{1}H and ^{13}C NMR spectroscopy, as well as by the data of two-dimensional spectra of COSY (^{1}H-^{1}H) and HMQC (^{1}H-^{13}C). The values of chemical shifts, multiplicity, and integrated intensity of ^{1}H and ^{13}C signals in one-dimensional NMR spectra were determined. Using spectra in the formats COSY (^{1}H-^{1}H) and HMQC (^{1}H-^{13}C), homo- and heteronuclear interactions were established, confirming the structure of the studied compounds.

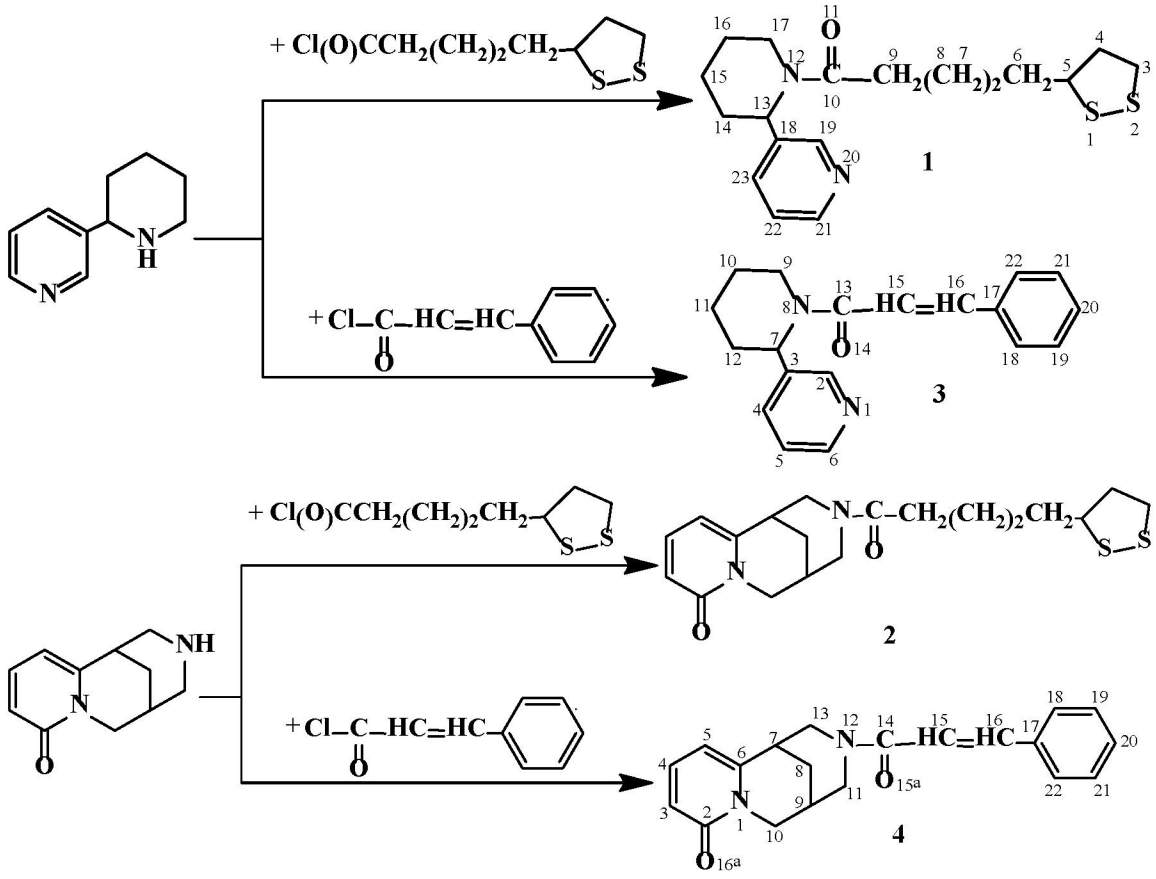
Key words: alkaloid, cytisine, anabazine, chemical transformation, N-acyl moiety, acid chloride.

Introduction

Interest in research on the chemical transformation of the alkaloids cytisine and anabazine is due to the wide spectrum of biological activity of their derivatives. To date, a large number of derivatives of alkaloids of cytisine and anabazine with various groups at the nitrogen atom have been synthesized [1-13]. The development of research on the search for new bioactive compounds has prompted us to synthesize a number of cinnamoyl derivatives of the above alkaloids. Many cinnamoyl derivatives are recommended for use as promising drugs for the treatment and / or prevention of arterial and/or venous thrombosis, acute coronary syndromes, restenosis, stable angina, cardiac arrhythmias, myocardial infarction, hypertension, heart failure, stroke [14, 15]. Lipoic acid (lipoate, vitamin N) is an important antioxidant; it plays the role of coenzyme in oxygen metabolism, especially in the pyruvate dehydrogenase complex [16]. The work of a number of researchers showed [14] that, when a hydrogen atom is replaced with nitrogen by acyl radicals, toxicity decreases and interesting biological properties manifest. There is a report in the literature of the authors of [17] who studied the reaction of the interaction of cytisine with cinnamic acid chloride in toluene, and the final product was obtained in low yield (45%). In the literature there is no information about obtaining a similar derivative of anabazine.

Results and discussions

Continuing studies on the modification of the cytisine and anabazine molecules, we synthesized their new acyl derivatives by reaction with acid chlorides of 5-[(3R)-dithiolan-3-yl]pentanoic (lipoic) and 3-phenylacrylate (cinnamoyl chloride) acids. The acylation reactions were carried out in absolute benzene in the presence of triethylamine under cooling. As the results of studying these reactions have shown, the interaction reactions in benzene proceed smoothly and lead to the formation of N-acyl derivatives of anabazine **1**, **3** and cytisine **2**, **4** with satisfactory yields.



The synthesized compounds **1**, **2** are oils, and **3**, **4** are white crystalline substances readily soluble in organic solvents.

The structure of compounds **1-4** was confirmed by IR, ^{1}H and ^{13}C NMR spectroscopy, two-dimensional spectra of COSY (^{1}H-^{1}H) and HMQC (^{1}H-^{13}C).

In the IR spectra of compounds **1-4**, the absorption bands of amide carbonyl appear in the regions of 1648 and 1643 cm^{-1}, respectively.

In the ^{1}H NMR spectrum of compound **1** in a broadband, high-field, twelve-proton multiplet at 1.05-1.83 ppm the alicyclic and aliphatic protons N-16, 16, 15, 15, 14, 14, 8, 8, 6, 6, 4, 4 were located. In a four-proton multiplet at 2.35-2.43 ppm the aliphatic protons H-7, 7, 9, 9 were located. In the broadened singlet signals, H-17ax protons, 3.58 - H-5, 3.75 - H-17eq, 5.76 - H-13 and 7.34 ppm were located at 2.82. - H-22. The remaining protons were located in multiplet signals at 3.09-3.14 (2H, H-3, 3), 7.53–7.55 (1H, H-23), and 8.37-8.42 ppm. (2H, H-19, 21).

In the ^{13}C NMR spectrum of compound **1**, the signals of the dithiolan fragment appeared at 38.64 (C-3), 40.02 (C-4) and 56.74 (C-5) ppm. The carbon atoms of the aliphatic chain appeared at 25.21 (C-8), 27.55 (C-7), 32.88 (C-9) and 34.76 (C-6) ppm. The carbon nuclei of the piperidine and pyridine nuclei resonated at 26.01 (C-16), 29.03 (C-14), 42.06 (C-17), 48.96 (C-13), 124.11 (C-22), 134.95 (C-23), 135.60 (C-18), 148.11 (C-19) and 148.65 (C-21) ppm. Carbon atoms of the carbonyl group C-10 were observed at 172.05 ppm.

The structure of compound **1** was also confirmed by two-dimensional HMQC NMR spectroscopy (^{1}H-^{13}C), which allows one to establish spin-spin interactions of a heteronuclear nature (Fig. 1). The observed correlations in the molecule are presented in the diagram. Heteronuclear interactions of protons with carbon atoms through one bond were established using ^{1}H-^{13}C HMQC spectroscopy for the following pairs present in the compound: H^{14}-C^{14} (1.39, 29.71), H^{15}-C^{15} (1.53, 20.41), H^{8}-C^{8} (1.52, 25.70), H^{6}-C^{6} (1.53, 35.53), H^{4}-C^{4} (1.83, 40.03, H^{9}-C^{9} (2.44, 33.48), H^{17}-C^{17} (2.83, 42.69), H^{5}-C^{5} (3.59, 57.33), H^{17}-C^{17} (3.80, 42.60), H^{13}-C^{13} (5.76, 49.54), H^{22}-C^{22} (7.35, 124.57), H^{23}-C^{23} (7.55, 135.36), $H^{19,21}$-$C^{19,21}$ (8.43, 148.45).

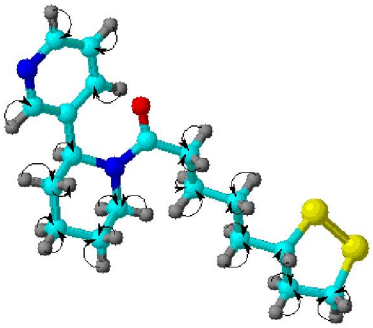


Figure 1 – The correlation scheme in the spectrum of HMQC compound **1**

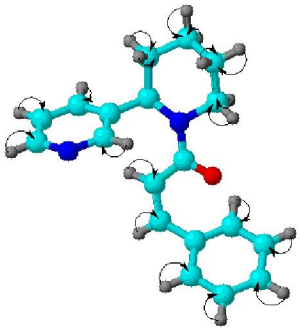


Figure 2 – The correlation scheme in the spectrum of HMQC compound **3**

From an analysis of ^{1}H NMR spectra of N-cinnamoylanabazine (**3**) and N-cinnamoylcytisine (**4**), one can assume the presence of several N-CO and CO-CH = CH-C_6H_5 isomers rotational in bonds. Since the barriers of these rotations are not large, they can lead to both the registration of spectra from several conformers and simply to a substantial broadening of the lines of the spectrum. In some cases, this did not allow the unambiguous assignment of signals.

The ^{1}H NMR spectrum of compound **3** was studied in most detail, where the piperidine cycle signals manifested themselves as multiplets at 1.30-1.42 (1H, H^{11ax}), 1.54-1.57 (2H, $H^{11eq,10ax}$), 2.36-2.46 (1H, H^{12ax}) and 3.43-3.46 (1H, H^{9ax}) ppm and broadened singlets at 1.79 (1H, H^{10eq}), 2.87 (1H, H^{12eq}), 4.22 (1H, H^{9eq}) and 5.87 (1H, H^{7}) ppm. Unsaturated aliphatic protons H15 and H16 resonated with a multiplet in the region of 7.56–7.69 ppm. Aromatic phenyl and pyridine protons manifested themselves as multiplets at 7.30-7.34 (5H, $H^{5,18,19,21,22}$), 7.56-7.69 (2H, $H^{4,20}$) and 8.44-8.47 (2H, $H^{2.6}$) ppm.

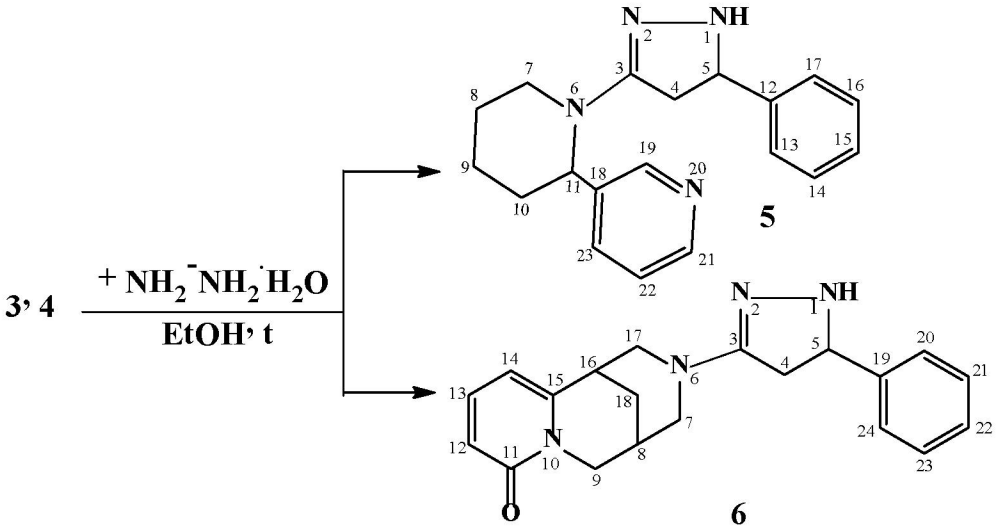
In the ^{13}C NMR spectrum of compound **3**, the signals of the carbon atoms of the piperidine ring appeared at 19.72 (C^{11}), 26.19 (C^{10}), 27.61 (C^{12}), 48.23 (C^{9}) and 49.84 (C^{7}) ppm. The carbon atoms of the phenyl and pyridine fragments are observed at 124.13 (C^{5}), 128.58 (C^{3}), 128.80 (C^{20}), 129.23 ($C^{19,21}$), 130.05 ($C^{18,22}$), 134.92 (C^{4}), 135.68 (C^{17}), 148.28 (C^{6}) and 148.65 (C^{2}) ppm. Signals with chemical shifts at 118.83 and 142.68 ppm. correspond to carbon atoms in the double bond of C^{15} and C^{16}, respectively. In the field of a weak field at 166.27 ppm the carbon atoms of the C^{13} carbonyl group were resonated.

The structure of compound **3** was also confirmed by two-dimensional HMQC NMR spectroscopy (^{1}H-^{13}C), which allows one to establish spin-spin interactions of a heteronuclear nature (Figure 2). The observed correlations in the molecule are presented in the diagram. Heteronuclear interactions of protons with carbon atoms through one bond were established using 1H-13CHMQC spectroscopy for the following pairs present in the compound: H^{11}-C^{11} (1.56, 20.37), H^{10}-C^{10} (1.60, 26.65), H^{12}-C^{12} (2.34, 28.02), H^{9}-C^{9} (4.24, 42.78), H^{7}-C^{7} (5.90, 50.36), H^{5}-C^{5} (7.31, 124.58), $H^{18,19,20,21,22}$-$C^{18,19,20,21,22}$ (7.28, 129.33), H^{15}-C^{15} (7.60, 119.22), H^{4}-C^{4} (7.55, 135.27), H^{16}-C^{16} (7.56, 143.13) и $H^{2,6}$-$C^{2,6}$ (8.45, 148.86).

The chemical shifts of the cinnamoyl moieties associated with the anabazine and cytisine groups are similar in the ^{1}H and ^{13}C NMR spectra. A slight predominance of the mesmeric effect of the cytisine fragment leads to a slight shift to the weakly field region of the signals of the cinnamoyl fragments in compound **4** as compared with derivative **3**. Thus, the olefin protons of the cinnamoyl group H^{15} and H^{16} of compound **4** appear at 6.49-6.75 and 7.16-7.64 ppm. respectively, whereas similar olefin protons of compound **3** resonate in one region at 7.56-7.69 ppm. The same situation is observed for free-standing C^{13} carbonyl atoms: in the spectrum of compound **3**, they appeared at 166.27 ppm, and in the case of compound **4**, at 165.65 ppm.

The cyclocondensation reaction of hydrazines with α, β-unsaturated ketones is an important synthetic approach to the preparation of 1,2-azoles. Some pyrazole derivatives exhibit the properties of analgesics and platelet aggregation inhibitors [18], have a strong antibacterial [19] and anesthetic [20] effect.

In order to further study the properties and possibilities of transformation of the obtained N-cinnamoylanabazine (**3**) and N-cinnamoylcytisine (**4**), we studied their interaction with hydrazine hydrate. It was found that the interaction of acrylamide derivatives **3**, **4** with hydrazine hydrate in ethanol leads to the formation of the corresponding pyrazole derivatives **5** and **6**, which are formed, possibly as a result of intramolecular cyclocondensation of the intermediate hydrazones formed.



In the ^{1}H NMR spectrum of compound **6** in the most strongly field region of the spectrum at 1.87-1.99 ppm two-proton multiplet manifested cytisine protons H-18. In the broadband multiplet at 2.25-3.33 ppm the six-proton multiplet resonated with the cytisine protons H-8, H-16 and H-7 and the pyrazole protons H-4. In the next five-proton multiplet at 3.58-4.63 ppm. the cytisine protons H-17 and H-9 and the other pyrazole proton H-5 were located. At 6.11-6.20 ppm protons H-12 and H-14 of the pyrazole ring resonated with a two-proton multiplet. In the seven-proton multiplet at 6.97-7.64 ppm housed the cytisine proton H-13, the proton of the amino group H-1 and the aromatic protons H-20-24.

In the ^{13}C NMR spectrum of compound **6**, the signals of carbon atoms of cytisine rings are observed at 25.80 (C-18), 27.52 (C-8), 33.76 (C-16), 48.75 (C-9), 49.18 (C-7), 51.21 (C-17), 105.27 (C-14), 116.31 (C-12), 139.30 (C-13), 150.19 (C-15) and 170.85 (C-11) ppm. Signals with chemical shifts at 34.79, 52.82, and 162.64 ppm. correspond to carbon atoms C-4, C-5 and C-3, respectively. Carbons of the aromatic ring appeared at 126.32 (C-22), 128.51 (C-21, 23), 129.25 (C-20, 24) and 141.62 (C-19) ppm.

The structure of compound **6** was also confirmed by two-dimensional HMQC (^{1}H-^{13}C) NMR spectroscopy, which allows one to establish spin-spin interactions of a heteronuclear nature. The observed correlations in the molecule are shown in Figure 3. Heteronuclear interactions of protons with carbon atoms through one bond were found for pairs: H^{18}-C^{18} (1.88, 26.44), H^{8}-C^{8} (2.44, 28.40), H^{16}-C^{16} (2.52, 34.62), H^{7}-C^{7} (2.74, 48.79), H^{4}-C^{4} (3.10, 34.89), H^{5}-C^{5} (4.22, 53.55), H^{17}-C^{17} (4.43, 51.92), H^{9}-C^{9} (4.53, 48.45), H^{14}-C^{14} (6.15, 105.77), H^{12}-C^{12} (6.21, 117.00), $H^{21,23}$-$C^{21,23}$ (7.09, 129.08), H^{22}-C^{22} (7.12, 126.67), $H^{20,24}$-$C^{20,24}$ (7.32, 129.32) и H^{13}-C^{13} (7.28, 139.80).

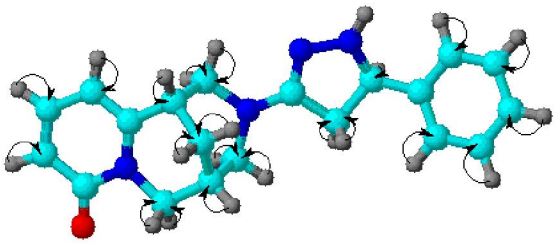
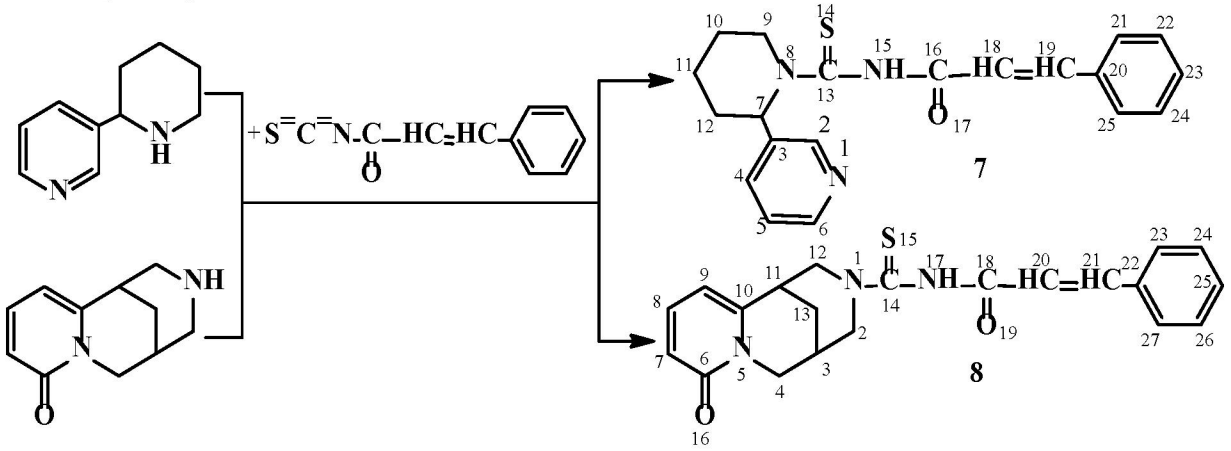


Figure 3 – The correlation scheme in the spectrum of HMQC compound **6**

NMR spectroscopic study of the obtained pyrazole derivatives **5** and **6** showed that the anabazine and cytisine fragments mainly retain their regions of chemical shifts in the ^{1}H and ^{13}C NMR spectra upon transition from cinnamoyl derivatives to pyrazole.

In order to expand the possibility of functionalization of cytisine and anabazine molecules, it was interesting to synthesize new thiourea derivatives **7**, **8** by interaction with cinnamoylisothiocyanate. Cinnamoylisothiocyanate was prepared by reacting cinnamic acid chloride with potassium thiocyanate in acetone under heating. The obtained cinnamoylisothiocyanate reacted with anabazine and cytisine to form the corresponding derivatives **7** and **8**.



The resulting target products **7**, **8** are well crystallized white crystalline substances with moderate solubility in organic solvents.

The structure and individuality of the synthesized compounds **7**, **8** were confirmed by IR, ^{1}H NMR spectroscopy and thin-layer chromatography.

In the IR spectra of the synthesized compounds **7**, **8**, there is an absorption band in the region of 1465 and 1550 cm^{-1}, characteristic of the C=S group, absorption bands of the amide group of C(O)NH appear in the region of 1691 and 1689 cm^{-1}. The intense spectrum of the amide group (N-C=O) cytisine alkaloid in the 1648 cm^{-1} region is present in the IR spectrum of compound **8**.

In the ^{1}H NMR spectrum of compound **7**, the piperidine cycle signals manifested themselves as multiplets at 0.99-1.00 (H^{10ax}), 1.31-1.34 (H^{11ax}), 2.52-2.55 (^{H12eq}) and 3.00-3.05 (H^{9ax}) ppm. Unsaturated protons H^{18} and H^{19} resonated with doublets at 6.87 (^{3}J 16.0 Hz) and 7.65 (^{3}J 15.6 Hz) ppm. Aromatic phenyl and pyridine protons were manifested by broadened singlets at 7.39 ($H^{5,22,23,24}$), 7.86 (H^{4}) and 8.66 (H^{2}) and doublets at 7.58 ($H^{21,25}$, ^{3}J 6.4 Hz) and 8.47 (H^{6}, ^{3}J 4.1 Hz) ppm The proton of the H^{15} amide bond resonated with a broadened singlet in the weakest field of the spectrum at 10.85 ppm.

In the ^{13}C NMR spectrum of compound **7**, the signals of the carbon atoms of the piperidine cycle appeared at 18.99 (C^{11}), 26.02 (C^{10}), 27.49 (C^{12}), 48.27 (C^{9}) and 59.00 (C^{7}) ppm. Carbon atoms of the phenyl fragment are observed at 128.49 ($C^{21,25}$), 129.60 ($C^{22,24}$), 130.83 (C^{23}) and 133.35 (C^{20}) ppm. The carbon atoms of the pyridine ring resonated at 124.11 (C^{5}), 134.93 ($C^{3,4}$), 148.52 (C^{2}) and 148.65 (C^{6}) ppm. Signals with chemical shifts at 120.80 and 143.27 ppm correspond to carbon atoms in the double bond of C^{18} and C^{19}, respectively. In the field of a weak field at 162.64 and 181.61 ppm. the amide and thioamide carbon atoms of C^{16} and C^{13} resonated, respectively.

The structure of compound **7** was also confirmed by two-dimensional NMR spectroscopy HMQC (^{1}H-^{13}C). The proposed correlation scheme is presented in the scheme.

In the analysis of ^{1}H NMR spectra of compounds **7**, **8**, characteristic proton signals for the alkaloid part are observed. Moreover, the anabazine and cytisine fragments mainly retain their regions of chemical shifts in the ^{1}H and ^{13}C NMR spectra, as is the case with cinnamoyl compounds **3**, **4** and pyrazole **5**, **6** nature.

Thus, for the first time, we obtained new N-acyl and thiourea derivatives of anabazine and cytisine, investigated the possibilities of their further chemical transformation into new potentially bioactive substances.

Experimental part

^{1}H and ^{13}C NMR spectra of compounds **1-8** were recorded on a JNM-ECA Jeol 400 spectrometer (frequencies 399.78 and 100.53 MHz, respectively) using a DMSO-d_6 solvent. Chemical shifts are measured relative to the signals of residual protons or carbon atoms of DMSO-d_6. The reaction progress and the purity of the obtained compounds were monitored by thin layer chromatography on SilufolUV-254 plates in isopropyl alcohol-ammonia-water 7:2:1, ethanol-chloroform 1:4 systems. The plates showed iodine vapor. The reaction products were isolated by recrystallization or column chromatography on alumina. All solvents used in the work were purified and absolutized by standard methods [21].

General procedure for the preparation of N-lipoylanabazine (1) and N-lipoylcytisine (2). To a solution of 1.425 g (8.78 mmol) of anabazine or 1.67 g (8.78 mmol) of cytisine, 1.22 ml (8.78 mmol) of triethylamine in 50 ml of benzene, a solution of 1.974 g (8.78 mmol) of lipoyl chloride [obtained from 4.5 g (21.95) was added with stirring mmol) of lipoic acid and 3.264 g (27.43 mmol) of thionyl chloride] dissolved in 25 ml of benzene. The reaction mixture was stirred for 3 hours at room temperature until a precipitate formed. The precipitate was filtered off, the mother liquor was evaporated, the residue was chromatographed on silica gel (eluent: benzene-chloroform). 0.92 g (64.56%), lipoylanabazine (**1**) and 1.28 g (76.60%), lipoylcytisine (**2**) were isolated as yellowish thick oils.

N-Cinnamoylanabazine (3). To a solution of 3 g (18.49 mmol) of anabazine in 150 ml of benzene, 2.57 ml (18.49 mmol) of triethylamine and a solution of 3.08 g (18.49 mmol) of cinnamoyl chloride in 50 ml of benzene were added with stirring. The reaction mixture was stirred for 3 hours at room temperature until a precipitate formed. The precipitated precipitate of triethylamine hydrochloride was filtered off, the mother liquor was evaporated, and the residue was chromatographed on alumina (eluent benzene, benzene-ethyl acetate, 100:1). Received 2.87 g (95.6%), N-cinnamoylanabazine (**3**) in the form of white crystals with so m.p. 95-98°C.

N-Cinnamoylcytisine (4). To a solution of 1.14 g (6.0 mmol) of cytisine in 50 ml of benzene, 0.6 g (6.0 mmol) of triethylamine and a solution of 1 g (6.0 mmol) of cinnamoyl chloride in 20 ml of benzene were added with stirring. The reaction mixture was stirred for 3.3 hours at room temperature until a precipitate formed. The precipitate of triethylamine hydrochloride was filtered off, the mother liquor was evaporated, and the residue was treated with diethyl ether. Obtained 0.95 g (95%), N-cinnamoylcytisine (**4**) in the form of a white powder with a yellowish tinge with so pl. 130-134°C. ^{1}H NMR spectrum, δ, ppm (J, Hz): 1.86-1.97 m (2H, $H^{8,8}$), 2.44 expanded singlet (1H, H^{9}), 2.90-3.40 m (3H. $H^{7,11ax,13ax}$), 3.63-3.97 m (2H, $H^{10ax,10eq}$), 4.24-4.65 m (2H, $H^{11eq,13eq}$, 6.14 d (2H, $H^{3,5}$. ^{3}J 6.1), 6.49-6.75 m (1H, H^{15}), 7.16-7.64 m (7H, $H^{4,15,18-22}$). ^{13}C NMR spectrum, δ_C, ppm: 25.95 (C^{8}), 27.86 (C^{9}), 35.13 (C^{7}), 49.05 (C^{10}), 51.31 (C^{11}), 53.04 (C^{13}), 105.29 (C^{5}), 116.40 (C^{3}), 128.85 (C^{15}), 129.24 ($C^{18,19,21,22}$), 129.99 (C^{20}), 135.55 (C^{4}), 139.09 (C^{16}), 141.32 (C^{17}), 150.47 (C^{6}), 162.66 (C^{2}), 165.65 (C^{14}) ppm. Cross peaks of HMQC NMR spectra (^{1}H-^{13}C), ppm: H^{8}-C^{8} (1.96, 26.60), H^{9}-C^{9} (2.44, 28.48), H^{7}-C^{7} (3.13, 35.65), H^{10ax}-C^{10ax}(3.59, 49.56), H^{10ax}-C^{10ax}(3.98, 49.58), H^{5}-C^{5} (6.14, 105.76), H^{3}-C^{3} (6.12, 116.82) и $H^{18,19,21,22}$-$C^{18,19,21,22}$ (7.37, 129.52).

1-(5-Phenyl-4,5-dihydro-1H-pyrazol-3-yl)anabazine (5). 2.33 g (7.97 mmol) of N-cinnamoylanabazine (**3**) was dissolved in 100 ml of ethanol and 1.9 ml was added dropwise. 39.85 mmol) hydrazine hydrate. The reaction mixture was stirred for 1 hour at 25°C and an additional (**7**) hours at 70-75°C, cooled and evaporated. The resulting mass was dissolved in $CHCl_3$ (300 ml), washed with water (3×60 ml) and dried over $MgSO_4$. The desiccant was filtered off, the solvent was evaporated under reduced pressure, the residue was chromatographed on an alumina column (eluent: benzene, benzene-chloroform, 100: 1). 2.028 g (87.03%) of product **5** was isolated as a yellow-green thick oil. ^{1}H NMR spectrum, δ, ppm. (J, Hz): 1.31-1.52 m (1H. H^{9ax}), 1.53-1.61 m (3H, $H^{8ax,10ax,9eq}$), 1.70-1.88 m (1H, H^{8eq}), 2.18-2.40 m (1H, H^{10eq}), 2.76-2.84 m (2H, $H^{4ax,7ax}$), 2.96-2.98 m (1H, H^{7eq}), 3.58-3.65 m (2H, $H^{4eq,H-11}$), 4.58 widened singlet (1H, H^{1}), 5.12-5.21 m (1H, H^{5}), 7.18-7.22 m (3H, $H^{14,15,16}$), 7.25-7.37 m (4H, $H^{13,17,22,23}$), 8.40-8.50 (2H, $H^{19,21}$). Cross peaks of COSY NMR spectra (^{1}H-^{1}H), ppm: H^{4ax}-H^{5} (2.76, 5.16 and 5.16, 2.75), $H^{13,17}$-$H^{14,16}$ (7.34, 7.16 and 7.16, 7.34), $H^{21,23}$-H^{22} (8.39, 7.34 and 7.34, 8.39). Cross peaks of HMQC NMR spectra (^{1}H-^{13}C), ppm: H^{4ax}-C^{4} (2.75, 42.19), H^{4eq}-C^{4} (3.64, 42.19), H^{5}-C^{5} (5.20, 70.38), H^{8ax}-C^{8} (1.53, 25.86), H^{8eq}-C^{8} (1.73, 25.86), H^{9ax}-C^{9} (1.37, 19.54), H^{9eq}-C^{9} (1.61, 19.54), H^{10eq}-C^{10} (2.25, 26.85), H^{11}-C^{11} (3.58, 42.12), H^{22}-C^{22} (7.34, 134.83).

1-(5-Phenyl-4,5-dihydro-1H-pyrazol-3-yl)cytisine (6). 0.33 g (1.03 mmol) of N-cinnamoylcytisine (**2**) was dissolved in a minimum amount of ethanol (~ 15 ml) and 0.50 ml was added dropwise (10.28 mmol) hydrazine hydrate. The reaction mixture was stirred for 2 hours at 25°C and an additional 6 hours at 70-75°C, cooled and evaporated. The resulting mass was dissolved in $CHCl_3$ (100 ml), washed with water (3×20 ml) and dried over $MgSO_4$. The drying agent was filtered off, the solvent was evaporated under reduced pressure, the residue was chromatographed on an alumina column (eluent: petroleum ether, petroleum ether-benzene, 100:1). 0.283 g (85.75%) of product **6** was isolated in the form of yellow needle crystals with a melting point of 122-125°C. ^{1}H NMR spectrum, δ, ppm. (J, Hz): 1.87-1.99 m (2H, $H^{18,18}$), 2.25-3.33 m (6H. $H^{4,4,7,7,8,16}$), 3.58-4.63 m (5H, $H^{5,9,9,17,17}$), 6.11-6.20 m (2H, $H^{12,14}$), 6.97-7.64 m (7H, $H^{1,13,20-24}$). ^{13}C NMR spectrum, δ_C, ppm: 25.80 (C^{18}), 27.52 (C^8), 33.76 (C^{16}), 34.79 (C^4), 48.75 (C^9), 49.18 (C^7), 51.21 (C^{17}), 52.82 (C^5), 105.27 (C^{14}), 116.31 (C^{12}), 126.32 (C^{22}), 128.51 ($C^{21,23}$), 129.25 ($C^{20,24}$), 139.30 (C^{13}), 141.62 (C^{19}), 150.19 (C^{15}), 162.64 (C^3), 170.85 (C^{11}). Cross peaks of HMQC NMR spectra (^{1}H-^{13}C), ppm: H^{18}-C^{18} (1.88, 26.44), H^8-C^8 (2.44, 28.40), H^{16}-C^{16} (2.52, 34.62), H^7-C^7 (2.74, 48.79), H^4-C^4 (3.10, 34.89), H^5-C^5 (4.22, 53.55), H^{17}-C^{17} (4.43, 51.92), H^9-C^9 (4.53, 48.45), H^{14}-C^{14} (6.15, 105.77), H^{12}-C^{12} (6.21, 117.00), $H^{21,23}$-$C^{21,23}$ (7.09, 129.08), H^{22}-C^{22} (7.12, 126.67), $H^{20,24}$-$C^{20,24}$ (7.32, 129.32), H^{13}-C^{13} (7.28, 139.80).

3-Phenyl-N-(anabazinocarbonothioyl)acrylamide (7). 1.62 g (0.01 mol) of anabazine was dissolved in 5 ml of acetone, then a solution (0.011 mol) of cinnamoylisothiocyanate in 10 ml of acetone was added dropwise with vigorous stirring. The mixture was stirred for 1 h at a temperature of 30°C. The completion of the reaction was monitored by TLC. The solution was cooled, the precipitated fine precipitate was filtered off, washed with a small amount of diethyl ether. After recrystallization from 2-propanol, 2.82 g (80.4%) of a white powder of 5 s melted was obtained. 150-151°C. The data of elemental analysis of compound **7** answered calculated. $C_{20}H_{21}N_3OS$. ^{1}H NMR spectrum, δ, ppm (J, Hz): 0.99-1.00 m (1H, H^{10ax}), 1.31-1.34 m (1H, H^{11ax}), 1.44-1.65 m (2H, $H^{10eq,11eq}$), 1.88-2.00 m (1H, H^{12ax}), 2.52-2.55 m (1H, H^{12eq}), 3.00-3.05 m (1H, H^{9ax}), 3.73-3.87 m (1H, H^{9eq}), 6.72 widened singlet (1H, H^7), 6.87 d (1H, H^{18}, ^{3}J 16.0), 7.39 widened singlet (4H, $H^{5,22,23,24}$), 7.58 d (2H, $H^{21,25}$, ^{3}J 6.4), 7.65 d (1H, H^{19}, ^{3}J 15.6), 7.86 widened singlet (1H, H^4), and 8.47 d (1H, H^6, ^{3}J 4.1), widened singlet 8.66 (1H, H^2), 10.85 widened singlet (1H, H^{15}). ^{13}C NMR spectrum, δ_C, ppm: 18.99 (C^{11}), 26.02 (C^{10}), 27.49 (C^{12}), 48.27 (C^9), 59.00 (C^7), 120.80 (C^{18}), 124.11 (C^5), 128.49 ($C^{21,25}$), 129.60 ($C^{22,24}$), 130.83 (C^{23}), 133.35 (C^{20}), 134.89 (C^4), 134.93 (C^3), 143.27 (C^{19}), 148.52 (C^2), 148.65 (C^6), 162.64 (C^{16}), 181.61 (C^{13}). Cross peaks of HMQC NMR spectra (^{1}H-^{13}C), ppm: H^{10ax}-C^{10} (1.00, 26.67), H^{11ax}-C^{11} (1.28, 19.67), H^{11eq}-C^{11} (1.55, 19.70), H^{10eq}-C^{10} (1.55, 26.80), H^{12ax}-C^{12} (1.90, 28.20), H^{12eq}-C^{12} (2.57, 28.11), H^{9ax}-C^9 (3.03, 48.86), H^{9eq}-C^9 (3.91, 48.87), H^7-C^7 (6.74, 59.48), H^{18}-C^{18} (6.90, 121.09), H^5-C^5 (7.39, 124.50), $H^{22,23,24}$-$C^{22.23.24}$ (7.40, 130.11), $H^{21,25}$-$C^{21,25}$ (7.58, 128.91), H^4-C^4 (7.87, 135.37), H^{19}-C^{19} (7.68, 143.50), H^6-C^6 (8.47, 148.93), H^2-C^2 (8.54, 148.93).

N-Citisino-3-carbonothioylphenylacrylamide (8). 1.9 g (0.01 mol) of cytisine was dissolved in 20 ml of acetone, then a solution (0.011 mol) of cinnamoylisothiocyanate in 10 ml of acetone was added dropwise with vigorous stirring. The reaction mixture, transparent with a yellow tint, was stirred for 2 hours at a temperature of 30^{0}C. The completion of the reaction was monitored by TLC. The solution was cooled, the precipitated white crystalline precipitate was filtered off, washed with a small amount of diethyl ether. After recrystallization from benzene, 2.32 g (61.3%) of white matter were obtained, 6 s. Mp. 177-178^{0}C. The data of elemental analysis of compound **8** answered calculated. $C_{21}H_{21}N_3O_2S$. ^{1}H NMR spectrum, δ, ppm (J, Hz): 1.84-1.87 m (1H, H^3), 2.47 widened singlet (1H, H^{13ax}), 2.65 widened singlet (1H, H^{13eq}),3.12 widened singlet (1H, H^{11}), 3.28 widened singlet (1H, H^{2ax}), 3.36-3.38 m (1H, H^{2eq}), 3.57-3.61 m (1H, H^{12ax}), 3.79-3.88 m (1H, H^{4ax}), 3.98-4.01 m (1H, H^{12eq}), 4.22-4.25 m (1H, H^{4eq}), 6.08-6.10 m (1H, H^9), 6.18-6.20 m (1H, H^7), 6.68-6.79 m (1H, H^{20}), 7.32-7.53 m (7H, $H^{8,21,23-26}$), 10.53 widened singlet (1H, H^{17}). ^{13}C NMR spectrum, δ_C, ppm: 25.31 (C^3), 28.90 (C^{13}), 35.47 (C^{11}), 48.41 (C^4), 55.45 (C^2), 58.68 (C^{12}), 105.08 (C^9), 116.95 (C^7), 120.86 (C^{20}), 128.43 ($C^{23,27}$), 128.85 ($C^{24,26}$), 129.57 (C^{25}), 130.79 (C^{22}), 139.36 (C^8), 142.85 (C^{21}), 149.42 (C^{10}), 161.97 (C^6), 162.70 (C^{18}), 180.65 (C^{14}). Cross peaks of HMQC NMR spectra (^{1}H-^{13}C), ppm: H^3-C^3 (1.87, 25.98), H^{13ax}-C^{13} (2.47, 29.50), H^{13eq}-C^{13} (2.66, 29.50), H^{11}-C^{11} (3.12, 36.12), H^2-C^2 (3.36, 56.72), H^{12ax}-C^{12} (3.53, 59.30), H^{4ax}-C^4(3.84, 49.34), H^{12eq}-C^{12} (3.98, 57/98), H^{4eq}-C^4 (4.24, 49.34), H^9-C^9 (6.09, 105.49), H^7-C^7 (6.20, 117.26), H^{20}-C^{20} (6.74, 121.45), H^8-C^8 (7.26, 139.76), H^{23-27}-C^{23-27} (7.32, 129.27), H^{21}-C^{21} (7.52, 142.80).

This work was financially supported by the Committee of Science of the Ministry of Education and Science of the Republic of Kazakhstan (PTF No. BR05236438-OT-18).

О.А. Нүркенов[1,4], Ж.С. Нұрмағанбетов[1,2], Т.М. Сейлханов[3], С.Д. Фазылов[1], В.М. Манашева[4], А.Р. Жасымбекова[4], А.С. Серікболов[4]

[1]ҚР Органикалық синтез және көмір химиясы институты, Қарағанды қ., Қазақстан;
[2]Қарағанды медицина университеті, Қазақстан;
[3]Ш. Уәлиханов атындағы Көкшетау мемлекеттік университеті, Қазақстан;
[4]Қарағанды мемлекеттік техникалық университеті, Қазақстан

ЦИТИЗИН ЖӘНЕ АНАБАЗИННІҢ ЖАҢА N-АЦИЛЬДІ ЖӘНЕ ТИОМОЧЕВИНДІ ТУЫНДЫЛАРЫНЫҢ СИНТЕЗІ МЕН ҚҰРЫЛЫСЫ

Аннотация. Ұсынылған жұмыста цитизин және анабазин алкалоидтары молекулаларының химиялық трансформациясы бойынша зерттеулердің нәтижелері, олардың N-циннамоильді туындылары, сондай-ақ оларды одан әрі қарай модификациялаудың ықтимал жолдары келтірілген. Цитизин мен анабазин алкалоидтарының ацилденген туындылары қатарынан жаңа биологиялық белсенді қосылыстарды іздестіру мақсатында циннамоилхлоридпен әрекеттесу реакциясы жүргізіліп, нәтижесінде одан әрі өзгеру мүмкіндіктеріне ие болатын N-циннамоилцитизин және N-циннамоиланабазин туындылары синтезделді. Еріткіштің табиғатына және ортаның сипатына байланысты зерттелетін реакцияларды жүзеге асырудың оңтайлы шарттары қарастырылған. Зерттелетін алкалоидтардың ацилдену реакциясы триэтиламиннің қатысуымен бензолда жақсы жүреді, сонымен қатар сәйкесінше 75 және 95% шығымдарды құрайтын тиісті анабазин мен цитизин алкалоидтары туындыларының пайда болуына әкеліп соқтырады. N-циннамоилцитизин және N-циннамоиланабазин туындыларын түзетін гидразинолиз реакциясы жүзеге асырылды. Алкалоидтардың акриламидті туындыларының этанолдағы гидразингидратпен өзара әрекеттесуі тиісті пиразолды туындылардың пайда болуына алып келеді және олар гидразондардың N-циннамоильді туындыларының молекулалық циклоконденсациясының нәтижесі болып табылады. Цитизин мен анабазиннен алынған N-циннамоильді туындылары гидразингидратпен өзара әрекеттесу реакцияларында одан әрі зерттелінеді. Этанолды ортада жүргізілген реакцияның нәтижесінде олардың тиісті пиразол туындылары алынды. Реакциялық ортадан бөлінген пиразолды қосылыстар аралық өнім түзетін гидразондардың ішкі молекулалық циклоконденсациясының нәтижесі болуы мүмкін. Циннамоилизотиоцианаттың жоғарыда көрсетілген алкалоидтармен өзара әрекеттесуі жаңа тиомочевиналы туындылардың синтезін жүзеге асырды. Цитизин және анабазин алкалоидтарының циннамоилизотиоционатпен өзара әрекеттесуі нәтижесінде олардың жаңа ацильді туындылары алынды. Циннамоилизотиоцианат корич қышқылының калий роданидімен ацетонда қыздыру арқылы өзара әрекеттесуі барысында синтезделінді. Синтезделген қосылыстардың құрылысы ЯМР ^{1}H - және ^{13}C-спектроскопия әдістерімен, сондай-ақ COSY (^{1}H-^{1}H) және HMQC (^{1}H-^{13}C) екі өлшемді спектрлерінің деректерімен зерттелді. Бір өлшемді ЯМР спектрлерінде ^{1}H және ^{13}C сигналдардың интегралдық қарқындылығы, мультиплеттілігі және химиялық ығысу мәндері анықталды. COSY (^{1}H-^{1}H) және HMQC (^{1}H-^{13}C) форматтарында спектрлер көмегімен зерттелетін қосылыстардың құрылымын растайтын гомо - және гетероядролық өзара әрекеттесулер орнатылды.

Түйін сөздер: алкалоидтар, цитизин, анабазин, химиялық трансформация, N-ацильді фрагмент, циннамоил хлорангидриді

О.А. Нуркенов[1,4], Ж.С. Нурмаганбетов[1,2], Т.М. Сейлханов[3], С.Д. Фазылов[1], В.М. Манашева[4], А.Р. Жасымбекова[4], А.С. Серикболов[4]

[1]Институт органического синтеза и углехимии РК, г. Караганда, Казахстан;
[2]Медицинский университет Караганды, Казахстан;
[3]Кокшетауский государственный университет им. Ш. Уалиханова, Казахстан;
[4]Карагандинский государственный технический университет, Казахстан.

СИНТЕЗ И СТРОЕНИЕ НОВЫХ N-АЦИЛЬНЫХ И ТИОМОЧЕВИННЫХ ПРОИЗВОДНЫХ АЛКАЛОИДОВ ЦИТИЗИН И АНАБАЗИН

Аннотация. В представленной работе приведены результаты исследований по химической трансформации молекул алкалоидов цитизин и анабазин с получением их N-циннамоильных производных, а также возможные пути их дальнейшей модификации. С целью поиска новых биоактивных соединений в ряду ацилированных производных алкалоидов цитизина и анабазина нами исследованы реакции с циннамоилхлоридом и возможности дальнейших превращений образующихся N-циннамоилцитизина и N-циннамоиланабазина. Рассмотрены оптимальные условия осуществления изучаемых реакций в зависимости от природы растворителя и характера среды. Установлено, что ацилирование изучаемых алкалоидов

успешно протекает гладко в бензоле в присутствии триэтиламина и приводят к образованию соответствующих производных анабазина и цитизина с выходами 75 и 95% соответственно. Осуществлен гидразинолиз образующихся N-циннамоилцитизина и N-циннамоиланабазина. Показано, что взаимодействие акриламидных производных алкалоидов с гидразингидратом в этаноле приводит к образованию соответствующих пиразоловых производных, которые, возможно, являются результатом внутримолекулярной циклоконденсации гидразонов N-циннамоильных производных. Полученные N-циннамоильные производные цитизина и анабазина подвергнуты дальнейшему изучению в реакциях взаимодействия с гидразингидратом. В результате проведенных реакций в среде этанола были получены соответствующие их пиразольные производные. Сделано предположение, что выделенные из реакционной среды пиразольные соединения, возможно, являются результатами внутримолекулярной циклоконденсации промежуточно образующихся гидразонов. Взаимодействием циннамоилизотиоцианата с вышеуказанными алкалоидами осуществлен синтез новых тиомочевинных производных. Взаимодействием цитизина и анабазина с циннамоилизотиоционатом получены новые ацильные производные. Циннамоилизотиоцианат был получен взаимодействием хлорангидрида коричной кислоты с роданистым калием в ацетоне при нагревании. Исследованы строения синтезированных соединений методами ЯМР ^{1}H- и ^{13}C-спектроскопии, а также данными двумерных спектров COSY (^{1}H-^{1}H) и HMQC (^{1}H-^{13}C). Определены значения химических сдвигов, мультиплетность и интегральная интенсивность сигналов ^{1}H и ^{13}C в одномерных спектрах ЯМР. С помощью спектров в форматах COSY (^{1}H-^{1}H) и HMQC (^{1}H-^{13}C) установлены гомо- и гетероядерные взаимодействия, подтверждающие структуру исследуемых соединений.

Ключевые слова: алкалоиды, цитизин, анабазин, химическая трансформация, N-ацильный фрагмент, хлорангидрид циннамоила.

Information about authors:

Nurkenov O.A. – Doctor of chemical sciences, Professor, Institute of Organic Synthesis and Coal Chemistry of the Republic of Kazakhstan, e-mail: nurkenov_oral@mail.ru;

Nurmaganbetov Zh.S. – candidate of chemical sciences, full professor, Institute of Organic Synthesis and Coal Chemistry of the Republic of Kazakhstan. e-mail: nzhangeldy@mail.ru, https://orcid.org/0000-0002-0978-5663;

Seilkhanov T.M. – candidate of chemical sciences, full professor, head of the laboratory of engineering profile NMR Kokshetau State University named after Sh. Ualikhanov, e-mail: tseilkhanov@mail.ru, https://orcid.org/0000-0002-2322-8863;

Fazylov S.D. – corresponding member of NAS RK, Doctor of chemical sciences, Professor, Institute of Organic Synthesis and Coal Chemistry of the Republic of Kazakhstan. e-mail: iosu8990@mail.ru, https://orcid.org/0000-0002-4240-6450;

Manasheva V.M. – undergraduate of the Karaganda State Technical University. e-mail: manasheva-venera@mail.ru, https://orcid.org/0000-0001-8354-9581;

Zhasymbekova A.R. – undergraduate of the Karaganda State Technical University. e-mail: aigera-93-93@mail.ru, https://orcid.org/0000-0003-1272-9096;

Serikbolov A.S. – undergraduate of the Karaganda State Technical University. e-mail: aidar_1996@mail.ru, https://orcid.org/0000-0002-0118-0221

REFERENCES

[1] Sadykov A.S., Aslanov H.A., Kushmuradov Yu.K. (1975) Quinolizidine alkaloids [Alkaloidy khinolizidinovogo ryada] Nauka, Moscow (in Rus).

[2] Nurkenov O.A., Fazylov S.D., Kulakov I.V., Musina L.A. (2010) Anabazine alkaloid and its derivatives [Alkaloid anabazin i yego proizvodnyye] Glasir, Karaganda (in Rus).

[3] Nurkenov O.A., Kulakov I.V., Fazylov S.D. (2012) Synthetic transformations of the cytisine alkaloid [Sinteticheskiye transformatsii alkaloida tsitizina] Glasir, Karaganda (in Rus).

[4] Nurkenov O.A., Gazaliev A.M., Seilkhanov T.M., Arinova A.E., Kabieva S.K., Fazylov S.D., Takibaeva A.T., Bakibaev A.A., Vorontsova O .A., Plotnikov E.V. (2016) Synthesis, structure and antioxidant activity of 4-cytisinyl-4-oxobutanoic acid [Sintez, stroyeniye i antioksidantnaya aktivnost' 4-tsitizinil-4-oksobutanovoy kisloty] News of the NAS of the Republic of Kazakhstan. Series of chemistry and technology, 3(417):114-119 (in Rus).

[5] Kulakov I.V., Nurkenov O.A. (2012) Synthesis and biological activity of derivatives of alkaloid cytosine [Sintez i biologicheskaya aktivnost' proizvodnykh alkaloida tsitizina] Chemistry in the interests of sustainable development, 3:275-289 (in Rus).

[6] Tlegenov R. (2008) Synthesis, structure and properties of derivatives of lupinine, anabazine, cytisine and a number of nitrogen-containing heterocycles [Sintez, stroyeniye i svoystva proizvodnykh lupinina, anabazina, tsitizina i ryada azotsoderzhashchikh geterotsiklov] Abstract. diss. Doct. chemical sciences, Tashkent (in Rus).

[7] Rakhimov Sh.B., Vinogradova V.I., Mirzaev Yu.R., Vypova N.L., Kazantseva D.S. (2006) Synthesis and biological activity of N-benzyl derivatives of cytosine [Sintez i biologicheskaya aktivnost' N-benzil'nykh proizvodnykh tsitizina] Chemistry of Natural Compounds, 4:373-378 (in Rus).

[8] Gazaliev A.M., Zhurinov M.Zh., Tuleuov B.I. (1991) Isolation, analysis, structure, biosynthesis and modification of the cytisine alkaloid [Vydeleniye, analiz, stroyeniye, biosintez i modifikatsiya alkaloida tsitizin] Chemistry of Natural Compounds, 3:301-313 (in Rus).

[9] Nasyrov S.Kh., Khazbievich I.S. (1982) Pharmacology of the alkaloid Anabasis Aphilla [Farmakologiya alkaloida Anabasis Aphilla] Fan, Tashkent (in Rus).

[10] Gazaliev A.M., Zhurinov M.Zh., Fazylov S.D. (1992) New bioactive derivatives of alkaloids [Novyye bioaktivnyye proizvodnyye alkaloidov] Gylym, Alma-Ata, 63-66 (in Rus).

[11] Tlegenov R.T.(2007) Synthesis and biological activity of N-acylated derivatives of anabazine alkaloid [Sintez i biologicheskaya aktivnost' N-atsilirovannykh proizvodnykh alkaloida anabazina] Chemistry of plant raw materials, 2:59-62 (in Rus).

[12] Dalimov D.N., Karimov D.T., Weizburg G.M., Abduvahabov A.A., Abdullaeva L.K., Kamaev F.G. (1988) The synthesis of a number of derivatives of alkaloids, nitrogen-containing heterocycles and their anticholinesterase activity [Sintez ryada proizvodnykh alkaloidov, azotsoderzhashchikh geterotsiklov i ikh antikholinesteraznaya aktivnost'] Chemistry of Natural Compounds, 6:825-831 (in Rus).

[13] Svintsitskaya N.I., Dogadina A.V., Ionin B.I. (2009) Synthesis and some transformations of anabazylethindimethylphosphonate [Cintez i nekotoryye prevrashcheniya anabaziletindimetilfosfonata] Journal of General Chemistry, 79(7):1104-1109 (in Rus).

[14] Abduvahabov A.A., Sadykov A.A., Dalimov D.N., Aslanov H.A. (1984) Alkaloids and their derivatives as a tool for studying the cholinergic system [Alkaloidy i ikh proizvodnyye kak instrument dlya izucheniya kholinergicheskoy sistemy] Fan UzSSR, Tashkent (in Rus).

[15] Saprykina V.A., Vinogradova V.I., Ambartsumova R.F., Ibragimov T.F., Sultankulov A., Shakhidoyatov Kh.M. (2004) 1,2,4-Thiadiazole derivatives of cytosine [1,2,4-tiadiazol'nyye proizvodnyye tsitizina] Chemistry of Natural compounds, 5:479-481 (in Rus).

[16] Savchenko A.A., Anisimova E.N., Borisov A.G., Kondakov A.E. (2011) Vitamins as the basis of immunometabolic therapy [Vitaminy kak osnova immunometabolicheskoy terapii] KrasSMU, Krasnoyarsk (in Rus).

[17] Abdullaev N.P., Makhmudov U.S., Tashhodzhaev B., Genzhemuradova G., Levkovich MG, Shakhidoyatov Kh. M. (2009) Structural features of N-acylcytisines [Strukturnyye osobennosti N-atsiltsitizinov] Chemistry of Natural compounds, 6:702-707 (in Rus).

[18] Takagi K., Tanaka M., Murakami Y., Morita H., Aotsuka T. (1986) Synthesis and reactions of some chromones, Eur. J. Med. Chem. Chim. Ther. 21:65-69 (in Eng).

[19] Ankhiwala M.D., Naik H.B. (1991) Chem. Abstr., 4:816 (in Eng).

[20] Kaname T., Masaaki T., Hikari M., Kuniyoshi O., Katsuyuki I., Naoki N., Masayuki O. (1987) Eur. J. Med. Chem., 22:239 (in Eng).

[21] Gordon A., Ford R. (1976) Sputnik chemist [Sputnik khimika] (trans. from English). Mir, Russia (in Rus).