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Chemical Journal of Armenia

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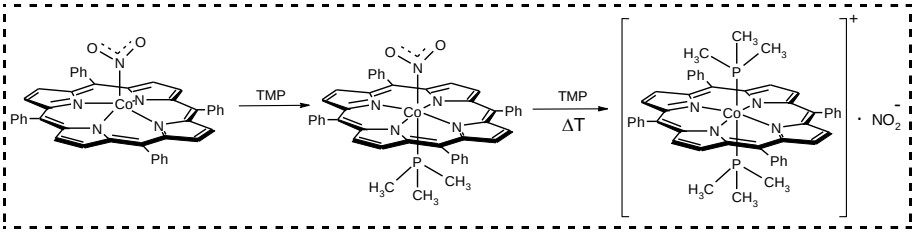
GRAPHICAL ABSTRACTS

Spectral study of trimethyl phosphine interaction with nitro complex of Co-meso-tetraphenyl porphyrin



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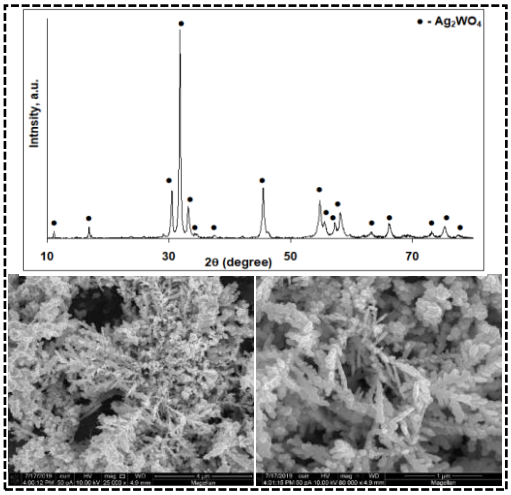

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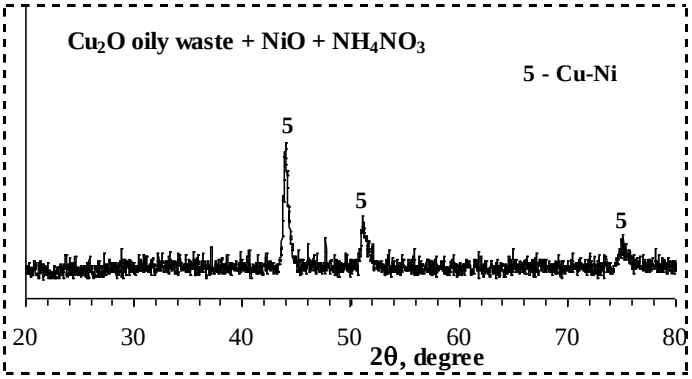

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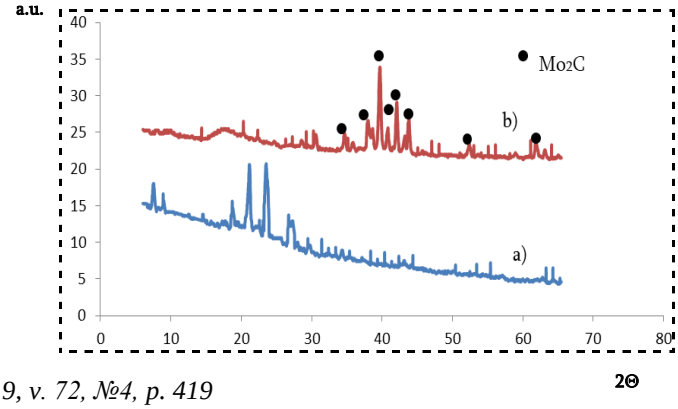

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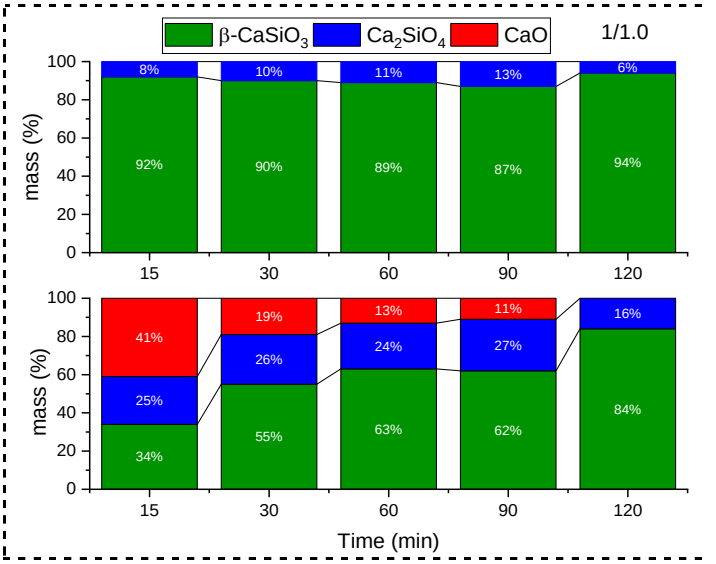

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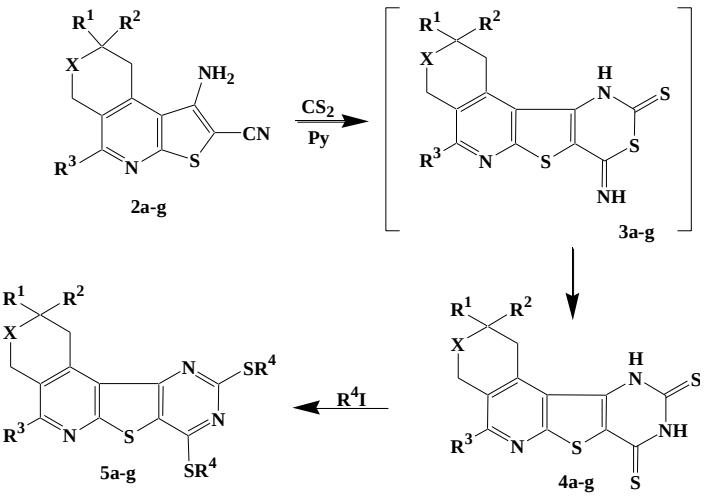

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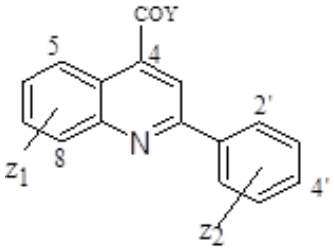

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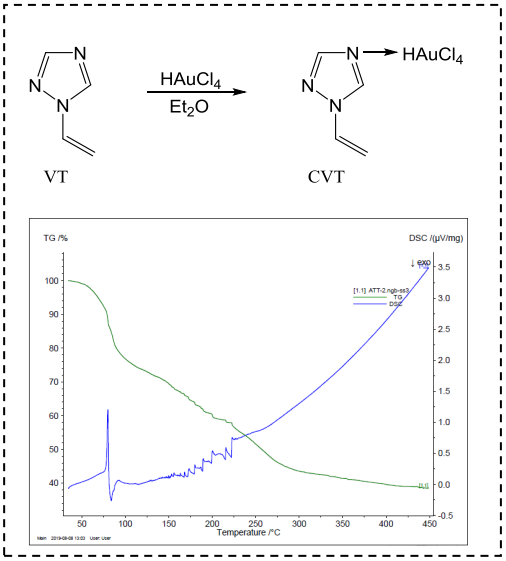

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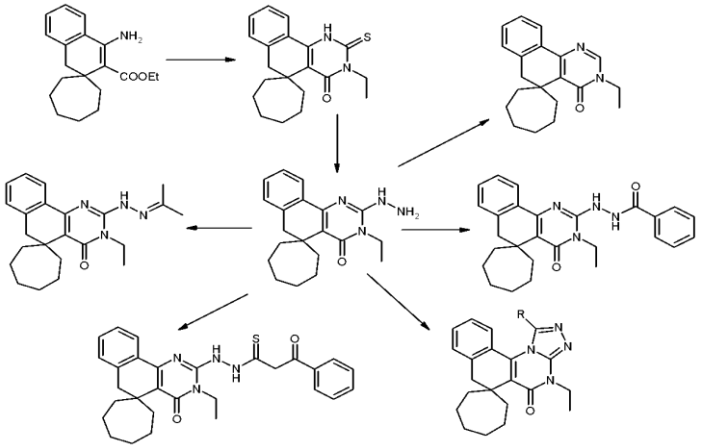

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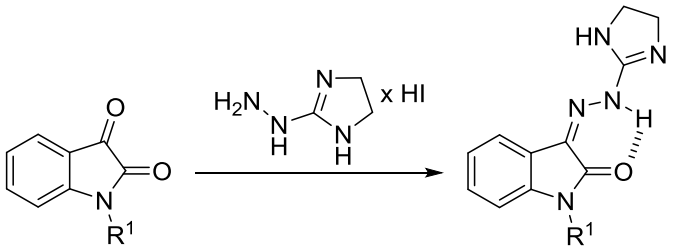

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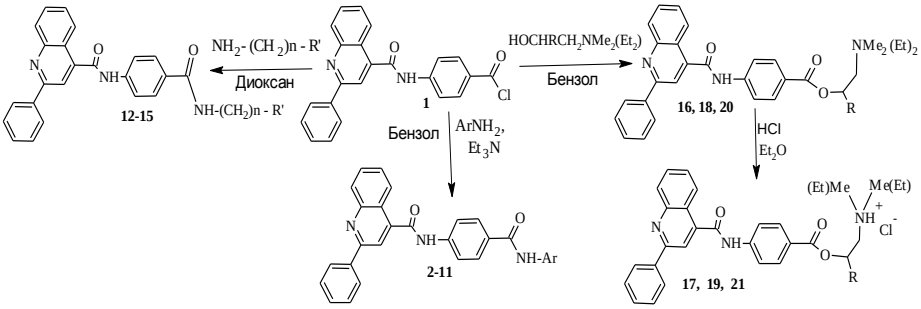

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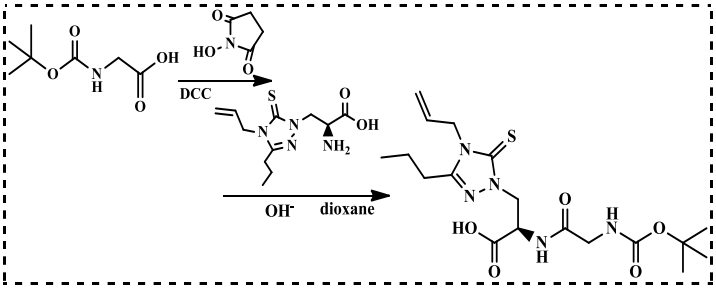

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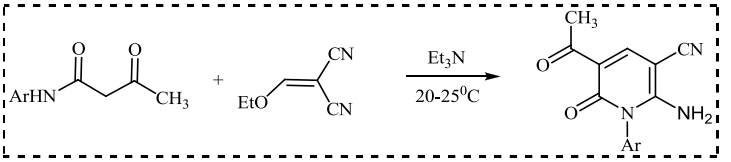

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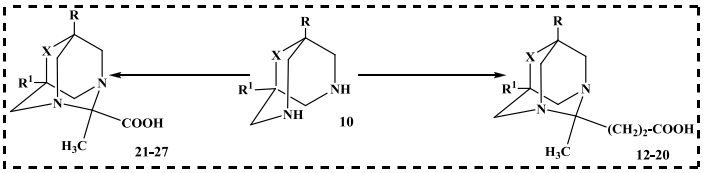
H.A. Panosyan



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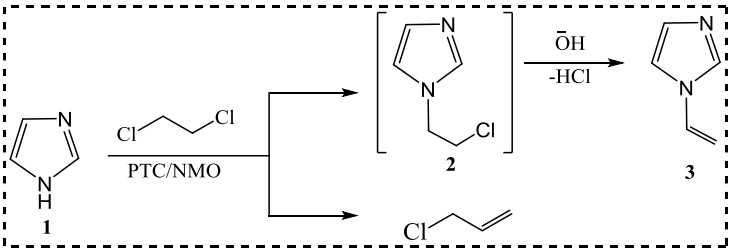
A.H. Hasratyan
A.A. Suqoyan
G.G. Danagulyan
H.S. Attaryan



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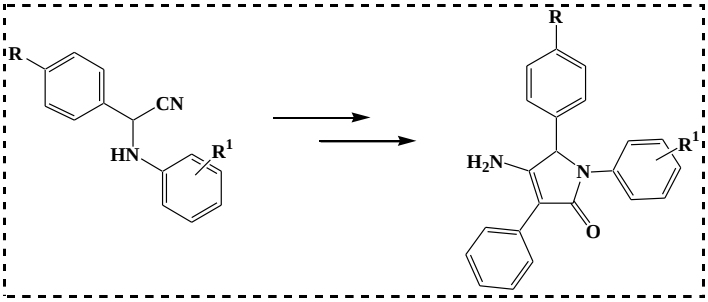

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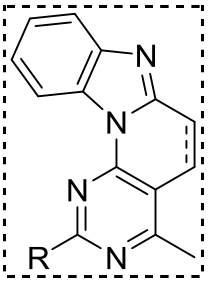
L.S. Hunanyan
A.T. Makichyan
V.S. Khamaryan
A.A. Harutyunyan
G.G. Danagulyan



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НАЦИОНАЛЬНАЯ АКАДЕМИЯ НАУК РЕСПУБЛИКИ АРМЕНИЯ
NATIONAL ACADEMY OF SCIENCES OF THE REPUBLIC OF ARMENIA

Հայաստանի քիմիական հանդես
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GENERAL AND PHYSICAL CHEMISTRY

SPECTRAL STUDY OF TRIMETHYLPHOSPHINE INTERACTION WITH NITRO COMPLEX OF CO-MESO-TETRAPHENYLPORPHYRIN

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Low-temperature reaction of trimethylphosphine (PMe_3) with sublimed layer of Co(TPP) (TPP - *meso*-tetraphenyl-porphyrinato dianion) nitro complex (Co(TPP)(NO_2)) leads initially to formation of the 6-coordinate nitro complex Co(TPP)(NO_2)(PMe_3) that at higher temperature under PMe_3 excess converts to the $\{Co^{III}(TPP)(PMe_3)_2\}\cdot NO_2^-$ as is shown by FTIR spectroscopy reinforced by the data with isotopic $^{15}NO_2^-$ group. Neither Co(TPP)(NO_2)(PMe_3) nor $\{Co^{III}(TPP)(PMe_3)_2\}\cdot NO_2^-$ take part in the oxygen atom transfer reaction from 6-coordinate nitro group or outer sphere NO_2^- anion.

Figs. 4, table 1, references 19.

Nitro complexes of cobalt porphyrins have ability to take part in stoichiometric and catalytic oxo-transfer reactions from the coordinated nitro group to various oxygen acceptors. It was shown by Goodwin and co-workers [1] that five-coordinate nitro complexes are active in the catalytic oxidation of alkenes, while six-coordinate complexes with nitrogen- or oxygen-bound ligands *trans* to the nitro group are not reactive because of unfavorable oxo-transfer thermodynamics. However, derivatives with weakly bound sixth ligands are capable of alkene oxidation perhaps due to the presence of five-coordinate nitro species that exist in equilibrium in a solution. Hence, the nature of the *trans* ligand appears to be an important factor regulating the oxo-transfer reactivity of (cobalt) nitroporphyrins. The six-coordinate nitro complexes of Co-porphyrins are known for trans nitrogen [2-4], sulfur [5], oxygen [6] and phosphorus [7] ligands. Triphenylphosphine was used as a phosphorus ligand and it was found that Ph_3P thermally abstracted an oxygen atom from the NO_2

moiety of $(NO_2)(H_2O)$CoIII(TPP) resulting in the formation of nitrosyl cobalt porphyrin (NO)Co(TPP) and oxidation of Ph_3P to triphenylphosphine oxide Ph_3P=O.

In this paper the interaction of trimethylphosphine (PMe_3) with nitro complex Co(TPP)(NO_2) was studied and it is shown that this reaction leads eventually to the formation of a cationic complex $\{Co(TPP)(PMe_3)_2\}^+$ and outer sphere NO_2^- anion. It is also shown that neither initially formed 6-coordinate nitro complex Co(TPP)$(NO_2)(PMe_3)$ nor eventually formed ion pair $\{Co(TPP)(PMe_3)_2\}^+ \cdot NO_2^-$ promote oxygen atom transfer reaction with formation of trimethylphosphine oxide ($O=PMe_3$) and nitrosylcobalt porphyrin (NO)Co(TPP).

Experimental Section

Co(TPP) was synthesized using a literature method [8]. NO_2 ($^{15}NO_2$) was obtained by oxidation of NO (^{15}NO) with an excess of pure dioxygen. NO was synthesized according to the procedure given in [9] and purified by passing it through KOH pellets and a cold trap (dry ice/acetone) to remove the higher nitrogen oxides and trace quantities of water. The purity was checked by IR measurements of the layer obtained by the slow deposition of NO onto the cold substrate of the optical cryostat (77K). The IR spectrum did not show the presence of N_2O, N_2O_3, or H_2O. ^{15}NO with 98.5% enrichment was purchased from the Institute of Isotopes, Republic of Georgia, and was purified by the same procedures. After preliminary drying under P_2O_5, the NO_2 ($^{15}NO_2$) was purified by fractional distillation using a low-temperature vacuum technique until a pure white solid was obtained. Sublimed layers of Co(TPP) were obtained on the cold (77K) KBr support of an optical cryostat according to a published procedure [10]. The sublimed layers of the nitro complexes Co(TPP)(NO_2) and Co(TPP)$(^{15}NO_2)$ were obtained by supplying a low pressure of NO_2 ($^{15}NO_2$) vapors on the amorphous layers of Co(TPP) as described elsewhere [11]. This procedure rapidly led to the formation of the nitro complex, which manifests itself by an intense $\nu_s(NO_2)/\nu_s(^{15}NO_2)$ band of coordinated NO_2 ($^{15}NO_2$) at 1283 cm^{-1} and 1265 cm^{-1} correspondingly. The unreacted NO_2 ($^{15}NO_2$) was then pumped out, the samples were cooled to 130 K, and small increments of PMe_3 ligand were introduced into the cryostat. Since PMe_3 may be oxidized to the phosphine oxide with an oxygen, as a source of PMe_3 air-stable silver iodide complex AgI(PMe_3) (Aldrich) that releases PMe_3 upon heating was used in the experiments. This complex was placed into glass tube provided with the vacuum valve and was preliminary vacuum-dried at RT. The tube was attached to the cryostat and the vapors of PMe_3 could be obtained in tube by mild heating. Small portions of PMe_3 were then introduced into the cryostat with layered Co(TPP)(NO_2) {Co(TPP)$(^{15}NO_2)$} and FTIR spectra were measured at

different temperatures of the substrates controlled by thermocouple. The FTIR spectra were acquired on a Nexus (Thermo Nicolet, USA) spectrometer.

Results and discussion

It has been shown previously that sublimed layers of *meso*-tetraphenyl porphyrinato cobalt(II) give the five-coordinate nitro complex upon interaction with NO_2 gas [11]. This layered complex was readily transformed to six-coordinate nitro complexes (B)Co(TPP)(NO_2) (B - N-, S- and O-donors) when exposed to the vapors of corresponding compounds [4-6]. Similarly, the introduction of trimethylphosphine (PMe_3) to the layered Co(TPP)(NO_2) led to the species with the new set of FTIR bands in the ranges where normal vibrations of coordinated nitro groups are disposed. The $\nu_{as}(NO_2)$, $\nu_s(NO_2)$, and $\delta(NO_2)$ bands of parent Co(TPP)(NO_2) are observed at 1470, 1283 and 806 cm^{-1} and shift to 1388, 1314 and 808 cm^{-1} (Fig. 1) after stepwise addition of PMe_3 vapors to the layers of Co(TPP)(NO_2) and its warming from 130K to 170K. They have their isotopic counterparts when Co(TPP)($^{15}NO_2$) was used. For this system the bands located at 1444, 1265 and ~800 cm^{-1} shift to 1368, 1288 and 802 cm^{-1} (Fig. 2) and in the spectral range free of the bands of 5-coordinate nitro complexes a new band at 950 cm^{-1} grows in intensity that belongs to the most intense band of coordinated PMe_3. From these data it can be concluded that interaction of trimethylphosphine with Co(TPP)(NO_2) led to the formation of six-coordinate nitro complexes, as shown in Scheme 1 (first reaction). Additionally in this temperature interval a small band in the range of 1230 cm^{-1} begins to grow (dashed arrow in the Fig.1) that has its isotopic analogue at ~1200 cm^{-1} in the experiments with $^{15}NO_2$ (Fig. 2).

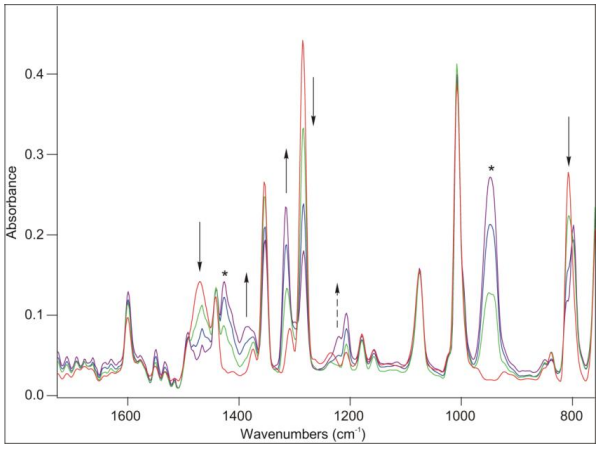

Fig.1. FTIR spectral changes upon stepwise addition of PMe_3 vapors to the layer of Co(TPP)(NO_2) and its warming from 130K to 170K. The bands of coordinated PMe_3 are denoted with asterisks.

Scheme

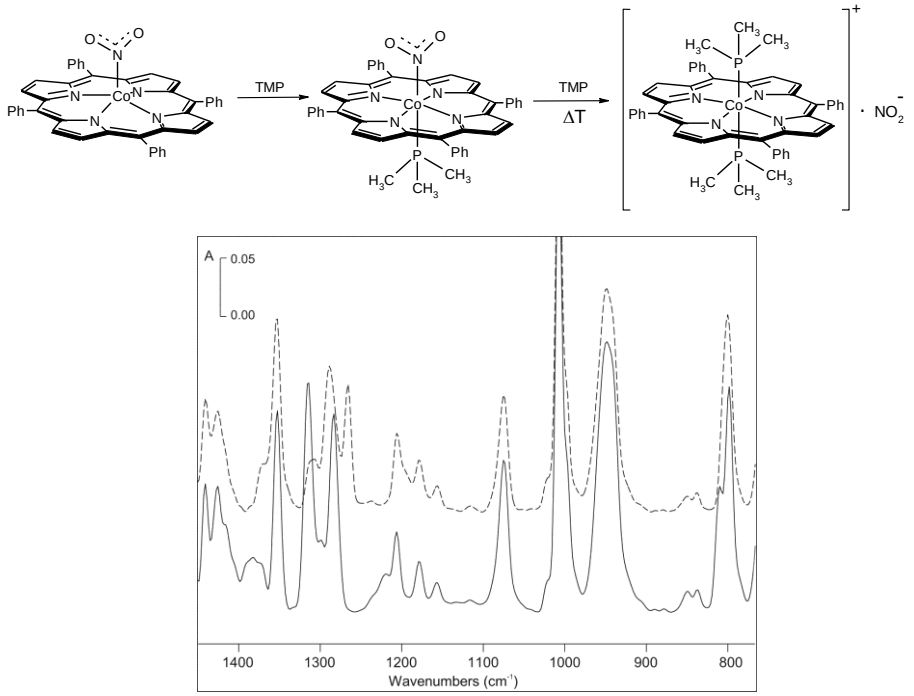

Fig. 2. FTIR spectra at 170K of mostly $Co^{III}(TPP)(PMe_3)(NO_2)$ (solid line) and $Co^{III}(TPP)(PMe_3)(^{15}NO_2)$ (dashed line).

It was found previously for the cobalt nitroporphyrin complexes with different *trans* ligands (L)Co(Por)(NO_2) (L=nitrogen-, sulfur- and oxygen-donors) that there was a negative correlation between the magnitude of the difference of coordinated nitro group asymmetric and symmetric modes $\Delta\nu=\nu_{as}(NO_2)-\nu_s(NO_2)$ and the σ-donor ability of the *trans* ligand [4-6]. A higher extent of the electron density transfer from the *trans* ligands to the nitro group led to the closer disposition of ν_{as} and ν_s, i.e., lesser $\Delta\nu$ values. The same pattern was reported for six-coordinate iron nitroporphyrin complexes [12]. In the case of PMe_3 as a *trans* ligand the values of $\nu_{as}(NO_2)$ and $\nu_s(NO_2)$ are closer to each other than for nitrogen, sulfur and oxygen σ-donor ligands (Table) indicating greater electron density transfer from phosphine to coordinated nitro-group.

Addition of new portions of PMe_3 into the cryostat and further increase in temperature leads to the growth in intensity of a previously noted weak band disposed at 1227 cm^{-1} (Fig. 3). This process is accompanied by complete disappearance of the bands of the six-coordinate nitrocomplexes with *trans* PMe_3 ligand (the weak remaining band at 1315 cm^{-1} belongs to the coordinated PMe_3). In the experiments with $^{15}NO_2$ an isotopic analogue of the 1227 cm^{-1} band appears at 1205 cm^{-1} (Fig. 4).

Table

Spectral characteristics of 6-coordinate nitro complexes (B)Co(TPP)(NO_2)[a]

Donor ligand (B)	ν_{as}	ν_s	δ	$\Delta\nu = \nu_{as} - \nu_s$	Ref.
-	1468(1440)	1282(1264)	805(796)	186(176)	[11]
Tetrahydrofuran	1462(1430)	1300(1279)	808(800)	162(151)	[6]
Acetone	1459(1429)	1300(1281)	810(802)	159(138)	[6]
Dimethylsulfide	1444(1413)	1298(1279)	810(802)	146(134)	[5]
Tetrahydrothiophene	1443(1413)	1300(1282)	810(802)	143(131)	[5]
Piperidine	1436(1403)	1305(1284)	815(805)	131(119)	[4]
Ammonia	1431(1400)	1309(1289)	814(805)	122(111)	[4]
Trimethylphosphine	1388(1368)	1314(1288)	808(802)	74(80)	[this work]

[a]Data for $^{15}NO_2$-labeled compounds are given in parenthesis

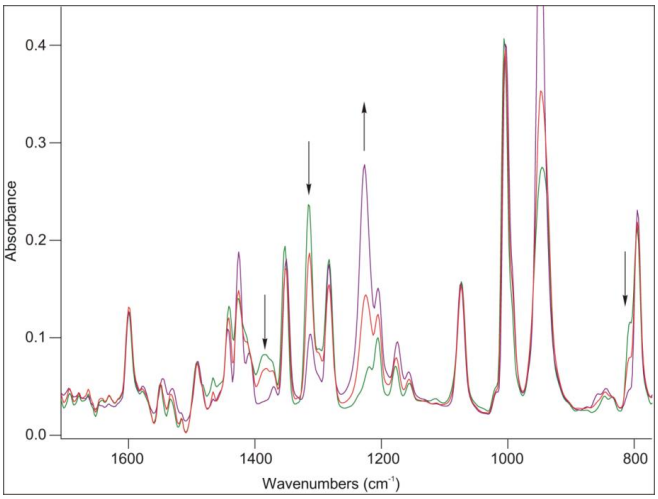

Fig. 3. FTIR spectral changes upon warming the layer, containing mostly $Co^{III}(TPP)(PMe_3)(NO_2)$ from 170K to room temperature.

These data testify for the detachment of the nitro group in the form of a nitrite anion and the occupation of its place by an additional phosphine molecule (the second reaction in the Scheme 1) as evidenced by a sharp increase in the intensity of the coordinated phosphine band with a maximum at 950 cm^{-1} (Fig. 3). A free anion NO_2^- (in the ground electronic state $^1A_1$) is characterized by the point symmetry C_{2v} and has full-symmetric valence vibration ν_1, deformational vibration ν_2, antisymmetric valence vibration ν_3. Indeed, in the nitrite anion NO_2^- that represents the limiting case with greatest extent of the electron density transfer, the $\nu_{as}(NO_2^-)$ and $\nu_s(NO_2^-)$ denoted in the case of anion as ν_3 and ν_1 correspondingly are close to each other, with ν_3 even lower than ν_1 [13]. The

band representing ν_3 is much more intense than that of ν_1 and usually overlaps it. The deformation mode ν_2 is weak and is located near 800 cm^{-1} where the intense porphyrin band is disposed. The fundamentals of NO_2^- are strongly dependent on the measurements conditions. Notably, the ν_3 frequency of $NaNO_2$ measured in Nujol mull is found at 1261 cm^{-1} [14], in aqueous solution it is disposed at 1236 cm^{-1} [14] and in a doped KBr crystal at 8K is reported to be at 1275(1250) cm^{-1} [15]. In the argon matrix, this band is located at 1244(1218) cm^{-1} [16] (data for $^{15}NO_2^-$ are given in parenthesis). These literature data show that both the range where band ν_3 is located and the value of isotopic shift are close to that observed in our system and support our conclusion. As can be seen from these data the ν_3 band shifts to the lower frequency when ionic interactions in the sample weaken.

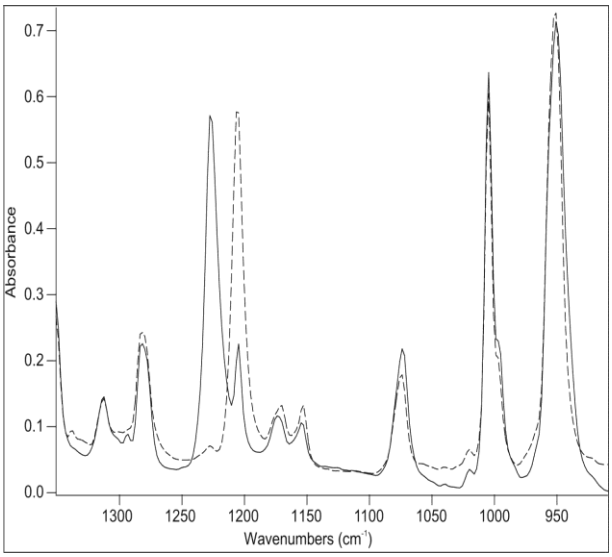

Fig. 4. FTIR spectra of $Co^{III}(TPP)(NO_2)+PMe_3$ (solid line) and $Co^{III}(TPP)(^{15}NO_2)+PMe_3$ (dashed line) after warming these systems to room temperature.

It should be noted that in the experiments with layered $Co(TPP)(NO_2)$, neither the formation of cobalt nitrosylporphyrin, nor the signs of trimethylphosphine oxidation were detected as seen in Figures 1 and 3. There are no new bands in the range 1600 -1700 cm^{-1} where ν(NO) of the five- or six-coordinated nitrosyl complexes of Co-porphyrins are located [5], nor in the range 1050-1200 cm^{-1} where the ν(PO) of free or coordinated trimethylphosphine oxide are disposed [18]. As noted above, when triphenylphosphine was used as a phosphorus ligand it was found that Ph_3P thermally abstracted an oxygen atom from the NO_2 moiety of $(NO_2)(H_2O)Co^{III}TPP$ resulting in the formation of nitrosylcobalt porphyrin (NO)Co(TPP) and oxidation of Ph_3P to triphenylphosphine oxide $Ph_3P{=}O$ [7]. Thus, the cobalt nitroporphyrin complexes with *trans* PMe_3 do not promote the oxo-transfer reaction in contrast to the triphenylphosphine under our

experimental conditions. The reasons for different oxo-transfer reactivity may be connected with the fact that the binding of trimethylphosphine ligand with cobalt nitroporphyrin complexes in $(PMe_3)Co(TPP)(NO_2)$ is much stronger. It is most likely that such a different behavior of the two phosphines is due to their significantly different electron-donating strength. The pK_a values of trimethylphosphine and triphenylphosphine are 8.65 and 2.73, correspondingly. Finally, we assume that the higher stability of the nitro complex with a trimethylphosphine ligand prevents an oxygen atom transfer in our system.

Co-ՄԵԶՈ-ՏԵՏՐԱՖԵՆԻԼՊՈՐՖԻՐԻՆԻ ՆԻՏՐՈ ԿՈՄՊԼԵՔՍԻ ՀԵՏ ԵՌՄԵԹԻԼՖՈՍՖԻՆԻ ՓՈԽԱԶԴԵՑՈՒԹՅԱՆ ՍՊԵԿՏՐԱԼ ՈՒՍՈՒՄՆԱՍԻՐՈՒԹՅՈՒՆԸ

Ա. Ա. ՀՈՎՀԱՆՆԻՍՅԱՆ, Գ. Գ. ՄԱՐՏԻՐՈՍՅԱՆ, Գ. Շ. ՀՈՎՀԱՆՆԻՍՅԱՆ և Տ. Ս. ԿՈՒՐՏԻԿՅԱՆ

Ֆուրիե սպեկտրաչափական եղանակով ուսումնասիրվել է եռմեթիլֆոսֆինի (PMe_3) փոխազդեցությունը Co-մեզո-տետրաֆենիլպորֆիրինի նիտրոկոմպլեքսի ($Co(TPP)NO_2$) հետ: Ռեակցիան ընթանում է երկու փուլերով: Առաջին փուլում ցածր ջերմաստիճաններում (120-170 K) դիտվում է Co-պորֆիրինի տրանս-եռմեթիլֆոսֆին պարունակող նիտրոկոմպլեքսի՝ $(PMe_3)Co(TPP)(NO_2)$ գոյացումը: Ֆոսֆինի նոր չափաբաժինները և տաքացումը մինչև սենյակային ջերմաստիճան հանգեցնում է իոնային զույգի առաջացման՝ բաղկացած երկեռմեթիլֆոսֆին պարունակող կատիոնից $[Co(TPP)(PMe_3)_2]^+$ և նիտրիտ-անիոնից՝ NO_2^-: Այդպիսով PMe_3 դուրս է մղում նիտրոլիգանդը նիտրիտ-անիոնի տեսքով: Ստացված արդյունքները լրացուցիչ հիմնավորում են ստացել $^{15}NO_2$ իզոտոպոմերի կիրառմամբ:

Co-պորֆիրինների նիտրոկոմպլեքսները ընդունակ են մասնակցելու թթվածնի ատոմի տեղափոխման ռեակցիաներում կոորդինացված նիտրոխմբից համապատասխան թթվածնի ակցեպտոր հանդիսացող մոլեկուլի վրա: Ուսումնասիրված համակարգը միկրոծակոտկեն թաղանթներում չի դրսևորում այդպիսի ունակություն, թեև 6-կոորդինացված նիտրոխմբից, թեև նիտրիտ-անիոնից, ի տարբերություն եռֆենիլֆոսֆինի: Դա, ամենայն հավանականությամբ, պայմանավորված է այդ երկու լիգանդների էլեկտրոնատոր հատկությունների զգալի տարբերությամբ:

СПЕКТРАЛЬНОЕ ИССЛЕДОВАНИЕ ВЗАИМОДЕЙСТВИЯ ТРИМЕТИЛФОСФИНА С НИТРОКОМПЛЕКСОМ Co-*МЕЗО*-ТЕТРАФЕНИЛПОРФИРИНА

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Методом Фурье ИК спектроскопии исследовано взаимодействие триметилфосфина (PMe_3) с нитрокомплексом Co-*мезо*-тетрафенилпорфирина. Реакция протекает в две стадии. На первой, при низких температурах (120-170 K), наблюдает-

ся образование 6-координированного нитрокомплекса Co-порфирина, содержащего *транс*-триметилфосфинный лиганд (PMe_3)Co(TPP)(NO_2). Подача новых порций PMe_3 и нагрев системы до комнатной температуры ведет к образованию ионной пары, состоящей из катионного ди-триметилфосфинного комплекса Co-порфирина и нитрит-аниона. Таким образом координированная нитрогруппа вытесняется триметилфосфином в виде нитрит-аниона.

Нитрокомплексы Co-порфиринов способны участвовать в реакции переноса атома кислорода с координированной нитрогруппы на соответствующий акцептор кислорода. Исследованная система, в отличие от трифенилфосфина, не проявляет такой способности ни от 6-координированной нитрогруппы, ни от нитрит-аниона, что, по-видимому, связано со значительным различием в электронодонорной силе этих лигандов.

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НАЦИОНАЛЬНАЯ АКАДЕМИЯ НАУК РЕСПУБЛИКИ АРМЕНИЯ
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Mg-CARBOTHERMAL REDUCTION OF SILVER TUNGSTATE IN COMBUSTION MODE AND SYNTHESIS OF W-Ag PSEUDOALLOY

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W-Ag pseudoalloy was synthesized via reduction of silver tungstate precursor with Mg+C combined reducer in the combustion mode by applying reactions thermo-kinetic coupling approach. It has been revealed that growth of the C/Mg ratio leads to decrease of both the combustion temperature and its velocity conditioned by the growth in the portion of low-caloric reaction of carbothermic reduction. The latter allows to control thermal regime of the reaction for the preparation of fine-grained W-Ag pseudoalloy. Optimum conditions for preparation of W-Ag composite powder were determined.

Figs. 7, table 1, references 20.

Introduction

In recent years, tungsten (W)-based heavy alloys have received increased use in both commercial and industrial areas. Most heavy alloys consist of W particles embedded in matrix of other metals or their alloys such as iron, nickel, silver or copper [1]. In particular, W-Ag alloys can be used as heat dissipation materials in the microelectronic devices that are prone to failure at high operating temperatures, for example, as diverter plates in fusion reactors. They combine the arc erosion and welding resistance of tungsten with the excellent thermal and electrical conductivities of silver. The thermal expansion coefficient of composites can be adjusted by changing their composition to match those of ceramic materials used as substrates in semiconductor devices [2-4]. Powder metallurgy is the technique utilized to manufacture W-Ag alloys, but due to the mutual insolubility of W and Ag and poor wettability of liquid Ag on W, sintering cannot easily produce dense and homogeneous structures [5-6].

Experimental studies relating to the mechanical properties of samples formed from nanocrystalline precursor powders show that these ultra-fine grained materials are fundamentally different from their normal, coarse-grained counterparts [2].

As there is no alloying between the silver and tungsten the properties of the composites depend on direct proportion of their composition, the size, morphology, and distribution of phases within the composite with finer particles giving improved performance [7].

In this work a new pathway for the preparation of W-Ag composite nanopowder/pseudoalloy by energy-saving combustion synthesis (CS) method [8-10] is reported. Silver tungstate is suggested to be used as an initial precursor. In our previous work [11], $Ag+WO_3$ mixture prepared by solution combustion synthesis method for obtaining W-Ag pseudoalloy was used. But in this case both the metals are in the same crystalline structure (Ag_2WO_4), thus the formation of more homogeneous composite is expected.

For reduction of silver tungstate a combined Mg+C reducer was used, which allows to control the reaction temperature in a wide range at the synthesis of W-Ag material. This approach is known as reactions thermo-kinetic coupling [12,13] and its essence consists in the coupling of a low exothermic reduction reaction with a high caloric one with a possible change of the reaction pathway [17-20].

It is worthy to note, that silver tungstate can exhibit three different structural phases; α-, β-, or γ-Ag_2WO_4. Among these polymorphs α-Ag_2WO_4 is the most thermodynamically stable, belonging to orthorhombic symmetry. In its molecule all W atoms are six-coordinated and form WO_6 octahedra. These WO_6, W_2O_6, and W_3O_6 octahedra are connected by sharing edges and grouped altogether at a particular position (Fig. 1). Nevertheless, the number of different sites occupied by the Ag atoms in Ag_2WO_4 is six [14-15].

Experimental part

The following raw materials were used in experiments: sodium tungstate ($Na_2WO_4 \cdot 2H_2O$, chemically pure grade), silver nitrate ($AgNO_3$, 7761-88-8, Czechia), magnesium (MPF-3, Russia, pure grade, particle size 0.15 *mm* < μ< 0.3 *mm*), carbon (P-803, Russia, μ < 0.1 *μm*).

Chemical precipitation synthesis route was employed for the preparation of α-Ag_2WO_4 nanoparticles. This method possesses good stoichiometric control and production of ultrafine particles with high purity and improved compositional homogeneity in a relatively short processing time at lower temperatures. Nanocrystalline silver tungstate samples were prepared by reacting aqueous solutions of silver nitrate and sodium tungstate. These solutions were mixed slowly in 2:1 molar ratio with contineous stirring at room temperature for 20 *min*, keeping the pH value at constant magnitude 7. The

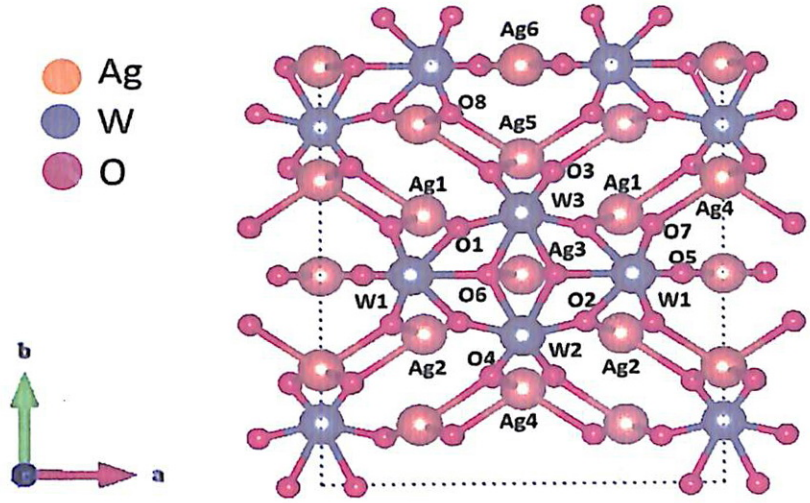

Fig. 1. Ball and stick model of the crystal structure of the α-Ag_2WO_4.

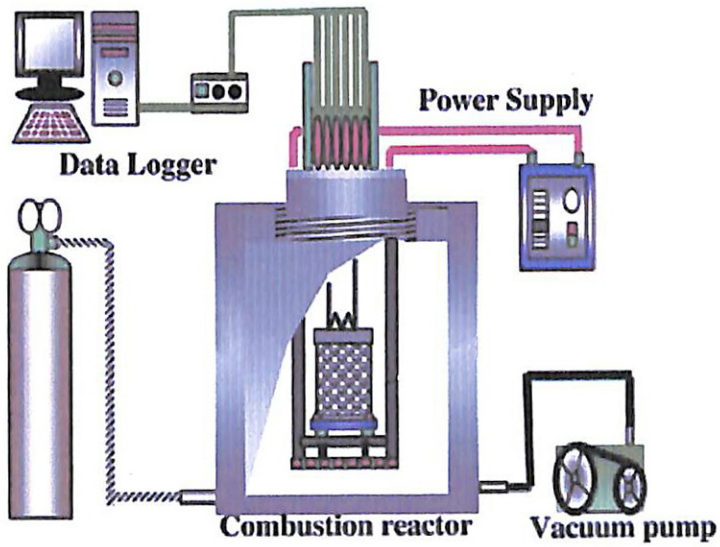

Fig. 2. The Scheme of experimental setup.

precipitate formed was centrifuged, filtered and washed by ethanol, then several times by distilled water. The product was dried at 70^{o}C for 4 *h*. The final product was light yellow in color.

After drying, the product was homogenized in a ceramic mortar with Mg/C mixture for 10 *minutes* and cylindrical samples with 1-1.5 $g \cdot cm^{-3}$ density, 20-25 *mm* height and 20 *mm* in diameter were prepared. The prepared samples were placed in a reaction chamber CPR-3L (Fig. 2) which was sealed, evacuated, purged with nitrogen (purity 99.97 *%*, oxygen content less than 0.02%) and filled to the desired pressure (0.5 *MPa*).

The combustion process was initiated with short heating of a tungsten spiral (18 *V*, 2 *s*) from the upper surface of the sample. The combustion temperature (T_c) and combustion velocity (U_c) were measured using two C-type tungsten-rhenium thermocouples (W-5Re/W-20Re), each 100 μm in diameter. The thermocouples were inserted into the sample at a depth of 10 *mm* with a distance 10 *mm* between each other. The standard measurement errors for T_c and U_c were ± 20^{o}C and 5% respectively. The output signals of thermocouples were transformed by a multichannel acquisition system and recorded by a computer with a frequency up to 2 *KHz*. The average of maxima for two temperature profiles was calculated as the combustion temperature (T_c). The average value of the combustion velocity was calculated by the formula: $U_c = L \cdot (\Delta t)^{-1}$, where L is the distance between the thermocouples, Δt is the time distance between the signals of thermocouples.

Phase composition of the samples was analyzed by X-ray diffraction (XRD; D5005, Bruker, USA) using CuKα1 radiation (λ = 1.5406 Å) with a step of 0.02° (2θ) and a count time of 0.4 *s*. To identify the products from the XRD spectra, the data were processed using the JCPDS database.

Results and discussion

Characterization of nanostructured precursor

It is well known that the selection of the starting materials can highly contribute to enhancing the structure and properties of the final products. Based on that, fine precursor representing silver tungstate, was prepared by chemical precipitation method using silver nitrate and sodium tungstate as raw materials.

$$2Ag(NO_3) + Na_2WO_4 \cdot 2H_2O = Ag_2WO_4\downarrow + 2NaNO_3 + 2H_2O$$

The composition of the product, ascertained by the XRD analysis, has shown that it is single phase α-Ag_2WO_4 (Fig. 3).

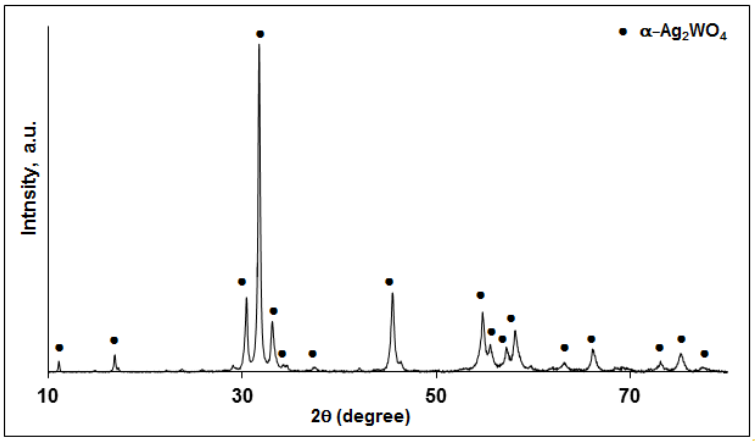

Fig. 3. XRD pattern of the product obtained by chemical precipitation method.

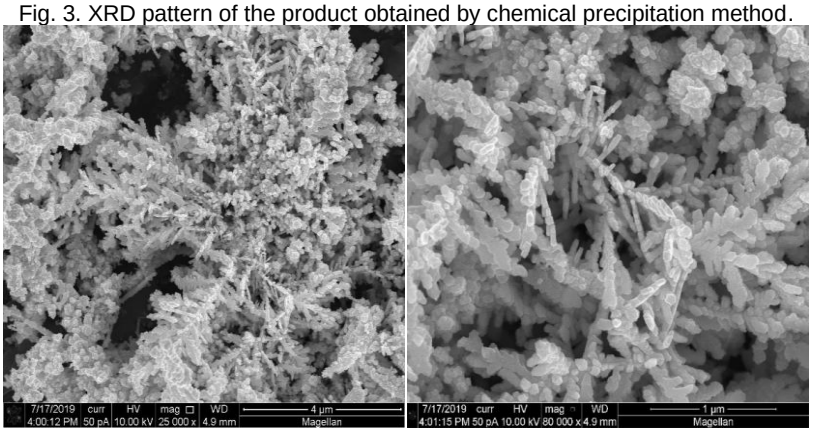

Fig. 4. SEM images of the product obtained by chemical precipitation method.

Microstructural examinations testify that the final product obtained by chemical precipitation represents fine-grained rod-like particles with average size 10-20 *nm* (Fig. 4).

Thermodynamic analysis results

Prior to the experimental investigations thermodynamical analysis has been performed in a wide range of reducers' amounts in order to reveal the possibility of silver and tungsten reduction from Ag_2WO_4 under the combustion mode, as well as to find the optimal conditions for formation of Ag-W alloy by using "ISMAN-THERMO" software package [16]. The latter enables to calculate adiabatic combustion temperature (T_{ad}) and equilibrium composition of combustion products. The main calculations were carried out for the pressure 0.5 *MPa*. As a result, corresponding phase diagram was constructed depending on magnesium and carbon amounts (Fig. 5). As can be seen, there are different areas of products formation depending on the amount of magnesium and carbon. Formation of the target product is achieveable in a definite area of magnesium (from 1.55 to 2.1 *moles*) and carbon (from 1.5 to 1.9 *moles*) amounts (marked on

Fig. 5). Within this area the calculated values of the adiabatic temperature changed from 1500 to 1900°C.

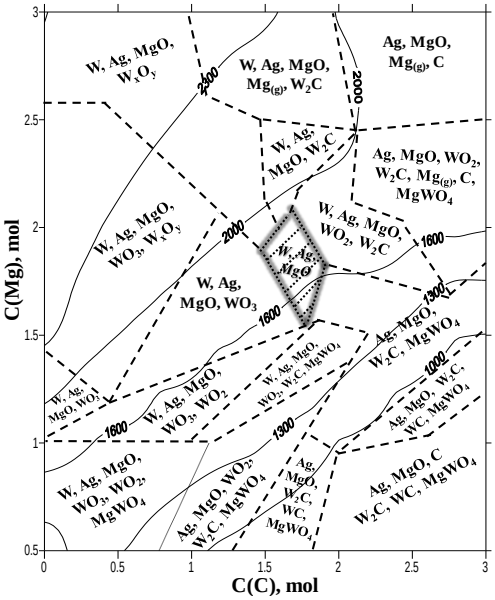

Fig. 5. Thermodynamic analysis results for the Ag_2WO_4-yMg-xC system, P = 0.5 *MPa.*

According to the thermodynamic calculations, within the whole interval of reducers' amount the main gaseous products are CO and CO_2. At that, the ratio of carbon oxides (CO/CO_2) depends on the temperature and with its increasing this ratio increases too.

For preparing tungsten-silver composite powders with homogenous microstructure characteristics and enhanced properties the SHS co-reduction of the prepared salt was performed. For selecting optimal composition of the Ag_2WO_4-yMg-xC initial charge and to reveal the influence of reducers' amount on the combustion parameters to yield the target W-Ag alloy a series of experiments was carried out at a constant magnesium content (1.6 *moles*) and a varying carbon amount within certain intervals, at nitrogen pressure of 0.5 *MPa* (Fig. 6). The mentioned amount of magnesium was selected on the basis of thermodynamically calculated optimal area.

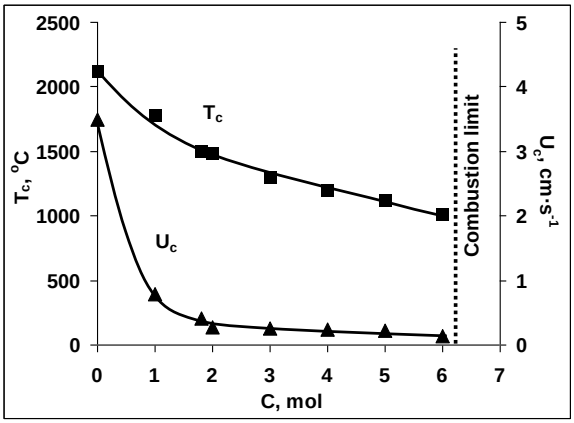

Fig. 6. Combustion temperature and velocity vs carbon amount for the Ag_2WO_4-yMg-xC system, P = 0 .5 *Mpa.*

According to the results obtained, with the increase of carbon amount in a green mixture, both combustion parameters (T_c, U_c) decrease, thus creating moderate thermal conditions for implementing the reduction reaction, which is very important for preparing nanomaterials. This phenomenon is conditoned by the growth in the portion of low-caloric carbothermal reactions in the system. As may be seen from Figure 6, increase of carbon amount (from 0 up to 6 *moles*) causes a drop in the combustion velocity by 25 times (from 3.50 to 0.14 *cm/s*), and combustion temperature - about 2 times (from 2100 to 1000°C). According to the results, at x = 6.25 *mole* combustion limit is observed.

Table

Phase composition of combustion products for the Ag_2WO_4+1.6Mg+xC mixtures

Carbon amount	Phase composition
x = (0-2) mole	Ag, W, MgO, $MgWO_4$
x = (2-3) mole	Ag, W, MgO
x = (4-6) mole	Ag, W, MgO, W_2C

To determine phase composition of the combustion products, XRD analysis was performed indicating that the reduction degree increases with the increase of carbon amount. According to the results obtained, magnesium tungstate was formed at small amounts of carbon (x < 2). The amount of magnesium tungstate decreases in parallel with the increase of carbon amount and fully disappears in the combustion products beginning at x = 2 *moles*. At higher amounts of carbon (x > 3), along with the metals formation of tungsten carbide was observed (Table).

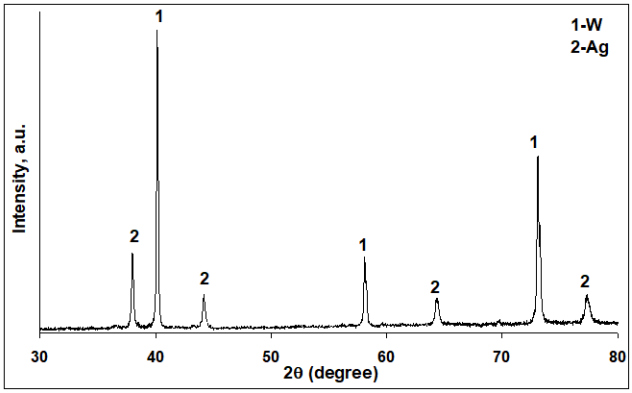

Fig. 7. XRD pattern of the combustion product for the Ag_2WO_4+1.6Mg+2.5C mixture after acid traetment.

For removing magnesia byproduct from the target metals, the reaction products after cooling, were crushed into a powder, subjected to acid treatment by hydrochloric acid (ω = 10%) at room temperature, washed with deionized water and dried in vacuum oven (at 90°C for 2 *hours*).

According to XRD analysis results, after acid leaching the product contained only target metals (Fig. 7).

Thus, it was established that the reduction of silver tungstate under combustion mode using a Mg+C combined reducer (in the ratio of 1.6:2.5 *moles*) enabled at moderate thermal conditions to obtain the target W-Ag composite powders with necessary purity.

ԱՐԾԱԹԻ ՎՈԼՖՐԱՄԱՏԻ ՄԱԳՆԵԶԻՈՒՄԱ-ԿԱՐԲՈԹԵՐՄ ՎԵՐԱԿԱՆԳՆՈՒՄՆ ԱՅՐՄԱՆ ՌԵԺԻՄՈՒՄ ԵՎ W-Ag ԿԵՂԾ ՀԱՄԱՁՈՒԼՎԱԾՔԻ ՍԻՆԹԵԶԸ

Մ. Կ. ՋԱՔԱՐՅԱՆ

Ուսումնասիրվել է այրման ռեժիմում W-Ag կեղծ համաձուլվածքի ստացման հնարավորությունն արծաթի վոլֆրամատից, Mg+C համակցված վերականգնիչով, կիրառելով ռեակցիաների ջերմակինետիկական զուգորդման մոտեցումը: Ցույց է տրվել, որ C/Mg հարաբերության մեծացմանը զուգընթաց նվազում է ինչպես այրման ջերմաստիճանը, այնպես էլ այրման ալիքի տարածման արագությունը՝ պայմանավորված ցածրկալորիական կարբոթերմ վերականգնման ռեակցիայի մասնաբաժնի ավելացմամբ: Վերջինս թույլ է տալիս կառավարել այրման պրոցեսի ջերմային ռեժիմը, ինչը կարևոր է նանոչափսի փոշիների ստացման համար: Գտնվել են օպտիմալ պայմաններ W-Ag կոմպոզիտային փոշու ստացման համար:

МАГНИЙ-КАРБОТЕРМИЧЕСКОЕ ВОССТАНОВЛЕНИЕ ВОЛЬФРАМАТА СЕРЕБРА В РЕЖИМЕ ГОРЕНИЯ И СИНТЕЗ ПСЕВДОСПЛАВА W-Ag

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В работе исследована возможность получения псевдосплава W-Ag путем восстановления вольфрамата серебра в режиме горения комбинированным восстановителем Mg+C с применением метода термо-кинетического сопряжения реакций. Выявлено, что с ростом отношения C/Mg имеет место уменьшение как температуры, так и скорости горения, обусловленное ростом доли низкокалорийной реакции карботермического восстановления. Последнее позволяет контролировать тепловой режим протекания реакции, что важно для получения наноразмерных материалов. Найдены оптимальные условия получения композитного порошка W-Ag.

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ՀԱՅԱՍՏԱՆԻ ՀԱՆՐԱՊԵՏՈՒԹՅԱՆ ԳԻՏՈՒԹՅՈՒՆՆԵՐԻ
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НАЦИОНАЛЬНАЯ АКАДЕМИЯ НАУК РЕСПУБЛИКИ АРМЕНИЯ
NATIONAL ACADEMY OF SCIENCES OF THE REPUBLIC OF ARMENIA

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COMBUSTION IN COPPER (I) OXIDE WASTE-NiO-NH_4NO_3 SYSTEM AND SYNTHESIS OF Cu-Ni ALLOYS

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In this work the reactions thermal coupling approach was applied for the joint reduction of Cu and Ni from the mixture of copper (I) oxide waste and nickel (II) oxide in the combustion mode, targeting the preparation of Cu+Ni composite powders and Cu-Ni alloys in a single step. The experiments for reduction of both the metals in the combustion wave were implemented in the presence of ammonium nitrate (Nt) without introducing any additional reducing agent. To achieve complete reduction of metals, combustion laws in the Cu_2O(oily waste)-NiO-Nt system by using copper oxide (I) waste with different content of oil and at different ratios of metal oxides in the initial mixture were investigated. Optimal conditions for obtaining Cu+Ni composite powders and Cu-Ni alloys from copper waste and NiO powder depending on the content of oil and ammonium nitrate were determined.

Figs. 8, references 19.

Introduction

Alloys based on copper and nickel are distinguished by excellent mechanical properties, corrosion resistance, technological effectiveness and special electrical properties, which lead to their widespread use in different technologies. Copper-nickel alloys are used in the electrical engineering, shipbuilding, aviation and space industry, in the production of nuclear reactors, medical equipment, dishes, devices with shape memory, for special coatings, as well as catalysts for the hydrogenation of various organic compounds, for deep

oxidation of CO and various hydrocarbons, dry reforming of methane with carbon dioxide, etc. [1,2].

In the wiring industry at production of copper wires and cables about 0.6-0.7 wt.% of copper is converted into waste representing mainly copper (I) oxide [3]. Therewith, on all stages of rolling for decreasing the friction forces of moving details, as well as preventing deep oxidation of the metal, hydrocarbon-based mineral oils are used as lubricants. Utilization of such wastes requires reliable methods for their reprocessing back into copper [4-5].

One of the ways for utilization of the oily copper wastes is to remove the oil with a suitable organic solvent and then reduce the oil-free waste to metallic copper. For this purpose, one can use both traditional furnace methods using carbon or hydrogen as a reducing agent [1,6,7] and the method of self-propagating high-temperature synthesis (SHS) [8,9] using a combined reducing agent: polystyrene [10-12].

The possibility of copper (II) oxide reduction under the combustion mode has been shown for the first time in [10] by using combined organic reducers: polystyrene (PS), polyethylene (PE), urotropin, etc. Then this approach was developed in [11-15] and extended for reduction of other oxides (Cu_2O, NiO, CoO, Co_3O_4) and oxygenous salts ($Ni_2(OH)_2CO_3$, $Cu_2(OH)_2CO_3$, $CoSO_4$), as well as for joint reduction of CuO with Cu_2O, CuO with NiO, NiO with Co_3O_4 to produce metal powders and alloys. In these cases, for which the reduction by polystyrene are weak exothermic reactions, it becomes necessary to use a high-caloric additive, containing polystyrene and a strong oxidizer – NH_4NO_3 (hereinafter Nt) and apply the coupling of low-caloric MeO+PS and high-caloric PS+Nt reactions approach in the combustion mode [16,17].

In the work [18] copper (I) oxide waste reduction was studied after preliminary removing the oil, which is a labor-intensive and expensive procedure. It was shown that complete reduction of copper from copper (I) oxide waste in the combustion mode is possible by using the PS+Nt mixture. Recently the complete reduction of copper from oily copper waste in the combustion mode was performed without preliminary cleaning stage adding only ammonium nitrate to the initial mixture. It was supposed that due to its hydrocarbonic nature, the oil could serve as a combined reducer instead of polystyrene for reduction of copper (I) oxide [19].

In this work the reactions' thermal coupling approach was applied for the joint reduction of copper (I) oxide waste and nickel oxide in the combustion mode targeting the preparation of composite powders and Cu-Ni alloys in a single step. To achieve this aim, combustion laws in the Cu_2O(oily waste)-NiO-Nt system by using the copper oxide (I) waste with different content of oil and at different ratios of metal oxides in the initial mixture were investigated. In this case, as well as at reduction of oily copper (I) oxide waste [19] the proposed approach intends to take the advantage of the hydrocarbonic nature of the oil and utilize it as a combined reducer for the joint reduction of copper and nickel

oxides. For increasing the exothermic effect of low caloric $Cu_2O+C_nH_m$ and $NiO+C_nH_m$ reactions and performing joint reduction of both the oxides to metallic Cu and Ni in combustion mode, the reactions' thermal coupling approach was applied.

Determination of optimal conditions of the process was based on the results of preliminary thermodynamic calculations for the system under study. Note that at certain ratio of the reagents the adiabatic temperature for PS + Nt reaction reaches 2000°C. Close values of T_{ad} were attained at using other hydrocarbons instead of PS, including the above mentioned mineral oils. In the case of Cu_2O–NiO-C_nH_m-Nt system the adiabatic temperature for the combined combustion-reduction process is within the range of 700-1200°C, which is sufficient for self-sustained reduction of copper and nickel oxides.

Materials and methods

The copper-containing oily waste of wiring industry used in this work represents mainly copper (I) oxide with small amount of metallic copper and comprises plate-like particles with linear size up to 1.6 *mm* (particles with linear size less than 0.4 *mm* account for about 90 wt.%) and thickness up to 0.25 *mm*. The composition of the initial copper waste was examined by XRD analysis (Fig. 1a) and particle size distribution was determined by sieve analysis (Fig. 1b). The content of mineral oil (a mixture of various unsaturated and saturated aliphatic and aromatic hydrocarbons, hereinafter C_nH_m) in the copper waste determined by the mass loss after diethyl ether treatment typically was up to 5 wt.%, and for special cases reached up to 15 wt.%. The content of carbon and hydrogen in the oil were approximately 85 and 15 wt.%, respectively.

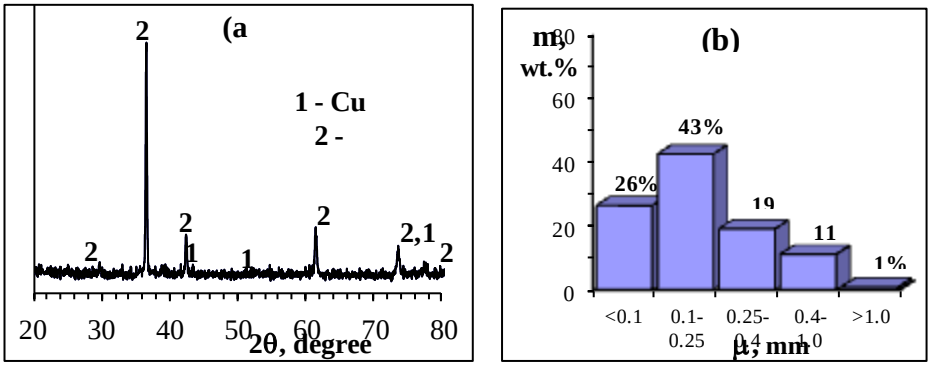

Fig. 1. XRD pattern (a) and histogram (b) of the inital copper (I) oxide waste.

Copper waste with particle size less than 1.6 *mm*, containing different amounts of oil (11 and 15 wt.%), nickel oxide powder (Pure grade, Russia) with particle size less than 0.1 *mm* (<0.05 *mm* - ~95 wt.%) and granulated ammonium

nitrate with granule size less than 3 *mm* (mark B, high grade, GOST 2-85, Russia) were used as the initial reagents (Fig. 2).

In experiments cylindrical pellets 20 *mm* in diameter and 45-50 *mm* height with 2.0÷2.5 $g \cdot cm^{-3}$ density (relative density: Δ=0.3÷0.5) were prepared from initial mixtures: [Cu_2O + **m**(oil)] + **y**NiO + **x**(Nt). Main variables in combustion experiments were **x** *(moles)*, **y** *(moles)* and **m** (wt.%) values. The prepared samples were placed in a reaction chamber CPR-2.5 L. The reactor was sealed, evacuated, purged with nitrogen (purity 99.97 %, oxygen content less than 0.02%) and filled to the desired pressure (typically 0.5 *MPa*). The combustion process was initiated with short heating of tungsten spiral (18 *V*, 2 *s*) from the upper surface of the sample. Combustion temperature (T_c) and combustion velocity (U_c) were measured by two K-type chromel-alumel thermocouples (with 0.2 *mm* in diameter) covered with a thin layer of boron nitride. The thermocouples were placed into the sample with depth of 10 *mm*, and 15-20 *mm* distance from each other. The standard errors of measurement for T_c and U_c were ± 10^oC and 5%, respectively. The output signals of thermocouples were transformed by a multichannel acquisition system and recorded by a computer with frequency up to 1 KHz. After cooling, the reacted samples were extracted from the reactor and crushed into a powder. Final products were examined by XRD analysis with monochromatic CuK_α radiation, wavelength 1.54056 Å (diffractometer DRON-3.0, Burevestnik, Russia) operated at 25 kV and 10 *mA*. To identify the products from the XRD spectra, the data were processed using the JCPDS database. The microstructure of powders was examined by scanning electron microscopes BS-300 and CamScan MV2300. Carbon content in the final product and in oil was determined using Leco SC-444 carbon/sulfur analyzer.

Results and discussion

Combustion laws of the Cu_2O(oily waste) + yNiO + xNH_4NO_3 mixtures

Combustion experiments for the [Cu_2O + **m** (oil)] + **y**NiO + **x**(Nt) mixtures were carried out in a wide range of the parameter **x** ($0 \le \mathbf{x} \le 1.2$) for copper waste with different contents of oil (**m**) and different ratios of metal oxides (**y**) in the initial mixture. The dependences of the combustion temperature and velocity, as well as mass loss of the samples versus parameters **x, m** and **y** were obtained, the chemical and phase compositions of the combustion products were determined. The reduction degree of the metals from oxides was primarily estimated from mass loss of the samples after combustion.

The choice of specific values and ranges of the parameters ***m*** and ***y*** was carried out on the basis of the data of combustion diagram for the [Cu_2O - **m**(oil)] - **x**(Nt) system in the coordinates ***m***(oil) - ***x*** (Nt) [10]. For experimental studies, two batches of waste with an oil content of ***m*** = 11, 15 wt.% and two compositions with a nickel oxide content of: ***y*** = 1 and 2 mol were selected. For

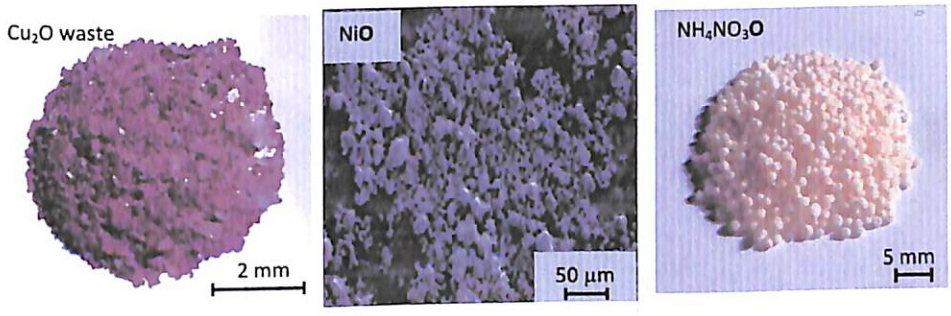

Fig. 2. Photos/micrograph of the inital copper (I) oxide oily waste, nickel oxide and ammonium nitrate.

each case the effect of the content of ammonium nitrate on the combustion laws, phase and chemical composition of the combustion products was studied.

Combustion laws of the [Cu_2O+11 wt.% (oil)] + yNiO + x(Nt) mixtures

The experimental results obtained for the [Cu_2O+11% (oil)]+NiO+**x**(Nt) and [Cu_2O+11%(oil)]+2NiO+**x**(Nt) mixtures at varying the parameter ***x*** in the intervals $0<x\leq0.9$ and $0<x\leq1.2$, respectively, are presented in Figures 3 and 4. As can be seen from Fig. 3a, at ***x*** = 0.2, a lower combustion limit is observed for the ammonium nitrate content in the initial mixture ***y***=1. In the case of ***y***=2 (Fig. 3b) a noticeable shift in the lower combustion limit (***x***=0.25) is observed towards high values of the parameter ***x***. Figure 3 also shows that in both cases, an increase in the parameter ***x*** leads to an increase in both the combustion temperature and velocity, as well as the loss in sample mass (**Δm**), which is associated with increasing the share of the strong exothermic reaction (C_nH_m+Nt) in the total process.

It should be noted that in the studied intervals of the parameter **x**, namely at $0.25\leq x\leq0.9$ and $0.35\leq x\leq1.2$ increase in the combustion parameters (T_c and U_c) shows a tendency to saturation. Figure 3a, b compares also the calculated mass loss data for complete joint reduction of metals (Cu, Ni) from a mixture of the corresponding oxides (solid curve) with experimental values (points) for different ***x*** values. The mismatch between the calculated and experimental values in the mass loss indicates to incompleteness of metal reduction and the presence of unreacted oxides of one or both metals in the final products.

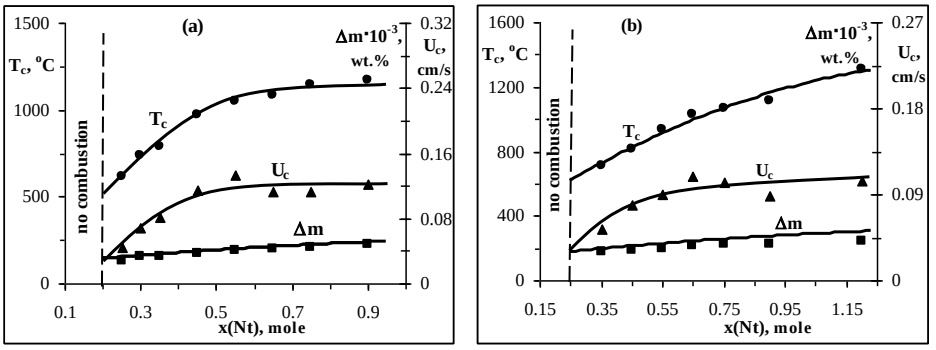

Fig. 3. Combustion temperature (T_c), velocity (U_c) and mass loss (Δm) vs. **x** value for the [Cu_2O-11wt.%(oil)]-NiO-**x**(Nt) (a) and [Cu_2O-11wt.%(oil)]-2NiO-**x**(Nt) (b) systems.

According to the results of XRD analysis, for both the systems under consideration, in the whole range of ***x*** parameter variation, complete reduction of the metals does not take place. Combustion products, except the reduced metals, contain also the oxides of corresponding metals, mainly NiO (Fig. 4). Note, that formation of monophase Cu-0.5Ni alloy (containing 32 wt.% Ni) and Cu-Ni alloy (containing 48 wt.% Ni) even at relatively high combustion temperatures has not been observed for lack of sufficient amount of the reducing agent (oil). Carbon content in the combustion products was measured to be 0.07-0.20 wt.%, at that low content of carbon was observed at higher amount of Nt.

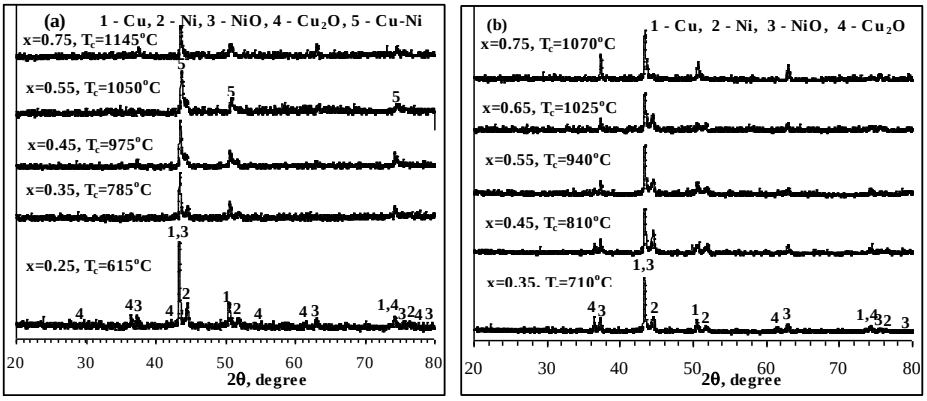

Fig. 4. XRD patterns of the combustion products for the [Cu_2O-11 wt.%(oil)]-NiO-**x**(Nt) (a) and [Cu_2O-11wt.%(oil)]-2NiO-**x**(Nt) (b) systems at different **x** values.

Thus, full joint reduction of both the metals and formation of Cu-Ni composite powders and alloys under the combustion mode by using copper waste with 11 wt.% of the oil content was not observed. Copper waste containing 11 wt.% of oil can be used only for obtaining Cu-Ni alloys with less than 32 wt.% of Ni. So for the SHS processing of the copper waste to Cu-0.5Ni and Cu-Ni alloys it is necessary to use copper waste with higher (more than 11 wt.%) content of oil.

Combustion laws of the [Cu_2O+15 wt.% (oil)]+yNiO+x(Nt) mixtures

In Figures 5 and 6 the results for combustion of the [Cu_2O-15wt.%(oil)]-**y**NiO-**x**(Nt) system at y=1 and 2 are presented. In this case lower combustion limit is observed at the same values (x=0.2 and x=0.25) as for the copper waste with 11 wt.% content of oil. It is obvious that increase in the parameter x in the intervals of $0.2<x\leq0.9$ (Fig. 5a) and $0.25<x\leq1.2$ (Fig. 5b) leads to the increase in both the combustion temperature and velocity, as well as in the mass loss of the samples (**Δm**), which is associated with an increase in the portion of the strong exothermic reaction (C_nH_m + Nt) in the total process similar to the case of using copper waste with 11 wt.% content of oil. Thus, combustion in the mentioned system leads to complete reduction of both the metals and formation of solid solutions or alloys of the reduced metals.

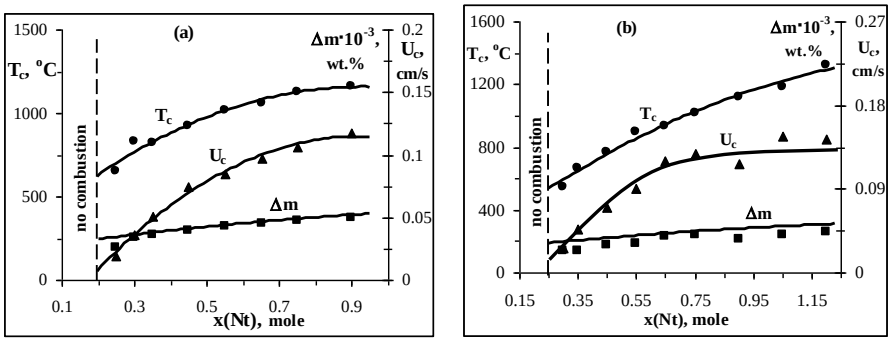

Fig. 5. Combustion temperature (T_c), velocity (U_c) and mass loss (Δm) vs. **x** for the [Cu_2O-15wt.%(oil)]-NiO-**x**(Nt) (a) and [Cu_2O-15wt.%(oil)]-2NiO-**x**(Nt) (b) systems.

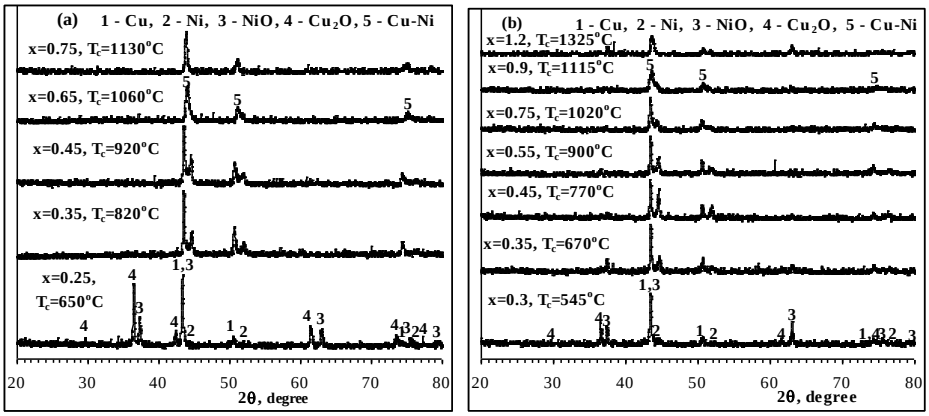

Fig. 6. XRD patterns of the combustion products for the [Cu_2O-15wt.%(oil)]-NiO-**x**(Nt) (a) and [Cu_2O-15wt.%(oil)]-2NiO-**x**(Nt) (b) systems at different **x** values.

According to the results of XRD analysis, in the case of the [Cu_2O-15wt.%(oil)]-NiO-**x**(Nt) system complete reduction of both the metals takes place with formation of a monophase product at $x>0.55$, representing Cu-0.5Ni alloy that contains 32 wt.% of Ni (Fig. 6a). Full reduction of the metals and formation of solid solution (Cu-0.5Ni alloy) is due to sufficient amount of the reducing agent (oil) and relatively high combustion temperatures ensuring the formation of reduced copper in the molten state that follows from the pictures shown in Fig. 7.

In the case of the [Cu_2O-15wt.%(oil)]-2NiO-**x**(Nt) system complete reduction of the metals is observed within the interval $0.55<x\leq0.9$ yielding a monophase Cu-Ni alloy that contains 48 wt.% of Ni at $x=0.9$. At $x>0.9$ due to an excess of the oxidizing agent, among the combustion products unreduced oxides remain too (Fig. 6b). Incompleteness of the reduction of metals is expressed also by the difference in the calculated **(**curve) and experimental (points) values of the mass loss (Fig. 5b).

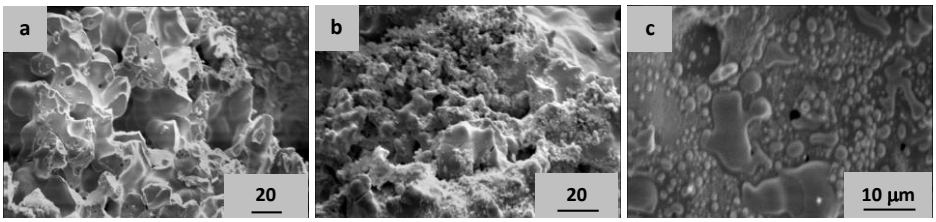

Fig. 7. Micrographs of fractures of the combustion product for the [Cu_2O+15wt.% (oil)]+NiO+0.75(Nt) mixture.

Thus, the results obtained demonstrated the possibility of complete reduction of both the metals and formation of Cu-0.5Ni and Cu-Ni composite powders or alloys under the combustion mode at using copper (I) oxide oily waste with 15 wt.% content of oil. Optimum conditions for obtaining Cu-0.5Ni and Cu-Ni alloys containing 32 and 48 wt.% Ni respectively were found out.

According to the selected optimum conditions, Cu-0.5Ni alloy was synthesized using copper oily waste with particle size less than1.6 *mm*. The synthesis was carried out in the tubular SHS-3L reactor with the charge composition [Cu_2O+15wt.% (oil)]+NiO+0.75(Nt) and mass m=300 *g*.

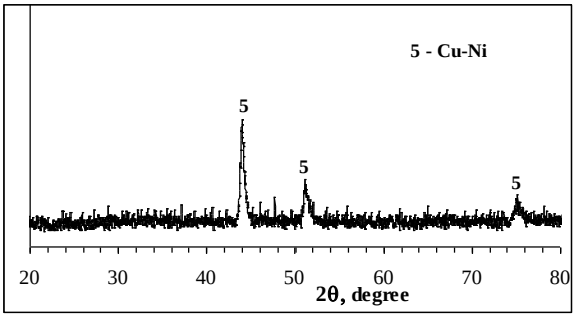

Fig. 8. XRD pattern of the final product synthesized in tubular SHS-3L reactor using 300 *g* of the initial [Cu_2O+15wt.% (oil)]+NiO+0.75(Nt) mixture.

Characterization of the obtained Cu-0.5Ni alloy was performed by XRD, SEM (Figs. 7, 8) and chemical analysis of free carbon. It should be noted, that at optimal conditions complete reduction of copper (I) oxide and nickel (II) oxide takes place with formation of a copper-nickel alloy and the combustion product represents a single-phase Cu-0.5Ni alloy with 0.15 wt.% of free carbon.

ԱՅՐՈՒՄԸ ՊՂՆՁԻ (I) ՕՔՍԻԴԱՅԻՆ ԹԱՓՈՆ-NiO-NH_4NO_3 ՀԱՄԱԿԱՐԳՈՒՄ ԵՎ Cu-Ni ՀԱՄԱՁՈՒԼՎԱԾՔՆԵՐԻ ՍԻՆԹԵԶԸ

Հ.Ա. ՄԱՀՄՈՒԴԻ, Վ.Վ. ՎԱՐԴԱՊԵՏՅԱՆ, Լ.Ս. ԱԲՈՎՅԱՆ և Ս.Լ. ԽԱՌԱՏՅԱՆ

Այրման պրոցեսում քիմիական ռեակցիաների ջերմային զուգորդման մոտեցմամբ ուսումնասիրվել է պղնձի օքսիդային թափոնի և նիկելի (II) օքսիդի համատեղ վերականգնումը՝ Cu+Ni կոմպոզիտային փոշիների և Cu-Ni համաձուլվածքի ստացման նպատակով: Այրման ալիքում երկու մետաղների վերականգնումն իրականացվել է ամոնիումի նիտրատի (Nt) առկայության պայմաններում՝ առանց ներմուծելու որևէ այլ վերականգնիչ: Մետաղների ամբողջական վերականգնման համար ուսումնասիրվել են այրման օրինաչափությունները (Cu2O թափոն-NiO-Nt) համակարգում՝ օգտագործելով հանքային յուղի տարբեր պարունակությամբ պղնձի օքսիդի (I) թափոններ և մետաղների օքսիդների տարբեր հարաբերակցությամբ ելային խառնուրդներ: Որոշվել են պղնձի օքսիդային թափոններից և NiO փոշուց Cu+Ni կոմպոզիտային փոշիների և Cu-Ni համաձուլվածքների ստացման օպտիմալ պայմանները՝ կախված յուղի և ամոնիումի նիտրատի պարունակությունից:

ГОРЕНИЕ В СИСТЕМЕ ОТХОДЫ ОКСИДА МЕДИ (I)-NiO-NH_4NO_3 И СИНТЕЗ СПЛАВОВ Cu-Ni

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В работе применен метод термического сопряжения реакций для совместного восстановления меди и никеля из смеси отхода оксида меди и оксида никеля (II) в режиме горения с целью одностадийного получения композитных порошков Cu+Ni и сплавов Cu-Ni. Эксперименты по восстановлению металлов в волне горения осуществлялись в присутствии нитрата аммония (Nt) без введения какого-либо дополнительного восстановителя. Для достижения полноты восстановления были исследованы закономерности горения в системе (отходы Cu_2O-NiO-Nt) с использованием отходов оксида меди (I) с различным содержанием минерального масла и различным соотношением оксидов металлов в исходной смеси. Определены оптимальные условия получения композиционных порошков Cu+Ni и сплавов Cu-Ni из отходов оксида меди (I) и порошка NiO в зависимости от содержания масла и нитрата аммония.

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ՀԱՅԱՍՏԱՆԻ ՀԱՆՐԱՊԵՏՈՒԹՅԱՆ ԳԻՏՈՒԹՅՈՒՆՆԵՐԻ
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НАЦИОНАЛЬНАЯ АКАДЕМИЯ НАУК РЕСПУБЛИКИ АРМЕНИЯ
NATIONAL ACADEMY OF SCIENCES OF THE REPUBLIC OF ARMENIA

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CATALYTIC PROPERTIES OF SUPPORTED Mo_2C SYNTHESIZED BY MICROWAVE IRRADIATION IN HYDRAZINE HYDRATE DECOMPOSITION REACTION

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Microwave-assisted synthesis and catalytic processes of Mo_2C/carrier systems have been studied. Catalytic tests were carried out on hydrous hydrazine decomposition reaction. Supported Mo_2C has shown catalytic activity in decomposition reaction. The catalytic activity changes depending on the carrier's characteristics. The highest catalytic activity is observed in the reaction with Mo_2C/γ-Al_2O_3 system (95.4%). In all cases decomposition of hydrazine was 100% selective with respect to ammonia and nitrogen.

Figs. 2, table 1, references 18.

Introduction

It is known that transition metal carbides show high catalytic activity in a number of reactions. For practical purposes, the catalysts are used in combination with different carriers, giving them different properties. As an example, alumina-supported molybdenum carbide (Mo_2C) was tested as a catalyst for hydrazine decomposition in a monopropellant thruster [1]. Also known the high catalytic activity of microwave-synthesized tungsten carbide-carbon (WC-C) system in hydrazine hydrate ($N_2H_4 \cdot H_2O$) decomposition [2]. The above mentioned metal carbides, in particular molybdenum carbide, were synthesized by various methods such as temperature-programmed reduction of molybdenum oxide [3], plasma-assisted synthesis [4], solution combustion synthesis [5], microwave-assisted synthesis [6].

The present work includes the study of the synthesis and catalytic properties of Mo_2C in a microwave oven in combination with different carriers. For the studies hydrazine hydrate decomposition was chosen as a model reaction.

In today's modern chemical industry, time is the most important and expensive capital. This quote is certainly also true for Science. Particularly a lot of experimental research is being done to develop, optimize and find new synthetic routes, which is a time-consuming process. From this point of view, any new synthesis method that will save time is extremely important to science as it allows more experiments to be done simultaneously to achieve the desired result. Microwave chemistry seems to meet this requirement and is an indispensable rapid synthesis tool in modern synthesis [7, 8, 9]. In the last decades, microwave chemistry has evolved significantly in different directions. Such areas are organic [10] and inorganic chemistry, in particular new and more effective synthesis of materials, analytical chemistry, biochemistry, catalysis and photochemical processes that have achieved great success in applying microwave irradiation as a source of heat [11].

Since the 1990s, there has been great interest in conducting heterogeneous catalytic reactions under the influence of microwave irradiation (MW) [12]. The results of research show that such speeds of chemical reactions cannot be achieved at conventional heating under the same conditions and time periods, which are possible in microwave ovens. The unique interaction between the catalyst and the microwave irradiation appears to be a means of speeding up the intermediate chemical reaction, which leads to similar results.

Microwave irradiation is electromagnetic radiation in the frequency range 0.3 to 300 *GHz*, which corresponds to wavelengths of 1 *mm* to 1 *m*. The frequency used in domestic microwave ovens is 2.45 *GHz* with a wavelength of 12.25 *cm*, which is used for the study of catalytic chemical reactions. Considering the recent experience, the following advantages and features of microwave heating can be distinguished: rapid heating and cooling of the system (homogeneous heating), obtaining of nanoparticles with relatively narrow particle size distribution and extremely short time of processes which bring to huge energy savings. Given the well-known fact that semiconductors (they are often heterogeneous catalysts, transition metal carbides, borides) are good microwave absorbers [13], there is a need to conduct heterogeneous catalytic processes under microwave irradiation. As was mentioned above, in the present work have been investigated the catalytic properties of microwave-synthesized Mo_2C (in the presence of different carriers) in the reaction of hydrazine hydrate decomposition. The choice of the hydrazine decomposition reaction is due to its high applicability. Depending on the direction of the hydrazine decomposition reaction, it is used for different purposes. Specifically, when the catalytic decomposition of hydrazine is accompanied by a large amount of heat dissipation (reaction I), it is used as monopropellant for satellite propulsion [14, 15]. Selective catalytic degradation of hydrazine hydrate leads to large amounts of pure hydrogen depletion for fuel cell (reaction II) [16]. In recent decades there have been numerous studies on the decomposition of hydrazine hydrate using different catalysts.

$$3N_2H_4 = 4NH_3 + N_2 \text{ (I)}$$
$$N_2H_4 = N_2 + 2H_2 \text{ (II)}$$

Although transition metal series carbides as catalysts have been extensively studied, there are few works in which carbides have been synthesized with a combination of carriers that may affect the carbide catalytic properties. The current work is dedicated to the study of the catalytic activity of microwave-assisted synthesized Mo_2C in the presence of different acidic carriers on the hydrazine hydrate decomposition reaction.

Materials and methods

Microwave-assisted synthesis of Mo_2C, Mo_2C/C, Mo_2C/ZSM12 and Mo_2C/γ- Al_2O_3.

The following materials were used to obtain molybdenum carbide in combination with different carriers: MoO_3 (high purity), carbon (VulcanXC-72R, Cabote corp. 250 m^2/g), zeolite (ZSM 12, 280 m^2/g, SiO_2/ Al_2O_3 – 25) and γ-Al_2O_3 (Rhone-poulene, 200 m^2/g).

Microwave synthesis of molybdenum carbide is well known in the literature [6]. In this study, carbide / carrier system synthesis was performed in a similar manner in the microwave oven. MoO_3 and carbon in stoichiometric ratio were taken to obtain pure carbide (Mo_2C).

$$2MoO_3 + 7C = Mo_2C + 6\ CO\ \{g\}$$

To obtain Mo_2C/C, in initial mixture carbon was taken in excess, according to the following reaction:

$$2MoO_3 + 11C = Mo_2C / C + 6\ CO\ \{g\}$$

For the synthesis of Mo_2C/ZSM12 and Mo_2C/γ-Al_2O_3 systems, MoO_3 / zeolite (ZSM12)/C and MoO_3 γ- Al_2O_3 / C were taken respectively. In all the mentioned systems the mass ratio of raw materials were calculated so that the mass fraction of the catalyst (Mo_2C) in the finished material was 70 wt.% [6]. Microwave-assisted synthesis of supported molybdenum carbide was performed in a quartz tube reactor in a nitrogen flow. The precursor was placed in the reactor, which was then purged with nitrogen for 2 *h* at room temperature. Domestic microwave oven (Electrolux EMS 2820) with a frequency of 2.45 *GHz* and 900 *W* was used to irradiate the tube for up to 600 *s* [6].

The crystal structure and phase composition of the products were determined by X-ray diffraction (XRD) analysis with Ni-filtered CuKα radiation 1, 54018 A^0 (D8 Advance, Bruker) operated at 40 *kV* and 40 *mA*. The average diameter of molybdenum carbide crystals was determined by the Scherer's method, from which the specific surface areas were evaluated. Since the adsorption method is not known for separately estimating the specific surfaces

of molybdenum carbides and carriers, the estimation was performed in the manner described above.

Synthesis temperature was measured from a window opened in the back of the microwave oven using an infrared pyrometer (Dostmann electronic GmbH HT 1800). Measurements showed that in all cases the temperature of the synthesis was 1050-1150^{o}C.

Catalytic experiments

The catalytic activity of supported Mo_2C was tested. For that 0.3 *g* of catalysts was taken and placed in a Teflon-lined autoclave with a volume of 65 cm^3 then 5 ml of diluted hydrous hydrazine 1% solution was poured. The closed autoclave was inserted in a microwave oven and irradiation was carried out at 180 *W* for 180 *sec*. After the test, the autoclave was removed from the oven, the catalyst was separated by filtration, and the hydrazine concentration was determined by iodometric titration method according to GOST 19503-88 [17]. Separately the catalytic activities of the carriers were tested. For the test 0.09 *g* (as the mass fraction of carriers in the outgoing catalyst mass 30% wt.) of carriers – C, γ-Al_2O_3, and zeolite ZSM 12 and 5 *ml* of 1% hydrous hydrazine solution were taken. It has been shown that the selectivity of hydrazine decomposition is 100% in relation to ammonia and nitrogen formation [6].

Results and discussion

Figure 1 shows the XRD patterns of the final product Mo_2C (fig.1). As it is seen within the sensitivity range of X-ray analysis, the conversion of initial mixture is 100%. The crystals of molybdenum carbide calculated from the XRD patterns with Scherrer's formula, have nano sizes (Table). The specific surface area of Mo_2C in Mo_2C/carrier (Mo_2C, Mo_2C/C, Mo_2C/ZSM12 and Mo_2C/γ-Al_2O_3) systems from the calculated crystal sizes was also estimated (Table).

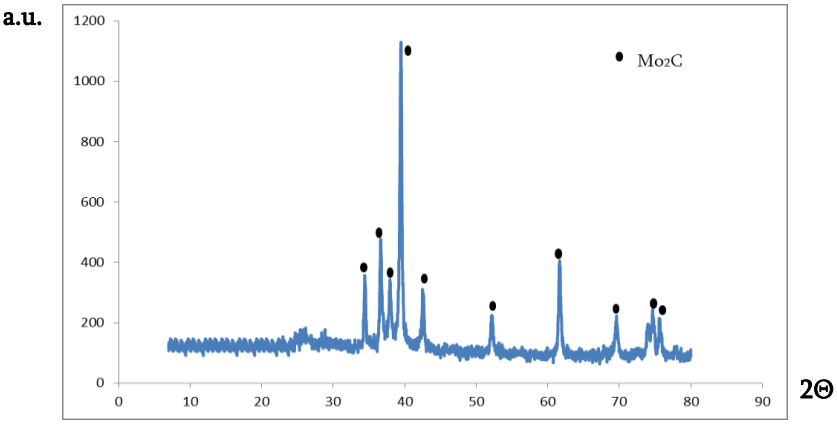

Fig. 1. XRD diffractogram of synthesized molybdenum carbide.

In Figure 2 the XRD patterns of the initial ZSM 12 and synthesized final product are presented. The precursor zeolite is characterized by $2\Theta = 7 and 9^{0}$ angles (Fig. 2a) [18]. After the synthesis, the XRD characteristic lines of the zeolites have disappeared, suggesting that the outgoing zeolite was subjected to phase conversion at high temperatures (Fig. 2b).

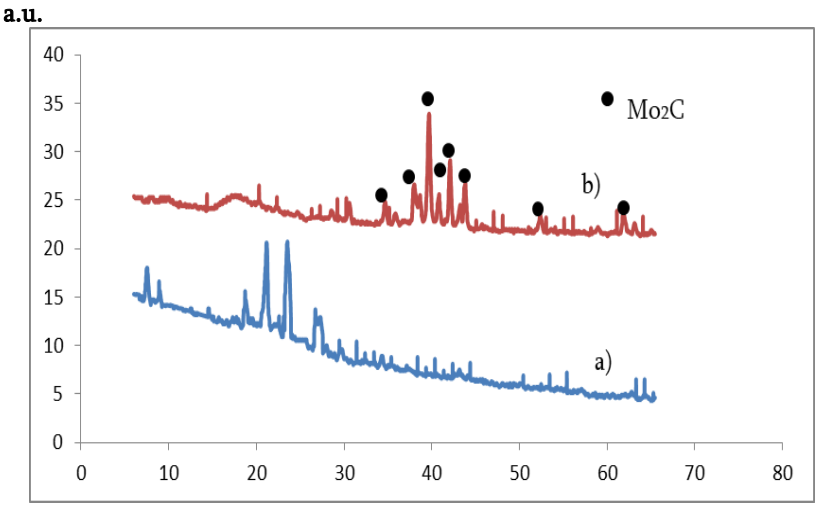

Fig. 2. XRD diffractograms of initial ZSM 12 a), and synthesized final product b).

In previous works it has been shown that the Mo_2C/C system has significantly high catalytic activity during hydrazine hydrate decomposition under the influence of MW [6]. Given this, an attempt has been made to combine different carriers with molybdenum carbide to increase its catalytic activity. For this purpose, carriers with different physicochemical properties, from weakly acidic to strong acidic properties, have been selected for the synthesis. Studies have shown that the percentage of hydrazine conversion depends on the carrier used. In our case, molybdenum carbide catalytic activity on different carriers can be presented in the following order:

$$Mo_2C/Al_2O_3 > Mo_2C/C > Mo_2C > Mo_2C /ZSM -12.$$

Since hydrazine is a basic molecule by its nature, it can be assumed that the first step of its interaction with the catalyst will be with the acid sites, which in some cases may be the limiting step (reaction 3)

$$N_2H_4 + S = N_2H_4{\cdot}S \ (3),$$

where S is the surface acidic site. This site can be both on the surface of the carbide and on the carrier. The carriers have almost no catalytic activity (Table) therefore the catalytic decomposition of hydrazine has been attributed to molybdenum carbide. The highest conversion rate was observed during the $Mo_2C/\gamma\text{-}Al_2O_3+N_2H_4{\cdot}H_2O$ reaction (Table). It is assumed that $\gamma\text{-}Al_2O_3$, having a pronounced acidic property, provides a high concentration of basic hydrazine at the catalyst surface, which in turn provides good microwave absorption at an appropriate temperature, which results in such a high yield (95% approx.).

Although literature acknowledges that zeolite systems have strong surface acidity, but in our case the Mo_2C/ZSM 12 + $N_2H_4 \cdot H_2O$ reaction shows the lowest conversion rate (Table). It is known that the degradation temperature of low SiO_2 containing ZSM 12 zeolites is about 700°C [18]. It is assumed that during the carbide synthesis, as already mentioned, degradation of the zeolite results in a loss of acidity.

The catalytic activity of individual carriers without the presence of a catalyst has also been studied. It is found that the carriers γ-Al_2O_3 and zeolite ZSM 12 show absolute catalytic inertia (Table). However, carbon shows some minor catalytic activity (approx. 8%, Table) which is explained by the formation of active centers on the surface of the carbon when it interacts with microwave irradiation.

As has been shown in the previous work [6], Mo_2C, Mo_2C/C has catalytic activity due to the presence of surface acid centers. However, our research has shown that the carriers have a large share in the catalytic process, which results in 100% selectivity.

Table

Sample	Conv. , %	d_{Mo_2C}, *nm*	S, m^2/g of Mo_2C	Conv., %/m^2 Mo_2C
70%Mo_2C /ZSM -12	41	23	28.4	1.44
70%Mo_2C/C	61.15	28	23.3	2.62
70%Mo_2C/ Al_2O_3	95.4	21	31.1	3.07
Mo_2C	52.5	30	21.8	2.41
C	8.03	–	–	–
Al_2O_3	0	–	–	–
ZSM -12	0	–	–	–

Conclusions

Microwave irradiation allows to synthesize Nano scale carrier-supported Mo_2C, which shows high selective catalytic activity in hydrous hydrazine decomposition reaction. The acidity of carriers plays a vital role on catalyst activity.

Acknowledgements

This work was supported by the State Committee of Science of Republic of Armenia18RF-114 (Raman Mnatsakanyan).

ՄԻԿՐՈԱԼԻՔԱՅԻՆ ԵՂԱՆԱԿՈՎ ԿՐԻՉՆԵՐԻ ՎՐԱ MO_2C-Ի ՍԻՆԹԵԶԸ ԵՎ ԴՐԱ ԿԱՏԱԼԻՏԻԿ ԱԿՏԻՎՈՒԹՅԱՆ ՈՒՍՈՒՄՆԱՍԻՐՈՒԹՅՈՒՆԸ ՀԻԴՐԱԶԻՆՀԻԴՐԱՏԻ ՔԱՅՔԱՅՄԱՆ ՌԵԱԿՑԻԱՅՈՒՄ

Ա. Մ. ԱՂՈՅԱՆ, Ռ. Ա. ՄՆԱՑԱԿԱՆՅԱՆ և Դ. Հ. ԴԱՎԹՅԱՆ

Իրականացվել է Mo_2C/կրիչ համակարգերի սինթեզը միկրոալիքային եղանակով և դրանց կատալիտիկ հատկությունների ուսումնասիրությունը՝ միկրոալիքային վառարանում: Կատալիտիկ փորձարկումները իրականացվել են հիդրազինհիդրատի քայքայման ռեակցիայում: Mo_2C/կրիչ համակարգերը ցուցաբերում են կատալիտիկ ակտիվություն քայքայման ռեակցիայում և կախված կիրառված կրիչի հատկություններից համակարգի կատալիտիկ ակտիվությունը փոփոխվում է: Ամենաարդյունավետ կատալիտիկ ակտիվությունը դիտվել է $Mo_2C/\gamma\text{-}Al_2O_3$ /հիդրազին ռեակցիայում (95.4%): Բոլոր դեպքերում հիդրազինի քայքայումն ընթացել է 100% ընտրողականությամբ՝ ամոնիակի և ազոտի առաջացմամբ:

КАТАЛИТИЧЕСКИЕ СВОЙСТВА НАНЕСЕННОГО MO_2C СИНТЕЗИРОВАННОГО МИКРОВОЛНОВОЙ РАДИАЦИЕЙ В РЕАКЦИИ РАЗЛОЖЕНИЯ ГИДРАЗИНГИДРАТА

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Изучены микроволновый синтез и каталитические процессы систем Mo_2C / носитель. Каталитические испытания были проведены по реакции разложения гидразинагидрата. Mo_2C на носителе показал каталитическую активность в реакции разложения. В зависимости от характеристик носителя она изменяется. Наибольшая каталитическая активность наблюдается при реакции с системой $Mo_2C/\gamma\text{-}Al_2O_3$ (95.4%). Во всех случаях разложение гидразина было на 100% селективным по отношению к аммиаку и азоту.

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ՀԱՅԱՍՏԱՆԻ ՀԱՆՐԱՊԵՏՈՒԹՅԱՆ ԳԻՏՈՒԹՅՈՒՆՆԵՐԻ
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НАЦИОНАЛЬНАЯ АКАДЕМИЯ НАУК РЕСПУБЛИКИ АРМЕНИЯ
NATIONAL ACADEMY OF SCIENCES OF THE REPUBLIC OF ARMENIA

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THE INFLUENCE OF AGING PHENOMENON IN SILICA HYDROGEL DERIVED FROM A SERPENTINE-GROUP MINERAL ON THE YIELDS OF CALCIUM SILICATE SPECIES

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In the paper the interaction between silica hydrogel species recovered from serpentine minerals $(Mg(Fe))_6[Si_4O_{10}](OH)_8$ and calcium hydroxide $Ca(OH)_2$ in aqueous medium by stirring in air at ambient pressure has been studied. The present research was aimed to investigate the effect of stirring time and the silica hydrogel aging on the yield of β-wollastonite produced by the heat-treatment of intermediates which had been precipitated in the boiling aqueous suspension prepared from the mentioned reagents. The data derived from the experiments have revealed that the portion of β-wollastonite in the products is variable and depends on the stirring time and the silica hydrogel aging. The replacement of the freshly synthesized silica hydrogel with the same one aged for six months' time leads to increase in stirring time from 15 min up to 120 min in order to achieve the higher yields of β-wollastonite.

Figs. 4, references 10.

A novel nontraditional approach to the chemical processing of dehydrated serpentinites[1] has allowed producing a silica hydrogel containing about 7 % of amorphous silicon dioxide SiO_2 [1]. The silica hydrogel is synthesized by the polycondensation of silicic acids formed from ortho- $[SiO_4]^{4-}$, di-$[Si_2O_7]^{6-}$,

[1] Serpentinite is a rock largely composed of serpentine group minerals $(Mg(Fe))_6[Si_4O_{10}](OH)_8$ belonging to phyllosilicate group, layer-type silicates or sheet silicates in other words.

$[Si_3O_{10}]^{8-}$, $[Si_4O_{13}]^{10-}$ and other silicate anions less polymerized and having oligomeric dimension which have been leached from the dehydrated silicate sheets of serpentine minerals [2].

Recent studies have shown that this silica hydrogel can not only be successfully used as a raw material for the production of a number useful silicate materials such as strontium and barium silicates but it also essentially simplifies the first stage of intermediates precipitation and decreases the temperatures of intermediates crystallization into final products on heating thereby streamlining the whole procedure of their syntheses [3, 4].

These findings suggest that the involvement of the silica hydrogel in the precipitation process which will be performed by stirring of the boiling aqua solution prepared from the silica hydrogel and calcium hydroxide $Ca(OH)_2$ is likely to facilitate the technology for calcium silicates production, particularly β-wollastonite (β-$CaSiO_3$), which is an interesting material for various domains of a modern engineering [5, 6].

For β-wollastonite synthesis, two routes are traditionally applied: (i) the solid state reaction between calcium carbonate $CaCO_3$ or dolomite $CaCO_3 \cdot MgCO_3$ and silicon dioxide SiO_2 within the temperature range of 1100–1350°C and (ii) the hydrothermal treartmeat. In the hydrothermal method, in the first stage, calcium silicate hydrates are produced by an hours-long hydrothermal treatment (2–7 *hours*) of an aqueous mixture of a source of CaO and SiO_2; in the second stage, these calcium silicate hydrates are transformed into β-$CaSiO_3$ by annealing in the temperature range of 800-1150^oC for hours (2–8 *hours*) [7, 8]. All these methods suggest either high temperature or autoclave treatment as well as a long process duration, and thus are great energy consuming.

It is well known that because of some structural redistributions and arrangements taking place between silica monomers, oligomers or particles in silica constituting gels during aging, silica gels are considered to be unbalanced systems [9, 10]. For this reason, balance disturbance of vulnerable gels during aging and the relation between the state of amorphous species and the crystalline phase depending on aging must be determined. Despite the industrial relevance and high commercial interest there has not been much progress in this field up to now. Hence, understanding of aging processes in the silica hydrogel on a scientific basis is essential in preparing a wide range of silicate compounds.

The present research is aimed to study the effect of structural changes in the aged silica hydrogel derived from serpentine minerals on the yields of calcium silicate species synthesized by the heat treatment of intermediates which had been previously precipitated via stirring of the boiling aqueous suspension prepared from the silica hydrogel and $Ca(OH)_2$.

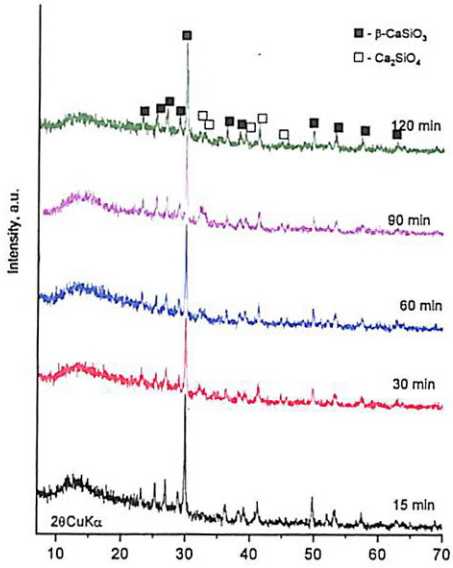

Fig. 1. XRPD patterns of the specimens which were produced by the heat treatment at 850°C of the precipitate samples prepared from Gel Sample №1 and $Ca(OH)_2$ by stirring for different times. ■– β-$CaSiO_3$; □–Ca_2SiO_4.

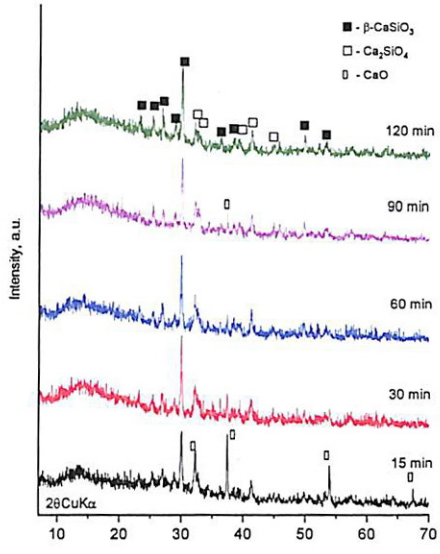

Fig. 2. XRPD patterns of the specimens which were produced by the heat treatment at 850°C of the precipitate samples prepared from Gel Sample №2 and $Ca(OH)_2$ by stirring for different times. ■–β-$CaSiO_3$; □–Ca_2SiO_4; ●–CaO.

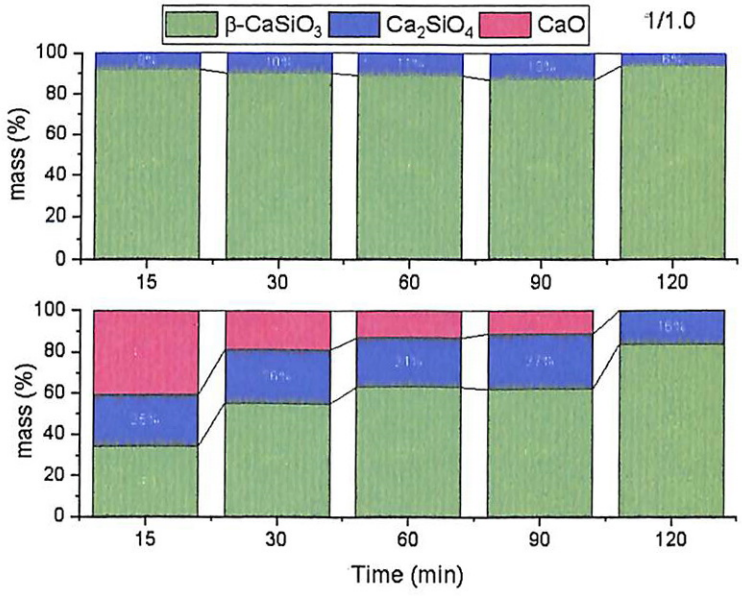

Fig. 3. Relative phase concentrations of the components in the products synthesized by the heat treatment at 850°C of the precipitate samples which were produced from $Ca(OH)_2$ and Gel Sample №1 (a) and Gel Sample №2 (b) by stirring for different times.

Experimental

A serpentinite sample located in Shorja (Armenia) was used as a precursor for the silica hydrogel production using the method described in the work [1].

Reagent grade CaO 98% (248568 Sigma-Aldrich) previously annealed at 1000°C for 0.5 *h* was used as a raw material for $Ca(OH)_2$ production.

For the intermediates precipitation two samples of suspension with liquid/solid ratio of 15 were prepared from the primary mixtures of $Ca(OH)_2$ and silica hydrogel with the CaO and SiO_2 molar ratio of 1:1. The frist sample was prepared from the silica hydrogel freshly synthesized (Gel Sample №1), the second one – from the same silica hydrogel aged for six months (Gel Sample №2). When the silica hydrogel was metered, SiO_2 content in the silica hydrogel that is 5.8% was taken into consideration in order to guaranty the molar ratios CaO to SiO_2. Each of the prepared samples was put into a vessel and stirred with mechanical stirrer for a certain time which is 15, 30, 60, 90 and 120 *min* in air at ambient pressure while being heated up to the temperature of 95°C (boiling point). Then each of the suspensions produced in the mixer was filtered. A gel-like mass remained on the filter was washed by distilled water and dried at the temperature of 100°C for 24 *h* in a dryer type KBC G – 100/250 manufactured by Premed (Warszawa, Poland). As a result, a white precipitate powder was produced.

Each of the ten precipitates produced was annealed at 850°C for 30 *min* and subjected to XRD analysis. Of the ten precipitate samples the two were selected for DTA from room temperature up to 1000°C.

X-ray powder diffraction (XRPD) measurements were made on a Dron-3 diffractometer (Russia) equipped with nickel filter, under the following conditions: CuKα-radiation; power supply 25 *kV*/10 *mA*; angular range 2θ=8°-70° at the room temperature in air. The mass of each test specimen was 250 mg. All the reflections were identified and interpreted using the ICDD-JCPDS database of crystallographic 2004.

DTA, thermogravimetry (TG) and DTG (differential thermogravimetric) measurements were performed by using a Derivatograph Q–1500D equipment manufactured by the MOM company (Hungary) in air at a heating rate of 10°C min^{-1}. The samples of equal mass were investigated in platinum crucibles.

Results and Discussion

The XRPD patterns of the heated precipitate specimens produced from the suspension samples which were prepared from the silica hydrogel and $Ca(OH)_2$ with the SiO_2: CaO molar ratio of 1:1 demonstrate that two species of calcium silicate, namely β-wollastonite (Card №84–0655) and larnite Ca_2SiO_4 (Card №33–0302) are precipitated (Fig. 1 and 2). A detailed analysis of the diffraction peaks recorded for all the samples has revealed that the portion of each phase in the final product depends on the two factors: stirring time and gel aging. β-$CaSiO_3$ and Ca_2SiO_4 peaks of different intencities are observable depending on

the stirring time and the aging of the silica hydrogel involved in the precipitation stage.

Based on the fact that the diffraction line intensity is proportional to the phase volume content, the relative concentration of each phase in the synthesized mixtures was estimated from the diffraction peaks intensities by the nonstandard method measuring the ratio of intensities of the different phases. The calculations were graphically represented in Fig. 3.

The higher yields of β-wollastonite are produced on heating up to 850°C in the intermediates prepared from Gel Sample №1 that is proved by the intensive peaks β-$CaSiO_3$ discovered in the corresponding patterns (Fig. 1). The highest concentration of β-wollastonite is fixed in the samples produced by stirring for 15 and 120 *min* (Fig. 3a). The increase in stirring time up to 90 min inclusive leads to a slight decrease of β-wollastonite amount (Fig. 3a).

Unlike the previous samples produced from Gel Sample №1, besides the reflections of wollastonte and larnite the ones of calcium oxide CaO (Card No 82–1690) are traceable in the XRPD patterns of the final products produced from Gel Sample №2 via stirring within the range of 15-90 *min* (Fig. 2). The appearance of CaO reflections indicates that as distinct from the previous samples $Ca(OH)_2$ is partly involved in the reaction with the SiO_2, which is a constituent part of the silica hydrogel, and the fifteen-minute stirring is not sufficient for the complete interaction between the initial reagents in the system (Fig. 3b). Only increase in stirring time up to 120 *min* provides the complete consumption of $Ca(OH)_2$ and thus higher concentration of β-wollastonite (Fig. 3b).

The DTA curves of the two precipitate samples prepared from Gel Samples №1 and 2 by the fifttten-minute stirring were considered. They display noticeable exothermic peaks of high intensities within the temperature range of 750-850°C with the maxima at 827 and 839°C (Fig. 4).

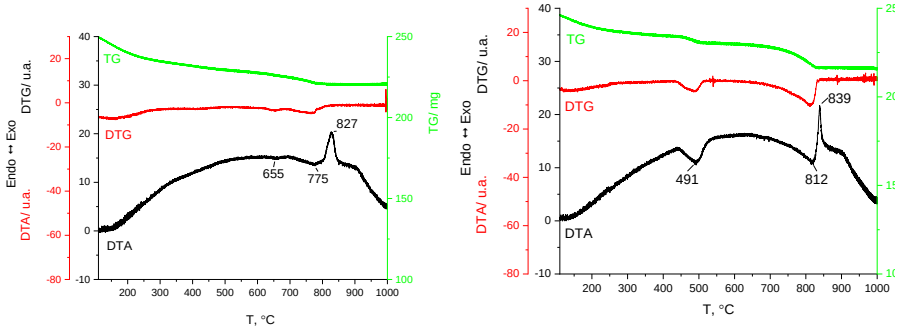

Fig. 4. Differential thermal curves for the precipitate samples produced from $Ca(OH)_2$ and Gel Sample №1 (a) and Gel Sample №2 (b) by the 15-minute stirring. TG thermogravimetric or weight loss curve, DTA differential thermal analysis curve. DTG differential thermal thermogravimetry curve. The vertical axis label applies to the DTA curve.

These exotherms are preceded by endothermic events with the minima at 775 and 812°C which are accompanied by mass loss that is proved by the trend

of the TG curves (Fig. 4). These endotherms are most likely produced by dehydroxylation – hydroxyl water formation and removal from the intermediates – and indirectly indicate chain-like calcium hydroxosilicate species formation during precipitation because only this type of Ca-containing silicate compounds can be easily transformed into such a calcium silicate species as wollastonite on heating. The intermediate calcium hydro- and hydroxosilicates can not be identified by XRD analysis because they were all produced in an amorphous state. Naturally, the mild conditions of the treatment (95°C, ambient pressure) can not provide the formation of any chain-like crystalline compounds easily trasformed into wollastonite configuration on heating up to 850°C. Crystalline compounds production such as tobermorite ($Ca_5Si_6O_{16}(OH)_2 \cdot 4H_2O$ or $Ca_5Si_6(O,OH)_{18} \cdot 5H_2O$) or xonotlite ($Ca_6Si_6O_{17}(OH)_2$) which are distinguished by chain-like structure and therefore considered the best intermediates for wollastonite synthesis is only achieved via hydrothermal treatment.

An endothermic event with the minimum at 491°C set on the DTA curve of the precipitate sample produced from Gel Smaple №2 is caused by the process of unreacted $Ca(OH)_2$ decomposition with the formation of H_2O and CaO (Fig. 4b) the reflections of which (Card №82–1690) are seen in the XRPD patterns of the same specimens produced after the heat treatment of the corresponding precipitates (Fig. 2).

Another endotherm barely detectable over 600°C on the DTA curve of the precipitate sample prepared from Gel Smaple №1 must have been caused by the decomposition of calcium carbonate $CaCO_3$ resulting in the formation of CO_2 and CaO (Fig. 4a). The lower intensity of this effect indicates a negligiable amount of $CaCO_3$ formed by CO_2 absorption from the air. But CaO reflections are not traceable in the XRPD patterns of the corresponding sample. It is quite logical to suggest that on heating up to 600°C CaO released by $CaCO_3$ decomposiotion immidiatedly reacts with the SiO_2 that remained in an amorphous state inside the intermediate, producing calcium silicate species and CO_2 and causing the endotherm barely detectable over 600°C on the DTA curve of the precipitate sample. As for the exothermic event that should be seen over 600°C and evidence the calcium silicate species formation, it is most likely overlapped by the endothermic process of CO_2 releasing that requires energy input more than the heat released by the reaction of calcium silicate species formation.

Both the intensive diffraction peaks of β-wollastonite and larnite fixed in the diffraction patterns of the heated specimens point to the fact that the strong exothermic peaks are originated by both β-wollastonite and larnite formation (Fig. 4).

The knowledge of the structural particularities of the silica constituting the silica hydrogel has allowed to gain an insight into the process occurring in the silica hydrogel during aging.

Recall that the structure of the silica is made up of mono- [SiO_4], one-, two-dimensional and oligomeric silicate units bound with each other by unsaturated, i.e. comparably weak bonds that distinguishes it from all other species of traditional silicon dioxide. In spite of the fact that the Si–O(Si) bonds arisen between the silicate anions during the polycondensation are less saturated, i.e. weaker, than the primary Si–O(Si) ones intrinsic in the silicate oligomers formed in magma prior serpentinization, they must have been marginally strengthened during the silica hydrogel aging. Naturally, more energy input is required for the cutting of siloxane bonds slightly strengthened by aging and thus silicate anions releasing. As a result, the stirring time must be prolonged so as to supply this extra energy needed for the Si–O(Si) bonds weakening, thereby insuring β-wollastonite high yields.

Conclusion

These studies have shown that a new species of silica hydrogel derived from serpentine minerals can be successfully used in the system SiO_2–CaO–H_2O as a source of silica for the development of a new route to β-wollastonite synthesis based on the heat treatment of the intermediates precipitated via stirring of the initial reagents without involving autoclave treatment and additional reagents.

The information obtained by collating the data has revealed that the stirring time and the silica hydrogel aging essentially affect the concentration of β-wollastonite in the final product. In order to guarantee the complete interaction between the SiO_2 and $Ca(OH)_2$ via a short-term procedure (fifteen-minute stirring) thus providing higher yields of β-$CaSiO_3$, the freshly synthesized silica hydrogel derived from serpentine minerals must be involved as a source of SiO_2 in the first stage of precipitation. If the aged silica hydrogel is used as a raw materal in the same system, higher yields of β-wollastonite are expected in the case of stirring time prolonging (up to 120 *min*). The Si–O(Si) bond's strength arisen between various silicate units in the silica during the polycondensation is the main factor playing a major role in the complete interaction of the silica with $Ca(OH)_2$. The cutting of the Si–O(Si) bonds partly strengthened by the silica hydrogel aging requires more energy that is provided by more prolonged stirring.

As can be seen from the experimenmtal data, the investigations of aging mechanisms and their influence on the final products are quite challenging. These studies are of great interest and practical value for the further development of a new simplified technology for the low-temperature production of β-wollastonite.

ՍԵՐՊԵՆՏԻՆԱՅԻՆ ԽՄԲԻ ՄԻՆԵՐԱԼԻՑ ՍՏԱՑՎԱԾ ՀԻԴՐՈՍԻԼԻԿԱԺԵԼԻ ԾԵՐԱՑՄԱՆ ԱԶԴԵՑՈՒԹՅՈՒՆԸ ԿԱԼՑԻՈՒՄԻ ՍԻԼԻԿԱՏԻ ԵԼՔԻ ՎՐԱ

Ա. Ռ. ԻՍԱՀԱԿՅԱՆ, Ն. Հ. ԶՈՒԼՈՒՄՅԱՆ, Ա. Մ. ԹԵՐՁՅԱՆ, Ս. Ա. ՄԵԼԻՔՅԱՆ և Հ. Ա. ԲԵԳԼԱՐՅԱՆ

Ուսումնասիրվել է սերպենտինային միներալներից ($((Mg(Fe))_6[Si_4O_{10}](OH)_8$) առաջացած հիդրոսիլիկաժելի և կալցիումի հիդրօքսիդի ($Ca(OH)_2$) փոխազդեցությունը: Այս աշխատանքի նպատակն է ուսումնասիրել ելային նյութերի խառնման տևողության և հիդրոսիլիկաժելի ծերացման ազդեցությունը β-վոլաստոնիտի ելքի վրա: Այն ստացվում է միջանկյալ նյութերի ջերմամշակման ընթացքում: Միջանկյալ նյութերը նատեցվել են ելանյութերի սուսպենզիայի մթնոլորտային ճնշման և եռման պայմաններում: Ուսումնասիրությունների արդյունքում ցույց է տրվել, որ վերջնական նյութի մեջ β-վոլաստոնիտի բաժինը փոփոխվում է կախված խառնման տևողությունից և հիդրոսիլիկաժելի ծերացումից: Թարմ պատրաստված հիդրոսիլիկաժելի փոխարինումը նույն հիդրոսիլիկաժելի հետ, որը պահվել է կես տարի, բերում է խառնման տևողության մեծացմանը՝ 15 րոպեից մինչև 120 րոպե, որպեսզի ստացվի մեծ ելքերով β-վոլաստոնիտ:

ВЛИЯНИЕ ПРОЦЕССА СТАРЕНИЯ В ГИДРОГЕЛЕ КРЕМНЕЗЕМА, ВЫДЕЛЕННОГО ИЗ МИНЕРАЛА ГРУППЫ СЕРПЕНТИНА, НА ВЫХОДЫ СИЛИКАТОВ КАЛЬЦИЯ

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В статье изучено взаимодействие в водной среде между гидрогелем кремнезема, выделенном из серпентиновых минералов $(Mg(Fe))_6[Si_4O_{10}](OH)_8$, и гидроксидом кальция $Ca(OH)_2$, осуществляемое посредством перемешивания при атмосферном давлении. Целью настоящего исследования являлось изучить влияние длительности перемешивания и старения гидрогеля кремнезема на выход β-волластонита, получаемого термической обработкой промежуточных соединений, которые были предварительно осаждены в кипящей водной суспензии, приготовленной из упомянутых реагентов. На основе экспериментов выявлено, что доля β-волластонита в конечном продукте варьирует и зависит от длительности перемешивания и старения гидрогеля кремнезема. Замена свежесинтезированного гидрогеля кремнезема тем же гелем, но выдержанном в течение полугода, приводит к увеличению длительности перемешивания от 15 до 120 *мин* для того, чтобы обеспечить высокие выходы β-волластонита.

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ՀԱՅԱՍՏԱՆԻ ՀԱՆՐԱՊԵՏՈՒԹՅԱՆ ԳԻՏՈՒԹՅՈՒՆՆԵՐԻ
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НАЦИОНАЛЬНАЯ АКАДЕМИЯ НАУК РЕСПУБЛИКИ АРМЕНИЯ
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SYNTHESIS AND ALKYLATION OF NEW DERIVATIVES OF CONDENSED THIENO[3,2-*d*]PYRIMIDINE-8,10-DITHIONES

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The Thorpe-Ziegler reaction has been carried out. Condensed 1-amino-2-substituted-thieno[2,3-*b*]pyridines were obtained from cyanopyridinethiones and halogen-containing compounds. Synthesized derivatives of 8-imino-pyrido- [3',2':4,5]thieno[3,2-*d*][1,3]thiazine-10-thiones with carbon disulfide in the presence of absolute pyridine were further recyclized with Dimroth rearrangement to obtain new derivatives of condensed thieno[3,2-*d*]-pyrimidine-8,10-dithiones. The thieno[3,2-*d*]pyrimidine-8,10-dithiones were alkylated with various alkyl halides to afford *S*-alkyl derivatives. The structures of newly synthesized compounds were confirmed by IR, ^{1}H NMR, MS spectral data and elemental analysis.

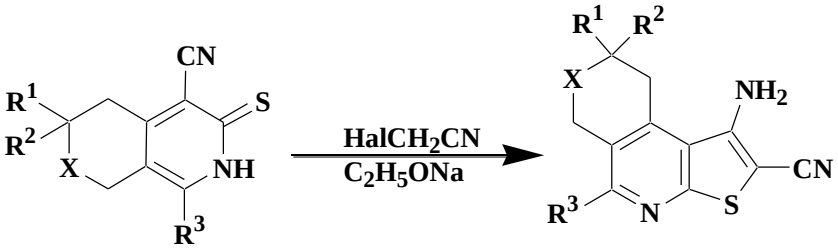
References 21.

Synthetic thiophenes have been reported to possess a wide range of therapeutic properties with diverse applications in medicinal chemistry and material science, attracting great interest in both industryand academia [1]. Pyridine and pyrimidine derivatives are known to form the basis of many medications. Pyrimidines and fused pyrimidines, being integral parts of DNA and RNA, play an essential role in several biological processes and also have considerable chemical and pharmacological importance as antibiotics, antibacterials, cardiovascular as well as agrochemical and veterinary products [1-4]. Heterocyclic compounds play an important role in designing new classes of structural entities of medicinal importance with potentially new mechanisms of action. In addition, during the last few years, condensed thienopyrimidine

derivatives have received considerable attention. Many of these derivatives were found to possess a variety of pronounced activities such as anti-inflammatory and analgesic [5-8], antimicrobial [9-13], anti-Avian influenza virus (H5N1) [14], anti-herpes simplex virus type 1 (HSV-1) and hepatitis-A virus (HAV), serotonin 5-HT6 receptor antagonist [15], antiarrhythmic [16] agent. Pyrimidine derivatives have been previously reported as platelet aggregation inhibitors, antagonists, anti-conceptive and anti-parkinsonism [17-20] agents. Heterocyclic compounds have also exhibited anthelmintic, anti HIV and hypoglycemic activities [21]. Therefore, obtaining new derivatives of these heterocycles to a great extent is a guarantee for revealing biological activity in synthesized compounds. In view of these observations and as continuation of our previous works on heterocyclic chemistry, we report herein the synthesis of some new heterocycle-containing pyridothienopyrimidine moieties and their chemical properties.

The synthesis of condensed 1-amino-2-substituted-thieno[2,3-*b*]pyridines (**2**) from 5-cyanopyridine-6-thiones (**1**) and halogen-containing compounds having the electron-withdrawing nitrile group in the *α*-position was carried out by the Thorpe-Ziegler reaction under the influence of sodium alkoxide (Scheme 1).

Scheme 1

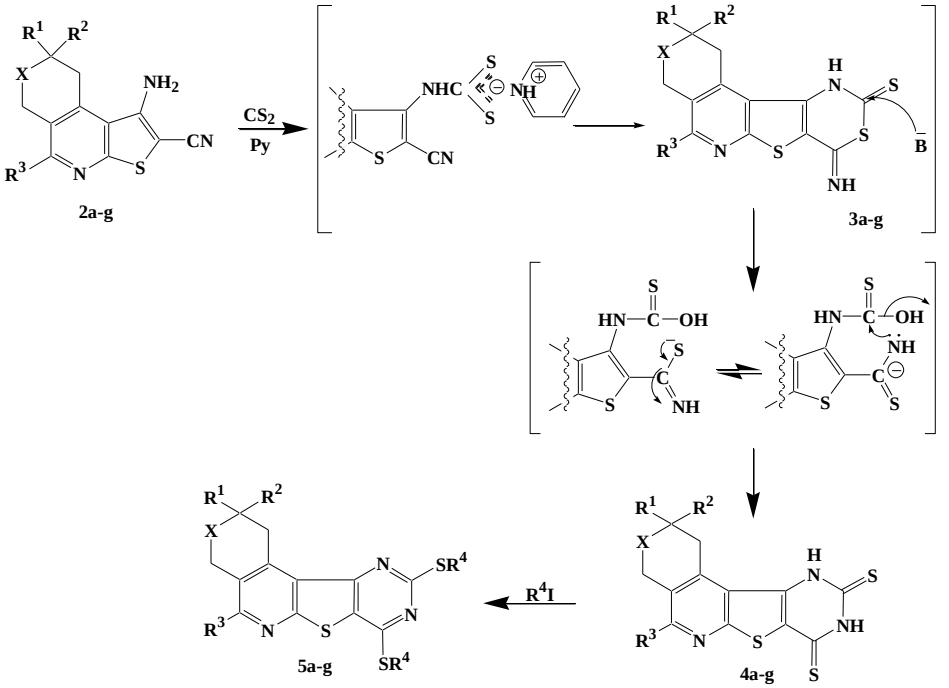


1a-g **2a-g**

1,2 a-b: X = CH_2, $R^1 = R^2 = H$; **1,2 c:** X = NCH_3, $R^1 = R^2 = H$;
1,2 d: X = O, $R^1 = H$, $R^2 = i\text{-}C_3H_7$; **1,2 g:** X = S, $R^1 = R^2 = H$;
1,2e,f: X = O, $R^1 = R^2 = CH_3$, **1,2a:** R^3 = pyrrolidil;
1,2b-e,g: R^3 = morpholyl; **1,2f:** R^3 = piperidyl.

By the interaction of 1-amino-2-cyano derivatives of thieno[2,3-*b*]pyridines (**2**) with carbon disulfide in a pyridine medium, we synthesized new derivatives of fused thieno[3,2-*d*]pyrimidine-8,10-dithiones (**4**). Reaction proceeded with the formation of intermediate compounds **3** (Scheme 2). Then thieno[3,2-*d*]-1,3-thiazines (**3**), an interesting example of rearrangement with Dimroth exchange and transformation observed under the action of alkali, were subjected to recycling, which led to the formation of reaction products. Intermediate product **3** was isolated, the structure of which was proved by the methods of NMR- and IR-spectroscopy and mass-spectrometry.

Scheme 2



2,3,4,5 a-b: X = CH_2, $R^1 = R^2 = H$; **2,3,4 c:** X = NCH_3, $R^1 = R^2 = H$;
2,3,4,5 d, 5 c: X = O, $R^1 = H$, $R^2 = i\text{-}C_3H_7$; **2,3,4 g:** X = S, $R^1 = R^2 = H$;
2,3,4,5 e,f, 5 g: X = O, $R^1 = R^2 = CH_3$, **2,3,4,5 a:** R^3 = pyrrolidil;
2,3,4 b-e,g, 5 b,d,e: R^3 = morpholyl; **2,3,4,5 f, 5 g:** R^3 = piperidyl;
5 a-c,e,f: $R^4 = CH_3$, **5 d,g:** $R^4 = C_2H_5$.

The signals of two NH group protons were observed in ^1H NMR spectra at ranges of 11.20 and 12.59 ppm, correspondingly, and in the IR spectra, the absence of an absorption signal for the C=NH group proved the structures of the synthesized compounds **4**. In continuation of this work, the corresponding S-alkyl derivatives were synthesized by the alkylation of compounds 4 by alkyl halides.

Experimental section

All chemicals, reagents, and solvents were of commercially high purity grade purchased from Sigma-Aldrich. Melting points (mp.) were determined on a Boetius microtable. They are expressed in degree centigrade (ºC). ^1H NMR spectra were recorded with a Varian Mercury 300VX spectrometer in DMSO-d_6:CCl_4 (1:3) at 300 *MHz* (^1H). Chemical shifts were reported as ppm (parts per million) relative to TMS (tetramethylsilane) as the internal standard. IR spectra were recorded on Nicolet Avatar 330-FTIR spectrophotometer and the reported wave numbers are given in cm^{-1}. TLC analyses were performed on Silufol UV-

254 plates using pyridine–ethyl acetate, 2:1, acetone–hexane, 1:1 as eluent; spots were developed with iodine vapor.

General procedure for the synthesis of thieno[2,3-*b*]pyridines 2a-b. A mixture of 0.01 *mol* of 5-cyanopyridinethiones **1** and 0.01 *mol* of chloroacetonitrile was added to sodium ethoxide solution obtained from 0.46 *g* (0.02 *mol*) of sodium metal and 50 *ml* of anhydrous ethanol. The reaction mixture was refluxed at 60°C for 2 *h*. The solution was cooled, 50 *ml* of cold water was added. The obtained precipitate was filtered off, washed with water, and dried. Recrystallized from ethanol.

1-Amino-5-pyrrolidin-1-yl-6,7,8,9-tetrahydrothieno[2,3-*c*]isoquinoline-2-carbonitrile (2a). Yield 2.3 *g* (78.3%), mp 232-236°C, R_f 0.48. Found, %: C 64.68; H 6.16; N 18.58; S 10.81. $C_{16}H_{18}N_4S$. Calculated, %: C 64.40; H 6.08; N 18.78; S 10.75. IR spectrum, *v*, cm^{-1}: 3480-3400 (NH_2); 2200 (CN); 1620 (C=O); 1600-1590 ($C=C_{Ar}$).^{1}H NMR spectrum, δ, ppm, MHz: 1.70-1.84 m (4H, $2CH_2$); 1.90-1.92 m (4- H, $(CH_2)_2$); 2.63 t (2 H, *J* = 5.6, CH_2); 3.21 t (2 H, *J* = 6.4, CH_2); 3.51-3.53 m (4 H, $N(CH_2)_2$); 5.69 s (2 H, NH_2).

1-Amino-7-methyl-5-morpholin-4-yl-6,7,8,9-tetrahydrothieno[2,3-*c*]-2,7-naphthyridine-2-carbonitrile (2c). Yield 2.3 *g* (74.1%), mp 270-271°C, R_f 0.68. Found, %: C 60.59; H 6.56; N 19.45; S 8.80. $C_{18}H_{23}N_5OS$. Calculated, %: C 60.48; H 6.49; N 19.59; S 8.97. IR spectrum, *v*, cm^{-1}: 3490-3400 (NH_2); 2200 (CN); 1630 (C=O); 1600-1580 ($C=C_{Ar}$). ^{1}H NMR spectrum, δ, ppm, MHz: 1.12 s (6H, $2CH_3$);2.10 s (3H, CH_3); 2.31 s (2H, 9-CH_2); 3.00-3.21 m (4H, $N(CH_2)_2$); 3.52 s (2 H, 6-CH_2); 3.61-3.80 m (4H, $O(CH_2)_2$); 6.33 s (2H, NH_2).

1-Amino-8-isopropyl-5-morpholin-4-yl-8,9-dihydro-6*H*-pyrano[4,3-*d*]thieno-[2,3-*b*]pyridine-2-carbonitrile (2d). Yield 2 *g* (56.5%), mp 264-265°C, R_f 0.54. Found, %: C 60.18; H 6.26; N 15.48; S 8.79. $C_{18}H_{22}N_4O_2S$. Calculated, %: C 60.31; H 6.19; N 15.63; S 8.95. ^{1}H NMR spectrum,δ, ppm, MHz: 1.02 d (3 H, *J* = 3.9, CH_3); 1.04 d (3 H, *J* = 4.7, CH_3); 1.80 okt (1 H, *J* = 6.2, CH); 3.02-3.37 m (7 H, CH_2, $N(CH_2)_2$ and OCH); 3.66-3.82 m (4 H, $O(CH_2)_2$); 4.59 d (1 H, *J* = 14.7) and 4.74 d (1 H, *J* = 14.3, OCH_2); 5.96 s (2 H, NH_2).

1-Amino-8,8-dimethyl-5-piperidin-1-yl-8,9-dihydro-6*H*-pyrano[4,3-*d*]thieno-[2,3-*b*]pyridine-2-carbonitrile (2f). Yield 2.5 *g* (74.9%), mp 238-239°C, R_f 0.58. Found, %: C 63.38; H 6.61; N 16.48; S 9.49. $C_{18}H_{22}N_4OS$. Calculated, %: C 63.13; H 6.47; N 16.36; S 9.36. ^{1}H NMR spectrum, δ, ppm, MHz: 1.30 s (6 H, $2CH_3$); 1.67-1.71 m (6 H, $3CH_2$); 3.08 s (2 H, CH_2); 3.11-3.18 m (4 H, $N(CH_2)_2$); 4.57 s (2 H, OCH_2); 5.91 s (2 H, NH_2).

1-Amino-8,8-dimethyl-5-morpholin-4-yl-8,9-dihydro-6*H*-thieno[2,3-*b*]thiopy-rano[4,3-*d*]pyridine-2-carbonitrile (2g). Yield 2.9 *g* (80.0%), mp 241-242°C, R_f 0.67. Found, %: C 56.73; H 6.06; N 15.46; S 17.64. $C_{17}H_{20}N_4OS_2$. Calculated, %: C 56.64; H 5.59; N 15.54; S 17.79. IR spectrum, *v*, cm^{-1}: 3490-3400 (NH_2); 2220 (CN); 1630 (C=O), 1600-1580 ($C=C_{Ar}$). ^{1}H NMR spectrum,

δ, ppm, MHz: 1.37 s (6 H, $2CH_3$); 3.04-3.38 m (6 H, $3CH_2$); 3.65-3.97 m (6 H, $3CH_2$); 6.48 s (2 H, NH_2).

The preparation of compound **2b, e** is given in [4].

General method for the synthesis of compounds 3b, c, e, g. A mixture of 0.01 *mol* of compound **2**, 9 *ml* of carbon disulfide and 15 *ml* of absolute pyridine was refluxed for 10 *h*. After cooling, the crystals were filtered, washed with water and dried. Recrystallized from DMF.

8-Imino-5-morpholin-4-yl-1,2,3,4,8,11-hexahydro-10*H*-[1,3]thiazino-[4',5':4,5] thieno[2,3-*c*]isoquinoline-10-thione (3b). Yield 3.7 *g* (95.2%), mp >360 °C, R_f 0.62. Found, %: C 52.41; H 4.56; N 14.26; S 24.81. $C_{17}H_{18}N_4OS_3$. Calculated, %: C 52.28;H 4.65; N 14.35; S 24.63. IR spectrum, *v*, cm^{-1}: 3450, 3130 (NH); 1650 (C=N), 1580 ($C=C_{Ar}$), 1150 (C=S). Mass spectrum, m/z ($I_{rel, \%}$): 390 [M^+] (100), 359 (33), 345 (34), 333 (40), 305 (10).

8-Imino-2,2,3-trimethyl-5-morpholin-4-yl-1,2,3,4,8,11-hexahydro-10*H*-[1,3]-thiazino[4',5':4,5]thieno[2,3-*c*]-2,7-naphthyridine-10-thione (3c). Yield 3.4 *g* (78.9%), mp 315-316°C, R_f 0.59. Found, %: C 52.51; H 5.47; N 16.06; S 22.30. $C_{19}H_{23}N_5OS_3$. Calculated, %: C 52.63; H 5.35; N 16.15; S 22.19. IR spectrum, *v*, cm^{-1}: 3450, 3120 (NH); 1630 (C=N), 1580 ($C=C_{Ar}$), 1180 (C=S). ^{1}H NMR spectrum, δ, ppm, MHz: 1.16 s (6H, $2CH_3$); 2.12 s (3H, CH_3); 2.33 s (2H, 9-CH_2); 3.10-3.28 m (4H, $(CH_2)_2$); 3.52 s (2 H, 6-CH_2); 3.61-3.80 m (4H, $O(CH_2)_2$); 10.33 br (1H, NH). 13.18 br (1H, NH).

8-Imino-2,2-dimethyl-5-morpholin-4-yl-1,4,8,11-tetrahydro-2*H*,10*H*-pyrano-[4'',3'':4',5']pyrido[3',2':4,5]thieno[3,2-*d*][1,3]thiazine-10-thione (3e). Yield 2.9 *g* (70.0%), mp >360°C, R_f 0.68. Found, %: C 51.29; H 4.86; N 13.43; S 23.00. $C_{18}H_{20}N_4O_2S_3$. Calculated, %: C 51.40; H 4.79; N 13.32; S 22.87. IR spectrum, *v*, cm^{-1}: 3405, 3100 (NH); 1650 (C=N), 1590 ($C=C_{Ar}$), 1150 (C=S). Mass spectrum, m/z ($I_{rel, \%}$): 423 [M^+] (43), 405 (5), 389 (7), 363 (8), 344 (100), 329 (7), 313 (20). ^{1}H NMR spectrum, δ, ppm, MHz: 1.31 s (6 H, $2CH_3$); 3.08 t (4 H, *J* = 1.5, $N(CH_2)_2$); 3.65 ddd (2H, *J* = 13.2, 4.5, 1.0) and 3.70 ddd (2 H, *J* = 13.2, 4.5, 0.9, $O(CH_2)_2$); 3.80 s (2 H, CH_2); 5.23-5.32 m (2 H, OCH_2); 10.18 br (2 H, NH, C=NH).

8-Imino-2,2-dimethyl-5-morpholin-4-yl-1,4,8,11-tetrahydro-2*H*,10*H*-thiopyra-no[4'',3'':4',5']pyrido[3',2':4,5]thieno[3,2-*d*][1,3]thiazine-10-thione (3g). Yield 3.6 *g* (82.7%), mp >360 °C, R_f 0.70. Found, %: C 49.39; H 4.71; N 12.97; S 29.25. $C_{18}H_{20}N_4OS_4$. Calculated, %: C 49.51; H 4.62; N 12.83; S 29.38. IR spectrum, *v*, cm^{-1}: 3420, 3130 (NH); 1630 (C=N), 1570 ($C=C_{Ar}$), 1140 (C=S). ^{1}H NMR spectrum, δ, ppm, MHz: 1.26 s (6 H, $2CH_3$); 3.35-3.38 m (6 H, $N(CH_2)_2$); 3.65-3.80 m (6 H, $O(CH_2)_2$); 5.18-5.32 m (2 H, OCH_2); 3.89 t (2 H, *J* = 2.1, SCH_2); 10.18 br.s (1 H, NH); 13.55 br (1H, NH).

Preparation of compounds 4a, d, f (General method). A mixture of 0.01 *mol* of compound **2** and 7.6 *g* (0.1 *mol*) of carbon disulfide in 15 ml of absolute pyridine was boiled for 10 *h*. The product formed after cooling was collected, crystals were filtered off and washed with alcohol.

5-Pyrrolidin-1-yl-1,2,3,4-tetrahydropyrimido[4',5':4,5]thieno[2,3-*c*]isoquino-line-8,10(9*H*,11*H*)-dithione (4a). Yield 1.8 *g* (47.8%), mp >360°C, R_f 0.48. Found, %: C 54.72; H 4.71; N 14.77; S 25.42. $C_{17}H_{18}N_4S_3$. Calculated, %: C 54.52; H 4.84; N 14.96; S 25.68. IR spectrum, *v*, cm^{-1}: 3400, 3360 (NH); 1560 (C=C_{Ar}), 1170 (C=S). ^{1}H NMR spectrum, δ, ppm, MHz: 1.72 m (2 H, 2-CH_2); 1.84 m (6 H, 3-CH_2, 2CH_2); 2.79 m (2 H, 4-CH_2); 3.39 m (2 H, 1-CH_2); 3.68 t (4 H, *J* = 3.1, N(CH_2)$_2$); 11.98 br.s (1 H, NH); 12.52 s (1 H, NH).

2-Isopropyl-5-morpholin-4-yl-1,4-dihydro-2*H*-pyrano[4'',3'':4',5']pyrido-[3',2':4,5]thieno[3,2-*d*]pyrimidine-8,10(9*H*,11*H*)-dithione (4d). Yield 3.5 *g* (80.7%), mp >360°C, R_f 0.55. Found, %: C 52.38; H 5.16; N 12.69; S 22.32. $C_{19}H_{22}N_4O_2S_3$. Calculated, %: C 52.51; H 5.10; N 12.89; S 22.13. IR spectrum, *v*, cm^{-1}: 3330, 3410 (NH); 1580 (C=Cap), 1150 (C=S). Mass spectrum, m/z ($I_{rel, \%}$): 434 [M^+] (5), 326 (20), 283 (5), 124 (20), 78 (15), 43 (29), 34 (56). ^{1}H NMR spectrum, δ, ppm, MHz: 1.03d (3 H, *J* = 6.7, CH_3); 1.07 d (3 H, *J* = 6.7, CH_3); 1.84 ok (1 H, *J* = 6.7, CH); 3.12 dd (*J* = 7.3, 10.2) and 3.63 ddd (2 H, *J* = 17.3, 4.0, 1.3, CH_2); 3.17-3.44 m (5 H, OCH, N(CH_2)$_2$); 3.70 ddd (2 H, *J* = 11.4, 6.5, 3.0) and 3.81 ddd (2 H, *J* = 11.4, 6.3, 3.0, O(CH_2)$_2$); 4.72 s (2 H, OCH_2); 11.20 br.s (1 H, NH); 12.59 br.s (1 H, NH).

2,2-Dimethyl-5-piperidin-1-yl-1,4-dihydro-2*H*-pyrano[4'',3'':4',5']pyrido-[3',2':4,5]thieno[3,2-*d*]pyrimidine-8,10(9*H*,11*H*)-dithione (4f). Yield 3.5 *g* (83.7%), mp >360°C, R_f 0.62. Found, %: C 54.34; H 5.16; N 13.71; S 22.72. $C_{19}H_{22}N_4OS_3$. Calculated, %: C 54.52; H 5.30; N 13.38; S 22.98. IR spectrum, *v*, cm^{-1}: 3580, 3410 (NH); 1570 (C=C_{Ar}), 1180 (C=S). Mass spectrum, m/z ($I_{rel, \%}$): 418 [M^+] (5), 385 (13), 187 (20), 186 (7), 80 (25), 46 (45), 32 (15). ^{1}H NMR spectrum, δ, ppm, MHz: 1.38 s (6 H, 2CH_3); 1.79 s (6 H, 3CH_2); 3.21 t (4 H, *J* = 3.6, N(CH_2)$_2$); 3.38 s (2 H, CH_2); 4.68 s (2 H, OCH_2); 11.62 br.s (1 H, NH); 12.21 s (1 H, NH).

Preparation of compounds 4b, c, e, g (General method). A mixture of 0.01 *mol* of compound **2**, 30 *ml* of a 5% potassium hydroxide solution was heated on a boiling water bath for 1 *h*. After cooling, the resulting solution was acidified with acetic acid, the precipitated crystals were filtered off, washed with water and dried. Recrystallized from nitromethane.

5-Morpholin-4-yl-1,2,3,4-tetrahydropyrimido[4',5':4,5]thieno[2,3-*c*]isoquino-line-8,10(9*H*,11*H*)-dithione (4b). Yield 76.9%, mp >360°C, R_f 0.59. Found, %: C 52.12; H 4.78; N 14.47; S 24.52. $C_{17}H_{18}N_4OS_3$. Calculated, %: C 54.28; H 4.65; N 14.35; S 24.63. IR spectrum, *v*, cm^{-1}: 3400, 3310 (NH); 1560 (C=C_{Ar}), 1130 (C=S). ^{1}H NMR spectrum, δ, ppm, MHz: 1.63-1.81 m (4H, 2CH_2); 2.58-2.72 m (4H, 2CH_2); 3.25-3.79 m (8H, 4CH_2); 11.67 br.s (1 H, NH); 12.10 br (1H, NH).

2,2,3-Trimethyl-5-morpholin-4-yl-1,2,3,4-tetrahydropyrimi-do[4',5':4,5]thieno-[2,3-*c*]-2,7-naphthyridine-8,10(9*H*,11*H*)-dithione (4c). Yield 80.8%, mp 285-286°C, R_f 0.74. Found, %: C 52.79; H 5.23; N 16.32; S 22.04. $C_{19}H_{23}N_5OS_3$. Calculated, %: C 52.63; H 5.35; N 16.15; S 22.19. IR

spectrum, *v*, cm^{-1}: 3380, 3290 (NH); 1590 (C=C_{Ar}), 1120 (C=S). ^{1}H NMR spectrum, δ, ppm, MHz: 1.16 s (6H, $2CH_3$); 2.09 s (3H, CH_3); 2.30 s (2H, 9-CH_2); 3.12-3.23 m (4H, $N(CH_2)_2$); 3.53 s (2 H, 6-CH_2); 3.60-3.80 m (4H, $O(CH_2)_2$); 11.28 br (1H, NH); 12.25 br (1H, NH).

2,2-Dimethyl-5-morpholin-4-yl-1,4-dihydro-2*H*-pyrano[4'',3'':4',5'] pyrido-[3',2':4,5]thieno[3,2-*d*]pyrimidine-8,10(9*H*,11*H*)-dithione (4e). Yield (85.7%), mp >360 °C, R_f 0.71. Found, %: C 51.32; H 4.86; N 13.23; S 23.01 $C_{18}H_{20}N_4O_2S_3$. Calculated, %: C 51.40; H 4.79; N 13.32; S 22.87. IR spectrum, *v*, cm^{-1}: 3330, 3410 (NH), 1580 (C=C_{Ar}), 1150 (C=S). Mass spectrum, m/z ($I_{rel,\ \%}$): 420 [M^+] (I00), 405 (I0), 389 (16), 377 (8), 363 (25), 362 (33), 350 (35). ^{1}H NMR spectrum, δ, ppm, MHz: 1.30 s (6 H, $2CH_3$); 3.08 t (4H, *J* = 1.5, $N(CH_2)_2$); 3.71 ddd (2 H, *J* = 13.2, 3.5, 0.8) and 3.80 ddd (2 H, *J* = 13.2, 3.5, 0.9, $O(CH_2)_2$); 3.80-3.89 m (2 H, CH_2); 5.18-5.32 m (2 H, OCH_2); 11.67 br.s (1H, NH); 12.23 s (1 H, NH).

2,2-Dimethyl-5-morpholin-4-yl-1,4-dihydro-2*H*-thiopyrano[4'',3'':4', 5']-pyrido[3',2':4,5]thieno[3,2-*d*]pyrimidine-8,10(9*H*,11*H*)-dithione (4g). Yield 1.8 *g* (74.6%), mp >360°C, R_f 0.69. Found, %: C 49.42; H 4.53; N 12.72; S 29.29. $C_{18}H_{20}N_4OS_4$. Calculated, %: C 49.51; H 4.62; N 12.83; S 29.38. IR spectrum, *v*, cm^{-1}: 3400, 3320 (NH), 1590 (C=C_{Ar}), 1140 (C=S). ^{1}H NMR spectrum, δ, ppm, *MHz*: 1.24 s (6 H, $2CH_3$); 3.21-3.38 m (4H, $N(CH_2)_2$); 3.59-3.75 m (4H, $O(CH_2)_2$); 3.82-3.98 m (2 H, CH_2); 5.81-5.93 m (2 H, SCH_2); 11.35 br (1H, NH); 12.27 br (1H, 1NH).

General procedure for alkylation of compounds 5a-g: To a sodium methylate solution prepared from 0.46 *g* (0.02 *mol*) of sodium and 15 *ml* of methanol, 0.01 *mol* of pyridinethione **4** was added. Then, 2.84 *g* (0.02 *mol*) of methyl iodide (or EtI) was added dropwise with stirring. The mixture was stirred at 60°C for 5 *h*, cooled and diluted with 50 *ml* of water. The precipitated crystals were filtered off, washed with water, dried, and recrystallized from methanol.

8,10-Bis(methylthio)-5-pyrrolidin-1-yl-1,2,3,4-tetrahydropyrimido-[4',5':4,5]-thieno[2,3-*c*]isoquinoline (5a). Yield 3.5 *g* (87.0%), mp 215-217°C, R_f 0.45. Found, %: C 56.38; H 5.64; N 13.77; S 23.74. $C_{19}H_{22}N_4S_3$. Calculated, %: C 56.69; H 5.51; N 13.92; S 23.89. ^{1}H NMR spectrum, δ, ppm, MHz: 1.78 m (2 H, 2-CH_2); 1.82 m (2 H, 3-CH_2); 1.98 m (4 H, $2CH_2$); 2.61-2.79 m (8 H, 4-CH_2, $2SCH_3$); 3.48 t (4 H, *J* = 3.0, $N(CH_2)_2$); 3.78 m (2H, 1-CH_2).

8,10-Bis(methylthio)-5-morpholin-4-yl-1,2,3,4-tetrahydropyrimi-do[4',5':4,5]-thieno[2,3-*c*]isoquinoline (5b). Yield 3.8 *g* (89.5%), mp 204-205°C, R_f 0.65. Found, %: C 54.60; H 5.46; N 13.45; S 23.09. $C_{19}H_{22}N_4OS_3$. Calculated, %: C 54.52; H 5.30; N 13.38; S 22.98. ^{1}H NMR spectrum, δ, ppm, MHz: 1.65-2.05 m (4H, $2CH_2$); 2.55-2.82 m (8H, $2SCH_3$, CH_2); 3.18-4.01 m (10H, $5CH_2$).

2-Isopropyl-8,10-bis(methylthio)-5-morpholin-4-yl-1,4-dihydro-2*H*-pyrano-[4'',3'':4',5']pyrido[3',2':4,5]thieno[3,2-*d*]pyrimidine (5c). Yield 4.5 *g* (97.2%), mp 220-223°C, R_f 0.52. Found, %: C 54.74; H 5.82; N 12.34; S

20.56. $C_{21}H_{26}N_4O_2S_3$. Calculated, %: C 54.52; H 5.66; N 12.11; S 20.79. ^{1}H NMR spectrum, δ, ppm, MHz: 1.03 d (3 H, *J* = 6.7, CH_3); 1.06 d (3 H, *J* = 6.0, CH_3); 1.83 ok (1 H, *J* = 6.7, CH); 2.60 s (3 H, SCH_3); 2.74 s (3 H, SCH_3); 3.12-3.42 m (6 H, CH_2, $N(CH_2)_2$); 3.71-3.95 m (5 H, OCH, $O(CH_2)_2$); 4.68 d (1 H, *J* = 14.7) and 4.71 d (1 H, *J* = 14.0, OCH_2).

8,10-Bis(ethylthio)-2-isopropyl-5-morpholin-4-yl-1,4-dihydro-2*H*-pyrano-[4'',3'':4',5']pyrido[3',2':4,5]thieno[3,2-*d*]pyrimidine (5d). Yield 3.7 *g* (75.2%), mp 190-192°C, R_f 0.46. Found, %: C 56.48; H 6.34; N 11.34; S 19.26. $C_{23}H_{30}N_4O_2S_3$. Calculated, %: C 56.30; H 6.16; N 11.42; S 19.60. ^{1}H NMR spectrum, δ, ppm, MHz: 1.03-1.07 m (6 H, $2CH_3$); 1.42-1.46 m (6 H, $2SCH_2\underline{CH_3}$); 1.84 ok (1 H, *J* = 6.0, CH); 3.15-3.41 m (10 H, CH_2, $2S\underline{CH_2}CH_3$, $N(CH_2)_2$); 3.69-3.86 m (5 H, OCH, $O(CH_2)_2$); 4.69 d (1 H, *J* = 14.6) and 4.72 d (1 H, *J* = 13.7, OCH_2).

2,2-Dimethyl-8,10-bis(methylthio)-5-morpholin-4-yl-1,4-dihydro-2*H*-pyrano-[4'',3'':4',5']pyrido[3',2':4,5]thieno[3,2-*d*]pyrimidine (5e). Yield 3.6 *g* (94.1%), mp 256-257 °C, R_f 0.58. Found, %: C 53.67; H 5.30; N 12.57; S 21.35. $C_{20}H_{24}N_4O_2S_3$. Calculated, %: C 53.54; H 5.39; N 12.49; S 21.44. IR spectrum, *ν*, cm^{-1}: 1570 ($C=C_{Ar}$). ^{1}H NMR spectrum, δ, ppm, MHz: 1.28 s (6 H, $2CH_3$); 2.60 s (3 H, SCH_3); 2.76 s (3 H, SCH_3); 3.23 m (4 H, $N(CH_2)_2$); 3.22-3.40 m (6 H, CH_2, $N(CH_2)_2$); 3.71-3.95 m (5 H, $O(CH_2)_2$); 4.65 s (2 H, OCH_2).

2,2-Dimethyl-8,10-bis(methylthio)-5-piperidin-1-yl-1,4-dihydro-2*H*-pyrano-[4'',3'':4',5']pyrido[3',2':4,5]thieno[3,2-*d*]pyrimidine (5f). Yield 3.3 *g* (74.7%), mp 200-203 °C, R_f 0.54. Found, %: C 56.38; H 5.74; N 12.69; S 21.33. $C_{21}H_{26}N_4OS_3$. Calculated, %: C 56.47; H 5.87; N 12.54; S 21.53. ^{1}H NMR spectrum, δ, ppm, MHz: 1.29 s (6 H, $2CH_3$); 1.83-1.85 m (6 H, $3CH_2$); 2.61 s (3 H, SCH_3); 2.78 s (3 H, SCH_3); 3.20-3.23 m (4 H, $N(CH_2)_2$); 3.42 s (2 H, CH_2); 4.62 s (2 H, OCH_2).

8,10-Bis(ethylthio)-2,2-dimethyl-5-piperidin-1-yl-1,4-dihydro-2*H*-pyrano-[4'',3'':4',5']pyrido[3',2':4,5]thieno[3,2-*d*]pyrimidine (5g). Yield 2.9 *g* (62.5%), mp 172-175°C, R_f 0.62. Found, %: C 58.41; H 6.54; N 11.67; S 20.35. $C_{23}H_{30}N_4OS_3$. Calculated, %: C 58.20; H 6.37; N 11.80; S 20.26. ^{1}H NMR spectrum, δ, ppm, MHz: 1.28 s (6 H, $2CH_3$); 1.43 m (6 H, $2SCH_2\underline{CH_3}$); 1.83 m (6 H, $3CH_2$); 3.17-3.22 m (6 H, CH_2, $2S\underline{CH_2}CH_3$); 3.42 m (4 H, $N(CH_2)_2$); 4.62 s (2 H, OCH_2).

ԿՈՆԴԵՆՍՎԱԾ ԹԻԵՆՈ[3,2-d]ՊԻՐԻՄԻԴԻՆ-8,10-ԴԻԹԻՈՆՆԵՐԻ ՆՈՐ ԱՆՑՅԱԼՆԵՐԻ ՍԻՆԹԵԶԸ ԵՎ ԱԼԿԻԼԱՑՈՒՄԸ

Ե. Գ. ՊԱՐՈՆԻԿՅԱՆ, Ա. Ս. ՂԱՐՈՒԹՅՈՒՆՅԱՆ և Շ. Ֆ. ՂԱԿՈԲՅԱՆ

Կոնդենսված 1-ամինո-2-ցիանոթիենո[2,3-b]պիրրիդինների ստացման համար կիրառվել է Տորպ-Ցիգլերի ռեակցիան: 5-Ցիանոպիրրիդինթիոնները հիմնային միջավայրում ցիկլացվել են α-դիրքում ակտիվ մեթիլենային խումբ պարունակող հալոգենիդների հետ: Ստացված թիենոպիրրիդինները բացարձակ պիրրիդինի միջավայրում ծծմբաածխածնի հետ փոխազդեցության արդյունքում առաջացրել են 8-իմինոպիրրիդո[3',2':4,5]թիենո[3,2-

d][1,3]թիազին-10-թիոններ: Վերջիններս, ռեակցիոն միջավայրում ենթարկվելով Դիմրոտի վերախմբավորման, հանգեցրել են նոր կոնդեսված հետերոցիկլիկ համակարգերի՝ թիենո[3,2-d]-պիրիմիդին-8,10-դիթիոնների առաջացման: Ալկիլհալոգենիդներով 10-դիթիոնների նոր կոնդեսված հետերոցիկլիկ համակարգերի ալկիլացմամբ սինթեզվել են համապատասխան S-ալկիլածանցյալները:

СИНТЕЗ И АЛКИЛИРОВАНИЕ НОВЫХ ПРОИЗВОДНЫХ КОНДЕНСИРОВАННЫХ ТИЕНО[3,2-d]ПИРИМИДИН-8,10-ДИТИОНОВ

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Осуществлена реакция Торпа–Циглера. Из циапиридинтионов и галогенсодержащих соединений под действием алкоголятов щелочных металлов получены конденсированные 1-амино-2-замещенные тиено[2,3-*b*]пиридины. Синтезированы производные 8-имино-пиридо[3',2':4,5]тиено[3,2-*d*][1,3]тиазин-10-тионов с сероуглеродом в присутствии абсолютного пиридина, которые далее подвергнуты рециклизации с перегруппировкой Димрота, что приводит к образованию новых прозводных конденсированных тиено[3,2-*d*]пиримидин-8,10-дитионов. Разработан новый метод, который позволил исключить из реакционной среды пиридин и увеличить скорость циклизаций. Алкилированием тиено[3,2-*d*]-пиримидин-8,10-дитионов различными алкилгалогенидами синтезированы *S*-алкилпроизводные.

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НАЦИОНАЛЬНАЯ АКАДЕМИЯ НАУК РЕСПУБЛИКИ АРМЕНИЯ
NATIONAL ACADEMY OF SCIENCES OF THE REPUBLIC OF ARMENIA

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NEW QUINOLINE CARBOXYLIC ACID DERIVATIVES IN THE SYNTHESIS OF BIOLOGICALLY ACTIVE SUBSTANCES. (Review)

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Data on the synthesis and biological properties of derivatives of quinoline-4-carboxylic acids over the past 10 years have been summarized. The review considers both the derivatives substituted at different positions of the heterocyclic ring and the derivatives of the carboxyl group of quinoline-4-carboxylic acid. Given the importance of quinoline derivatives in the search for new promising compounds of biomedical use [3-8], the review provides information on methods for the preparation and biological activity of the described new derivatives of substituted quinoline-4-carboxylic acids.

References 43.

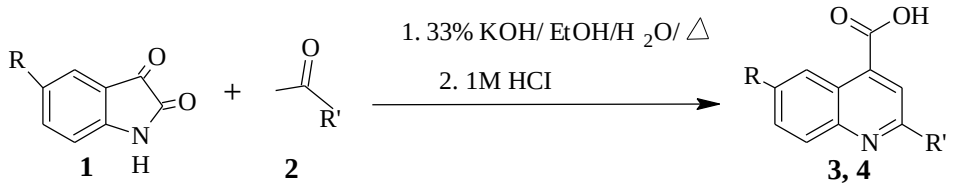
Introduction

Though after the discovery of the antigout and analgesic properties of 2-phenylquinoline-4-carboxylic acid (Cinchophen), undesirable side effects, associated with the use of the drug, were identified limiting its further use, quinoline-4-carboxylic acid continues to be considered as a promising scaffold for the creation of new multidirectional drugs [1]. Prerequisites for this are both a wide range of biological activity of quinoline-4-carboxylic acid derivatives and relatively well-developed methods for the synthesis of various derivatives of this acid [2]. Moreover, quinoline-4-carboxylic acid derivatives, for example 2-chloro, 2-hydrazine derivatives, can be used to synthesize other biologically active compounds based on them, which confirms the relevance of further targeted synthesis and study of new quinoline-4-carboxylic acid derivatives. This review summarizes the data predominantly of the last 10 years on the synthesis and biological properties of new derivatives of quinoline-4-carboxylic acid, including those substituted at different positions of the heterocyclic ring and derivatives of the carboxyl group of the acid.

Synthesis of quinoline-4-carboxylic acid derivatives

Under the conditions of the Pfitzinger reaction using isatins **1** and various substituted acetyl heterocyclic compounds **2**, 2-aryl-(hetaryl)quinoline-4-carboxylic acids **3** (R = H) and **4** (R = F, Cl, Br, NO_2) were synthesized in good yields. Quinolines **3** have pronounced antitumor, antituberculosis and antimalarial activity, and compounds **4** containing the CF_3 group have high antibacterial activity (Scheme 1) [9, 10].

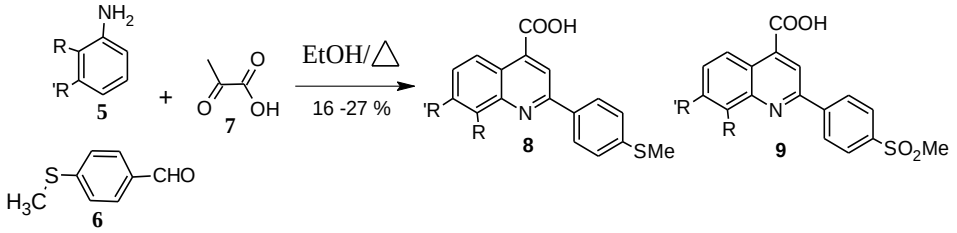
Scheme 1



3: R1 = furan-2-yl, 5-methylfuran-2-yl, 1,5-dimethylpyrrol-2-yl, 4-BrC_6H_4, CH = CHPh, CH = CH (4-ClC_6H_4), 2,4,5 -$Me_3C_6H_2$, naphthalen-2-yl, 1-hydroxynaphthalen-2-yl, anthracene-9-yl; **4:** R1 = 3,5- $(CF_3)2C_6H_3$, imidazol-1-yl, piperazin-1-yl, CH_2(4-$CF_3C_6H_4$).

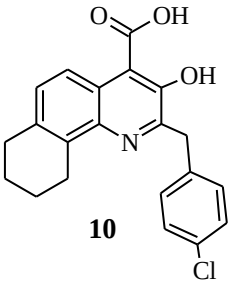
In a study on the search for new active antiinflammatory drugs in the series of **COX-2** enzyme inhibitors, by three-component condensation of substituted anilines **5**, 4-methylthiobenzaldehyde **6** and pyruvic acid **7**, new derivatives of quinoline-4-carboxylic acid **8** were synthesized in low yields, and the interaction of 1-[4-(methylsulfonyl)phenyl]ethanone with unsubstituted isatin **1** (R = H) afforded derivative **9** (Scheme 2) [11].

Scheme 2



Antiinflammatory drugs, derivatives of 2-(4-chlorobenzyl)-3-hydroxy-7,8,9,10-tetrahydrobenzo- [h]quinoline-4-carboxylic acid **10,** obtained by the methodology of convergent synthesis from the starting 3-(4-chlorophenyl)-2-oxopropyl acetate and 1,2,3,4-tetrahydronaphthalene were patented [12] (Scheme 3).

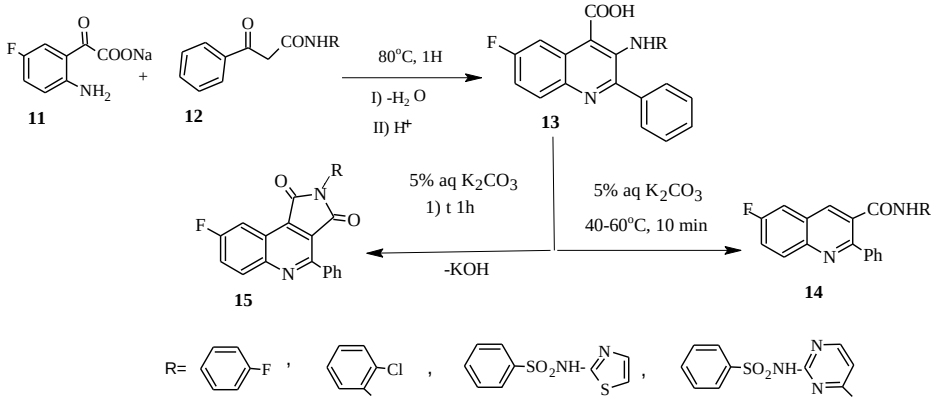
Scheme 3



10

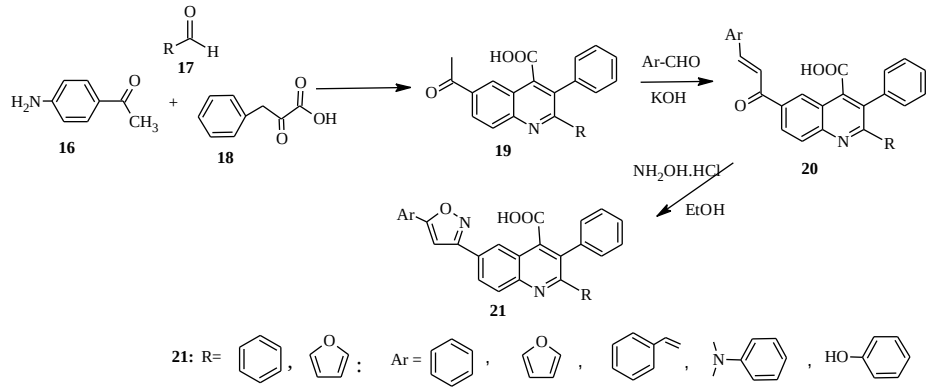
The high-yield synthesis of fluorine-containing quinoline-4-carboxylic acids by cyclo-condensation of the sodium salt of 2-amino-5-fluorophenylglyoxylic acid **11** with benzoylacetanilides **12** when boiling in DMF is described. Decarboxylation of **13** led to 6-fluoro-2-phenyl-3-(substituted amino)ketoquinolines **14**, and boiling - to 7-fluoro-1-(aryl)-3-phenylpyrrolo[3,4-c]quinolin-2,9-dions **15.** The compounds were effectively studied as amylolytic agents (Scheme 4) [13].

Scheme 4



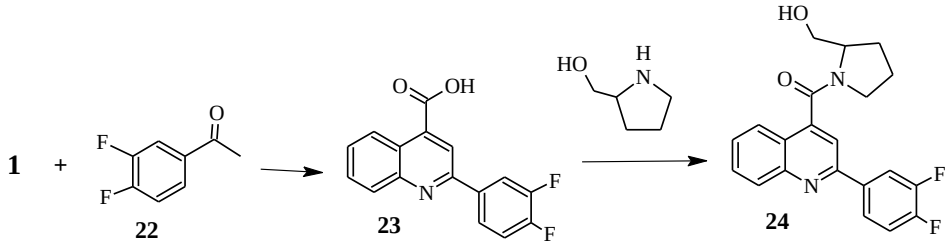
The synthesis of new 2,3-diaryl-6-acetylquinoline-4-carboxylic acids **19a-e** by three-component condensation of 4-aminoacetophenone **16,** benzaldehyde **17** or furan-2-carbaldehydes and phenyl-pyruvic acid **18** by the Doebner reaction is described. Compounds **19a-e** by interaction with various aromatic aldehydes in the basic medium were transformed to the corresponding chalcones **20a-e,** which were condensed with hydroxylamine hydrochloride in ethanol to heterocyclic derivatives of isoxazoles **21a-e.** The latter were tested for antibacterial and antifungal activity (Scheme 5) [14].

Scheme 5



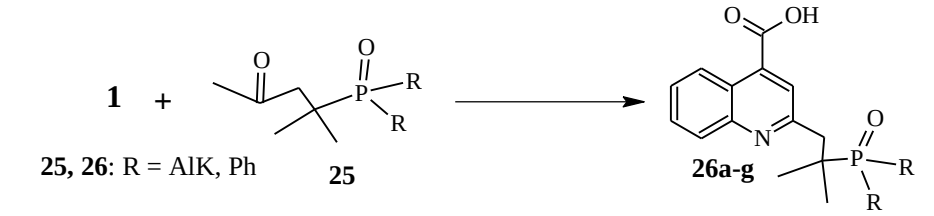
By the interaction of isatin **1** with 3,4-difluoroacetophenone **22** under the conditions of the Pfitzinger reaction, a number of quinolinecarbonylpyrrolidines **24** were synthesized, which were patented as compounds exhibiting high selectivity for GABA benzodiazepine receptors (Scheme **6**) [15].

Scheme 6



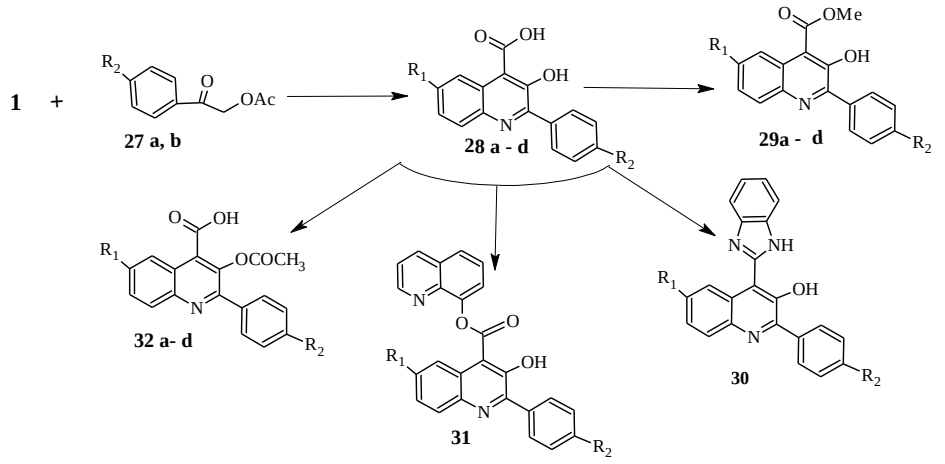
The work presents the synthesis of new derivatives of 2-[2-(dialkyl(diaryl)-phosphoryl)-2-methylpropyl]4-quinolinecarboxylic acids **26a-g** containing a phosphine oxide fragment; the synthesized derivatives were tested for antibacterial activity (Scheme 7) [16].

Scheme 7



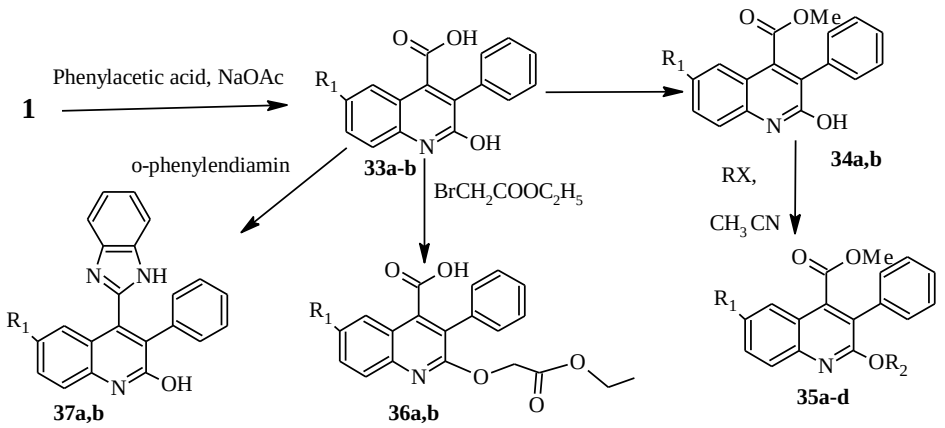
Two new series of 2-aryl-3-hydroxy- and 3-aryl-2-hydroxyquinoline-4-carboxylic acids **28a-d**, **33a, b** and their derivatives **29-32** and **34-37** are presented**.** Antioxidant activity was studied using the **ABTS** method (Scheme 8, 9**)** [17].

Scheme 8



R_1, R_2: CH_3, H (a), CH_3, CH_3(b), Br, H(c), Br, CH_3 (d).

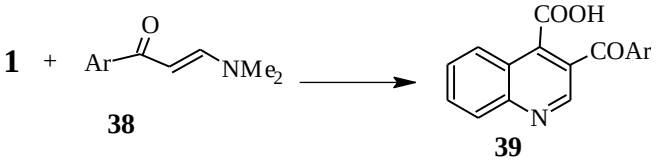
Scheme 9



R_1, R_2 : CH_3, CH_3 (a), Br, CH_3 (b), CH_3, CH_2Ph (c), Br, CH_2Ph(d)

A simple one-step method for the synthesis of quinoline-4-carboxylic acids **39** by the reaction of enaminones **38** and isatin using the conditions of the Pfitzinger reaction has been described (Scheme 10) [18].

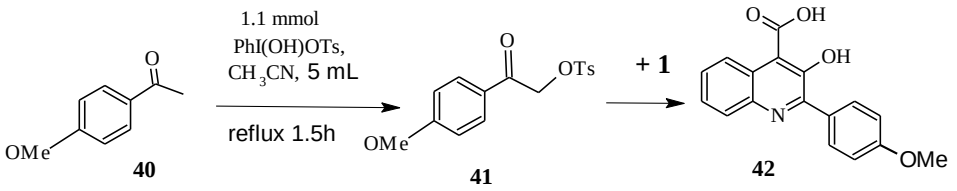
Scheme 10



The synthesis of 2-(4-methoxyphenyl)quinoline salicylic acid **42** from α-tosyloxyaceto-phenone and isatin **1** under the conditions of the Pfitzinger reaction has been developed. α-Tosyl-oxyacetophenone was obtained by boiling

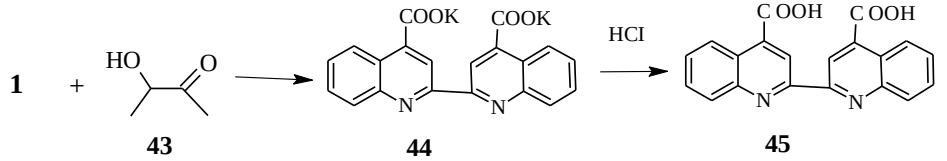
5 *ml* of 4-methoxyacetophenone **40** with Kosser's reagent [hydroxy(tosyloxy) iodo]benzene (HTIB) in acetonitrile (Scheme 11) [19].

Scheme 11



The synthesis of 2,2-biquinolyl-4,4-dicarboxylic acid **45** by the Pfitzinger reaction from isatin **1** and acetoin (2-hydroxy-butanone-3) **43** was registered in the work (Scheme 12) [20].

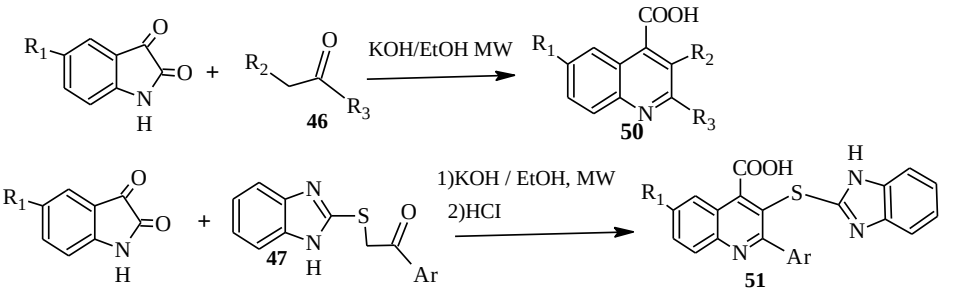
Scheme 12

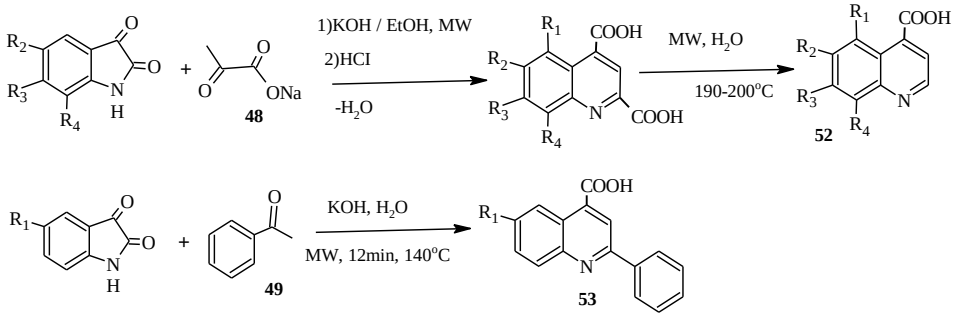


2a. Synthesis of quinoline-4-carboxylic acid derivatives using microwave irradiation and catalysts

Microwave irradiation was used to quickly and efficiently synthesize substituted quinoline-4-carboxylic acids **50a-q, 51a-d, 52a-k,** and **53** by reacting substituted isatines **1** with acyclic and cyclic ketones **46**, 2-(1-benzimidazol-2-ylthio)-1-arylethanones **47**, sodium pyruvate **48** and acetophenone **49** under the conditions of the Pfitzinger reaction (Scheme 13) [21-24].

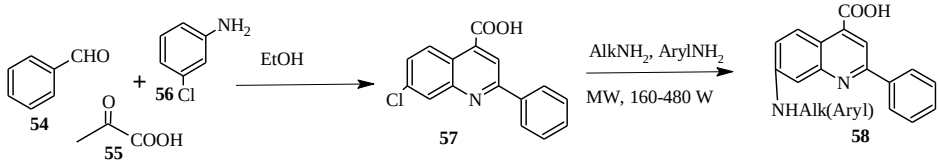
Scheme 13





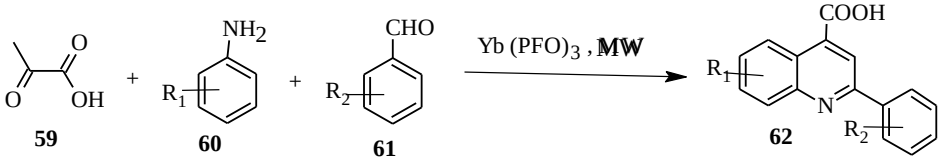
The main attention is paid to the synthesis of derivatives of 2-phenyl-7-substituted quinoline-4-carboxylic acids **58** under the influence of microwave irradiation with an output power of 160 to 480 W, the output varies from 90% to 95% and the reaction time is shorter than with the conventional method. The compounds are active against a wide range of microorganisms (Scheme 14) [25].

Scheme 14



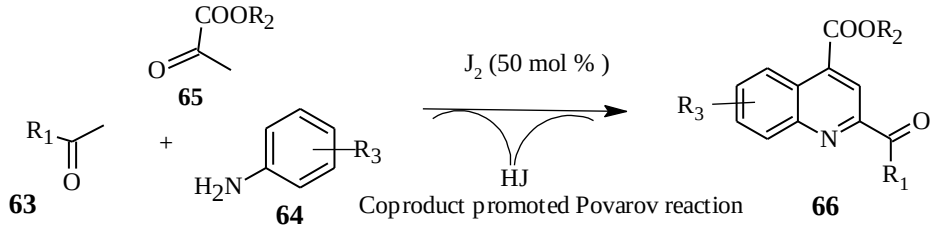
Ytterbium perfluorooctanoate [Yb (PFO) 3] effectively catalyzes the Doebner reaction and is described as a new procedure for the preparation of quinoline-4-carboxylic acid derivatives **62** using the three-component reaction of combining pyruvic acid **59**, amines **60** and aldehydes **61** in water. This process is quick, easy and environmentally friendly, and the catalyst is repeatedly processed with sequential activity (Scheme 15) [26].

Scheme 15



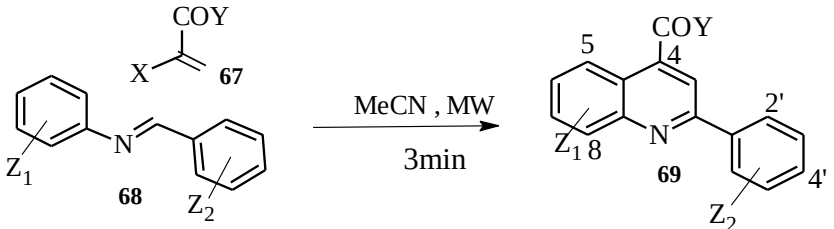
A highly efficient method for the synthesis of substituted quinolones 66 from methylketones 63, arylamines 64 and α-ketoesters 65 has been developed. This reaction uses a catalytic amount of HI-coproduct as a promoter for the synthesis of substituted quinolones (Scheme 16) [27].

Scheme 16



Rapid synthesis of quinoline-4-carboxylic acid derivatives **69** has been achieved by the reaction of 2-methoxyacrylates or acrylamides **67** with *N*-arylbenzaldimines **68** in acetonitrile under $InCl_3$ catalysis and microwave irradiation. The yield of the product was up to 57% within 3 min. The role of indium chloride and ytterbium triflate was specified using ^{13}C NMR data and model theoretical studies (Scheme 17) [28].

Scheme 17



Z_1=H, 6-F, 6-Cl, 6-Br, 8-F.

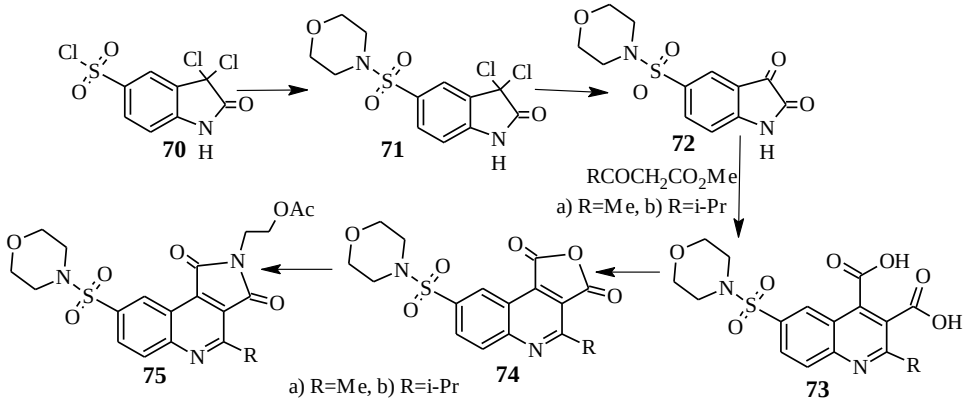
Z_2=2',3' or 4'-F,4'-Br, 3',4'-OMe, NHBr, NH-CH(Ph)Et

X=OMe; Y=OEt,OMe,NHBr,NH-CH(Ph)Et

Multisubstituted Carboxamides of 4-Quinoline Carboxylic Acids

The connection between synthesis, biological assessment and SAR is described for a series of new inhibitors of caspase-3 1,3-dioxo-2,3-dihydro-1H-pyrrolo[3,4-c]quinoline **75**. The inhibitory activity of the synthesized compounds is highly dependent on the nature of the substituent in position 4 in the nucleus frame structure. 4-Methyl and 4-phenyl substituted derivatives are the most active compounds in this series; caspase-3 with an IC50 of 23 and 27 nM, respectively, was inhibited (Scheme 18) [29].

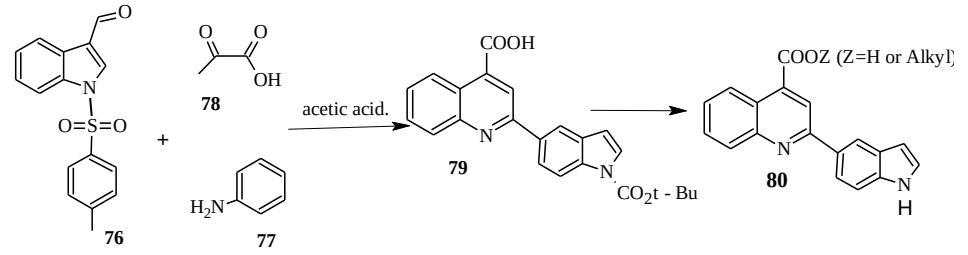
Scheme 18



The patented work relates to a method for producing a pharmaceutical preparation of 2-(N-Boc-3-indolyl)-4-quinolinecarboxylic acid **79** and carboxylate **80,** which inhibits the growth of bacterial microorganisms.

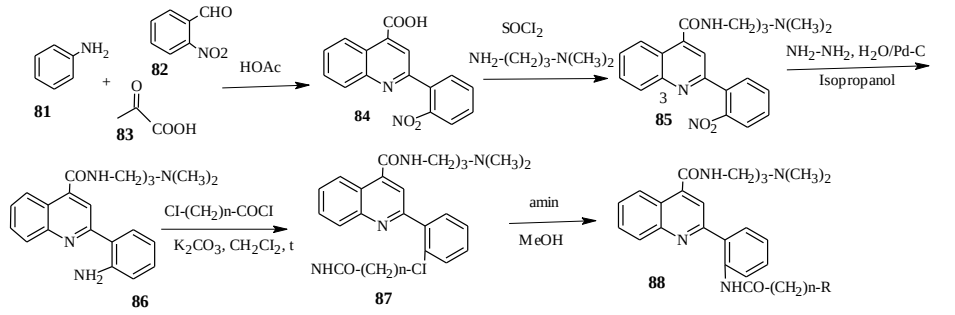
2-(N-Boc-3-indolyl)-4-quinolinecarboxylic acid was obtained under the conditions indicated in Scheme 19) [30].

Scheme 19



A number of new derivatives of 2-phenylquinoline-4-carboxylic acid **84** were synthesized from aniline **81**, 2-nitrobenzaldehyde **82**, pyruvic acid **83** under the conditions of the Doebner reaction, followed by amidation **85**, reduction **86**, acylation **87** and amination **88**. We studied the antibacterial activity of these compounds. Results showed that some compounds exhibited good anti-bacterial activity against *Staphylococcus aureus* (Scheme 20) [31].

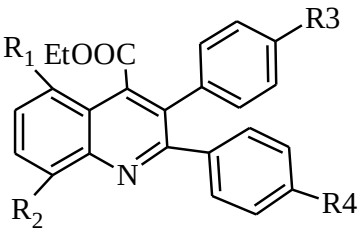
Scheme 20



R=-N(C$_2$CH$_4$)$_2$N-, -NC$_4$H$_8$, -N(Et)$_2$, -NC$_5$H$_{10}$, NH$_2$ (CH$_2$)$_3$ NMe$_2$, - NH (CH$_2$)$_3$ -NEt$_2$, - NC$_4$H$_8$O,

The patent describes the preparation of polysubstituted quinoline-4-carboxylates **89a-h** as anti-microbial agents (Scheme 21) [32].

Scheme 21

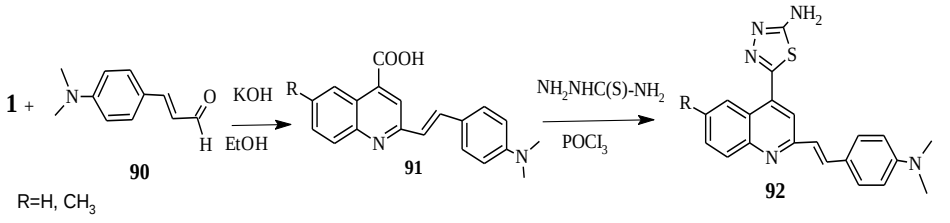


89a-h

89a-h: 5.8-Dichloro-2,3-diphenyl- (a), 5,8-dichloro-2- (4-chlorophenyl) -3-phenyl- (b), 5,8-dichloro-3- phenyl-2-p-tolyl- (c), 5,8-dichloro-4-methoxyphenyl) -2-phenyl- (d), 5,8-dichloro-3- (4-methoxy phenyl) -2- p-tolyl (e), 5,8-dichloro-2-n-pentyl-3-phenyl- (f), 6-chloro-2-n-propyl-3- (3,4-methylenedioxy) - (g) 5,8-dichloro-2-n-propyl-3-phenyl- (h).

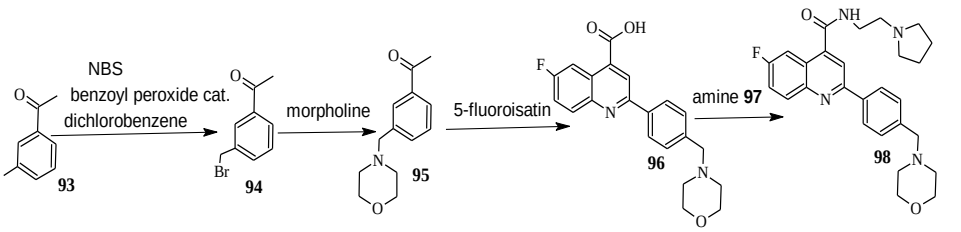
A new series of 4,6-disubstituted-2-(4-(dimethylamino)styryl)quinolines **91**, **92** were synthesized and the antitumor activity of all compounds was studied by MTT analysis against two cancer cell lines. A discussion of the results showed that some derivatives exhibited the highest antitumor activity against the tested cell lines compared to control preparations (Scheme 22) [33].

Scheme 22



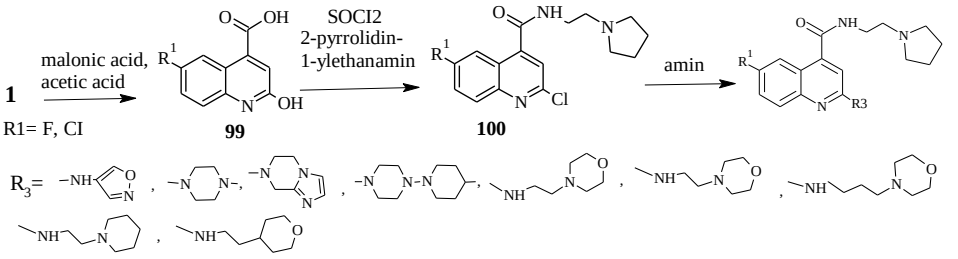
The authors have developed an effective method for the synthesis of a quinoline-4-carboxylic acid derivative from a series of carboxamides with multi-stage antimalarial activity *in vivo*. 6-Fluoro-2-[3-(morpholinomethyl)phenyl]-N-[2-(pyrrolidin-1-yl)ethyl]quinoline-4-carboxamide **98** was obtained from a mixture of 6-fluoro-2-[3-(morpholinomethyl)phenyl]quinoline-4-carboxylic acid **96** and 2-pyrrolidin-1-ylethanamine **97** under the conditions indicated in Scheme 23 [34].

Scheme 23



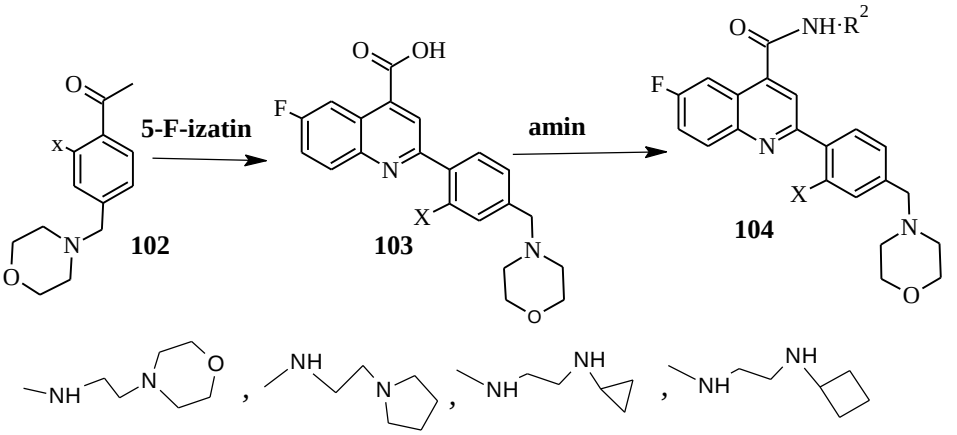
The synthetic pathway for the preparation of a number of carboxamides with aromatic R_3 substituents is presented. The synthesis of compound **101** was achieved by treating 2-hydroxy-quinoline-4-carboxylic acid **99** with thionyl chloride in DMF, followed by reaction with 2-pyrrolidin-1-ylethanamine in THF which resulted in carboxamides **100** treated with a series of amines **101** (Scheme 24) [35].

Scheme 24



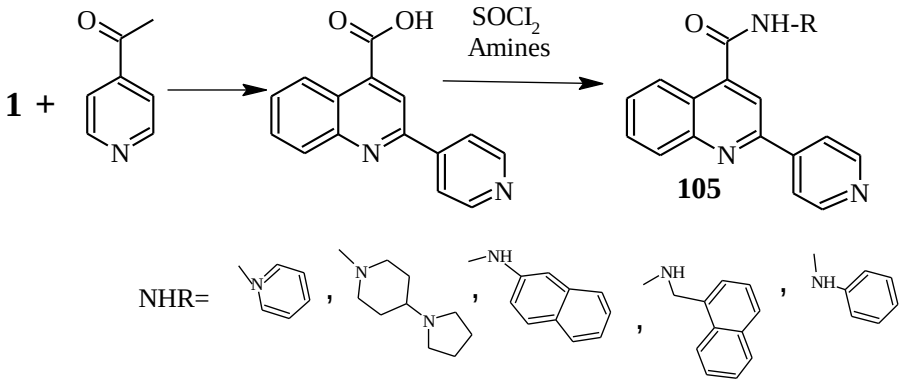
As described in the work, the Pfitzenger reaction of 5-fluorisatin with the corresponding methyl ketone **102** afforded acids **103** and treatment of the latter with the corresponding amines at room temperature yielded the target amides **104a-d.** Optimal conditions for the synthesis of methyl ketone have been developed (Scheme 25) [36].

Scheme 25



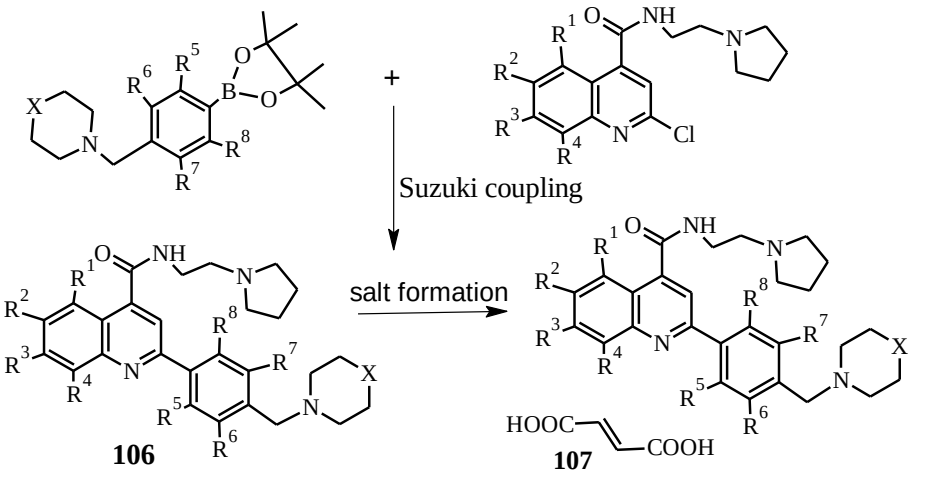
In the work, analogues of quinoline-4-carboxamides **105** were used to study SAR. All compounds were synthesized, as indicated in the diagram, with slight changes for each analog. The general procedure for the preparation of quinoline-4-carboxamide analogues is given in Scheme 26 [37].

Scheme 26



The patent relates to a new class of inhibitors of quinolone-4-carboxamide Pf3D7 of the general formula **106 (107),** their use in medicine and, in particular, malaria, the methods for their preparation and the intermediate compounds used in such processes (Scheme 27) [38].

Scheme 27



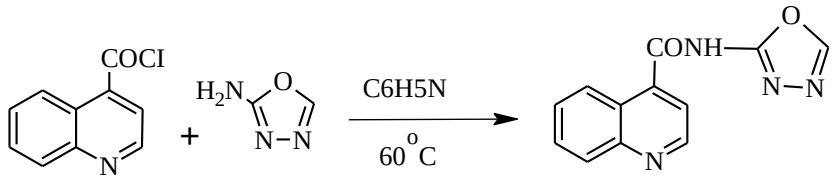
106 107

R_1, R_2, R_3, R_4, R_5, R_6, R_7 and R8 irrespective of each other = H, CI or F,X = -O-.

Heterylamides of substituted-4-quinolinecarboxylic acids

The synthesis of 4-quinolinecarboxylic acid heterylamide **110** was achieved by condensation of equimolecular amounts of quinoline-4-carboxylic acid chloride **108** and 2-amino-1,3,4-oxadiazole **109** with gentle boiling in pyridine for 4 hours (Scheme 28) [39].

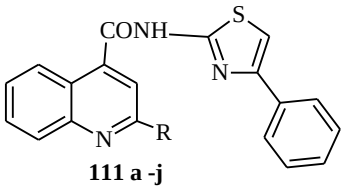
Scheme 28



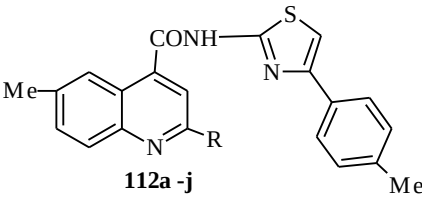
108 **109** **110**

In this work, we report the synthesis of a large number of 2-substituted heterylamides - **111a-j** and 6-R-2-substituted cinchoninic acids **112a-j** by the interaction of the corresponding acid chlorides with heterylamines in benzene or dichloroethane in the presence of several drops of DMF when boiling (Scheme 29) [40].

Scheme 29



111 a -j

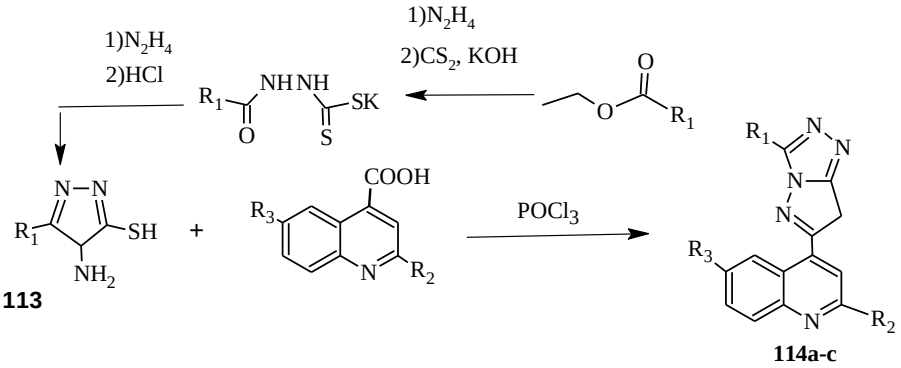


112a -j

111a-j, 112a-j: R = 4-nitrophenyl (a), 3-nitrophenyl (b), diphenyl-4-yl (c), 5-nitro-2-furyl (d), 2-yenyl (e), 5-nitro-2-thienyl (f), 5-nitro-2-thienyl vinyl (e), 2-thienyl vinyl (f), 2,2-bitienyl-5-yl (g), 5-nitro-2,2 β-bitienyl-5-yl (h), 2,2-bitienyl-5-vinyl (i), 5-nitro-2,2-bitienyl-5-yl vinyl (j) as viral inhibitors.

The authors found that substituted 4-amino-4H-1,2,4-triazole-3-thiols **113a-f** of quinoline-4-carboxylic acids when heated with phosphoryl chloride, cyclized to form substituted 4-([1,2,4] triazolo [3,4-b]-[1,3,4]thiadiazol-6-yl)quinolines **114a-c** with various substituents R1-R3. This reaction can be used for the combinatorial synthesis aimed at studying them for biological activity (Scheme 30) [41].

Scheme 30



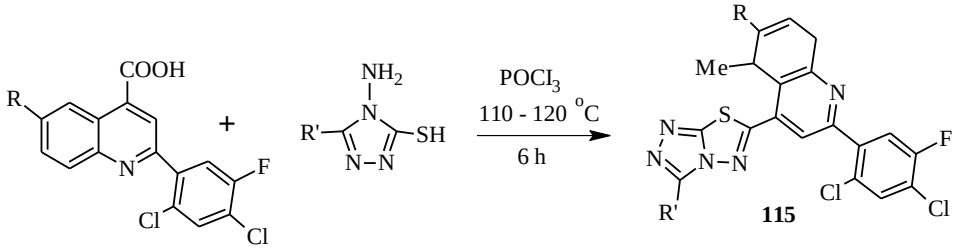
113 **114a-c**

114a-c: R_1 = Et (a), Pr (b), 2-furyl (c), Ph (d), $PhCH_2$ (e), 4-$MeOC_6H4CH_2$ (f); II, R_2 = Me, R_3 = H (a), Cl (b), Br (c); R_2 = Ph, R_3 = H (d), Me (e), Br (f); R_2 = 4-MeC_6H_4, R_3=H (g); III, R1 = Et: R_2 = Me, R_3 = Cl (a), Br (b); R_2 = Ph, R_3 = H (c), Me (d), Br (e); R1 = Pr, R_2 = Ph, R_3 = Me (f), Br (g); R_1 = 2-furyl: R_2 = Me, R_3 = H (h); R_2 = Ph, R_3 = H (i), Br (j); R_1 = Ph: R_2 = Me, R_3 = H (k); R_2 = Ph,R_3 = Me (l), Br (m); R_2 = 4-MeC_6H_4, R_3 = H (n); R_1 = $PhCH_2$, R_2 = Ph, R_3 = Me (o), Br (p); R_1 = 4-$MeOC_6H_4CH_2$, R_2 = Ph, R_3 = Br (r); V, R_3 = H (a), Me (b), Cl (c), Br (d); VI, R_2 = Me (a), Ph (b), 4-MeC_6H_4 (c).

Upon condensation of substituted quinoline-4-carboxylic acids with various 3-substituted-4-amino-5-mercapto-1,2,4-triazoles, a number of still unregistered 3-substituted -1,2,4-triazolo[3,4-b]-1,3,4-thiadiazol-6-yl-2-(2,4-dichloro-5-

fluorophenyl)quinolines **115** were obtained. The new synthesized compounds were evaluated by their antibacterial activity (Scheme 31) [42].

Scheme 31

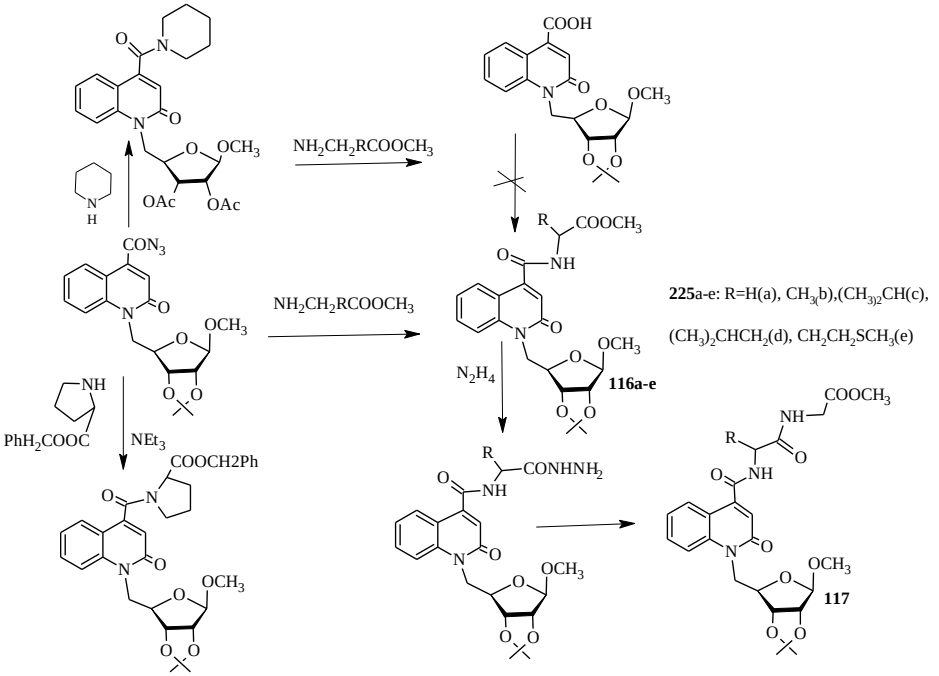


R = H, Br; R_1 = H, CH_3, $CH_3CH_2CH_2$, $C_6H_5CH_2$, $C_6H_5NHCH_2$, 2-$ClC_6H_4OCH_2$, 4-$ClC_6H_4OCH_2$, 2,4-$Cl_2C_6H_3OCH_2$, 3,4-$(CH_3)_2C_6H_3OCH_2$, 4-Cl-3-$CH_3C_6H_3OCH_2$

Quinoline nucleosides

The studies relate to the syntheses of a series of quinoline nucleosides substituted at position 4 with a number of amino acids and dipeptides of carboxamides as potential chemotherapeutic agents. Quinoline nucleosides containing a moiety of amino acid ester **117** were obtained by azide synthesis from **116a-e** esters (Scheme 32) [43].

Scheme 32



ՔԻՆՈԼԻՆ ԿԱՐԲՈՆԱԹԹՎԻ ՆՈՐ ԱԾԱՆՑՅԱԼՆԵՐԸ ԿԵՆՍԱԲԱՆՈՐԵՆ ԱԿՏԻՎ ՄԻԱՑՈՒԹՅՈՒՆՆԵՐԻ ՍԻՆԹԵԶՆԵՐՈՒՄ

Ա. Ն. ԻՍԱԽԱՆՅԱՆ և Ա. Ա. ՀԱՐՈՒԹՅՈՒՆՅԱՆ

Գրական ակնարկը ընդգրկում է վերջին 10 տարիներին բազմատեղակալված քինոլինային ցիկլեր և կարբօքսիլ խմբի տարբեր տեղակալված ածանցյալներ պարունակող քինոլին-4-կարբոնաթթուների ստացման մեթոդների և կենսաբանական ակտիվության վերաբերյալ տվյալներ: Ներկայացնելով քինոլինի ածանցյալների կարևորությունը կենսաբժշկական նպատակներով՝ նոր խոստումնալից միացությունների որոնման գործընթացում, ակնարկը տեղեկատվություն է տալիս տեղակալված քինոլին-4-կարբոնաթթուների նոր ածանցյալների կենսաբանական գործունեության մեթոդների վերաբերյալ:

НОВЫЕ ПРОИЗВОДНЫЕ ХИНОЛИНКАРБОНОВЫХ КИСЛОТ В СИНТЕЗЕ БИОЛОГИЧЕСКИ АКТИВНЫХ ВЕЩЕСТВ

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Обобщены данные за последние 10 лет по синтезу и биологическим свойствам производных хинолин-4-карбоновых кислот. В обзоре рассмотрены производные, замещенные по различным положениям гетероциклического кольца, и производные карбоксильной группы хинолин-4-карбоновой кислоты. С учетом важности производных хинолина в изыскании новых перспективных соединений биомедицинского применения в обзоре приведены сведения о способах получения и биологической активности описанных новых производных замещенных хинолин-4-карбоновых кислот.

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ՀԱՅԱՍՏԱՆԻ ՀԱՆՐԱՊԵՏՈՒԹՅԱՆ ԳԻՏՈՒԹՅՈՒՆՆԵՐԻ
ԱԶԳԱՅԻՆ ԱԿԱԴԵՄԻԱ
НАЦИОНАЛЬНАЯ АКАДЕМИЯ НАУК РЕСПУБЛИКИ АРМЕНИЯ
NATIONAL ACADEMY OF SCIENCES OF THE REPUBLIC OF ARMENIA

Հայաստանի քիմիական հանդես
Химический журнал Армении **72, №4, 2019** Chemical Journal of Armenia

OBTAINING A COMPLEX OF 1-VINYL-1,2,4-TRIAZOLE WITH GOLD CHLORIDE AND STUDY OF ITS THERMAL AND BIOLOGICAL PROPERTIES

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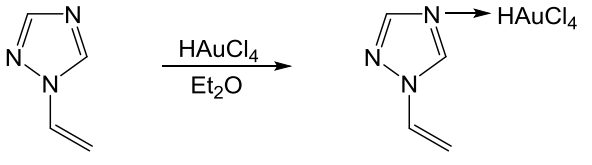
The complex (CVT) of 1-vinyl-1,2,4-triazole (VT) with $HAuCl_4$ was synthesized, its physicochemical characteristics were determined. It has been shown that the formation of the complex occurs through the triazole nitrogen atom N4. Using the results of thermogravimetric and elemental analyses, it has been found that regardless of the molar ratio of the starting components (VT: $HAuCl_4$ - 1:1; 1:2; 2:1), a complex of 1:1 composition is formed. The effect of compounds VT, $HAuCl_4$, and CVT on postganglionic sympathetic nerve fibers and adrenergic receptors was studied. It has been found that the tested compounds have a weak sympatholytic and adrenomimetic effect.

Figs. 3, table 1, references 13.

The coordination properties of azoles, the complexes of which are widely used primarily as biologically active preparations for various purposes [1–7], arouse great interest of researchers both in theoretical and applied aspects.

Analysis of the literature data [8–13] devoted to this problem shows that the coordination compounds of triazoles with noble metals, in contrast to transition metal complexes [8, 11, 14], have been little studied. To fill this gap, in the present work, the interaction of 1-vinyl-1,2,4-triazole (VT) with $HAuCl_4$ was studied for the first time.

At room temperature, mixing of the ether solution of $HAuCl_4$ with the ether solution of VT instantly leads to complexation of the donor-acceptor type with the participation of nitrogen N4, which has the highest electron density [15].



VT CVT

The manifestation of bidentality in VT with the participation of the second nitrogen atom, as shown in [16], is unlikely.

It has been established that regardless of the molar ratio of the starting components (Established VT: $HAuCl_4$ - 1:1; 1:2; 2:1), a complex (CVT) of 1:1 composition is formed.

A spectral study of the obtained complex (CVT) showed that the absorption of the unsaturated substituent (C=C) of the initial ligand (VT) in the 1653.4 cm^{-1} region was preserved and did not undergo significant shifts in the complex (1654.3 cm^{-1}). According to published data [17], this indicates that the vinyl fragment of VT does not participate in coordination with $HAuCl_4$.

Analysis of the IR spectrum of the obtained complex and comparison with the spectrum of the free ligand (VT) shows that there are noticeable short-wavelength shifts (10.2 cm^{-1}) of the absorption band related to valence oscillations of the triazole ring, which are observed in the ligand (VT) at 1509,6 cm^{-1}, respectively. High-frequency shifts of the oscillation band of the hetero ring indicate the formation of a complex through the N4 atom [17].

In the ^1H NMR spectrum of the complex (CVT), a weak-field shift of the 3-H and 5-H ring protons is observed ($\Delta\delta$ 0.28 and 0.24). Weak-field displacements for protons of H_A, H_B, and H_C of the vinyl substituent as compared with the ligand (VT) are not observed. The results also confirm the participation of the triazole cycle in coordination [7, 17].

To assess the thermal stability and the possibility of decomposition of the complex (CVT), a thermal study was carried out under dynamic heating conditions using the [TG / MS NETZSCH STA 449 (TG) QSM403 (MS)] device (Fig. 1).

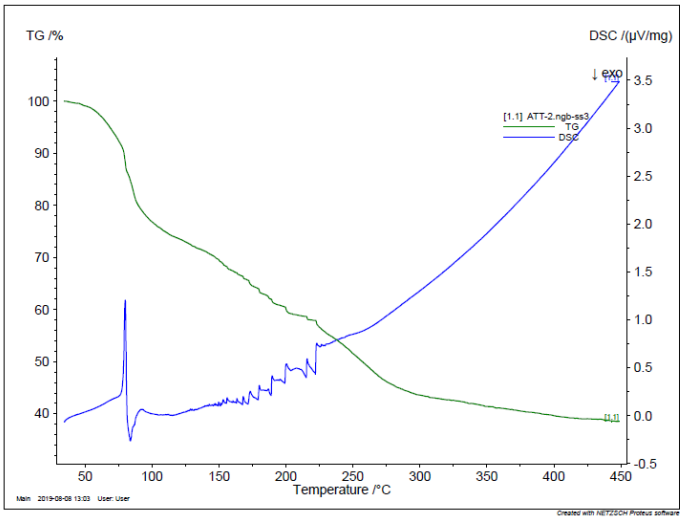


Fig. 1. Curves of thermogravimetric analysis of the complex (CVT).

It is noteworthy that the mass loss in the indicated temperature range does not affect the linear nature of the differential scanning calorimetry curve - DSC.

Intensive thermal decomposition (thermal destruction) begins at about 80°C and has a pronounced exothermic character, and its maximum value is fixed at a temperature of 90°C (DSC curve). This decay is completed at 160°C and according to the data of chromatography-mass spectroscopy analysis (Fig. 2) corresponds to the ligand splitting according to the Scheme:

$$[CVT] \xrightarrow{\triangle} VT + HAuCl_4$$

The mass loss in the temperature range of 80-160°C is ~25%, which according to the calculated data (21.84) practically corresponds to the splitting of one ligand molecule.

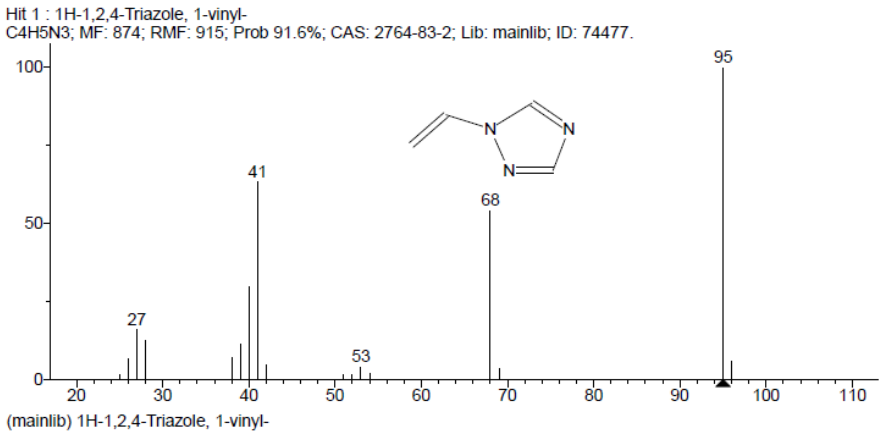


Fig. 2. Chromatography-mass spectral analysis of 1-vinyl-1,2,4-triazole released from the complex (CVT).

A further increase in temperature on the TG curve manifests as a slow mass loss and, at a temperature of ~250°C, according to the data of chromatography-mass spectral analysis (Fig. 3), the decomposition of $HAuCl_4$ begins according to the Scheme:

$$HAuCl_4 \xrightarrow{250^oC} HCl + AuCl_3$$

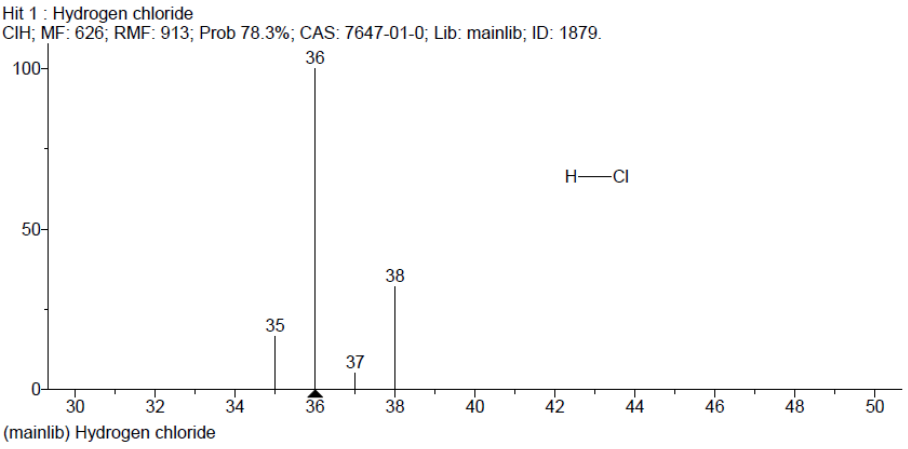


Fig. 3. Chromatography-mass spectral analysis of the released HCl from $HAuCl_4$.

According to the TG curves after 325°C, the residue is approximately 44.67%, which practically corresponds to the percentage (45.28) of the gold content in the complex.

Thus, the results of thermogravimetric and elemental analyses confirm that 1-vinyl-1,2,4-triazole (VT) forms a complex (CBT) with $HAuCl_4$ in an equimolar ratio.

The effect of VT, $HAuCl_4$, and CVT compounds synthesized at the Scientific Technological Center of Organic and Pharmaceutical Chemistry of the National Academy of Sciences of the Republic of Armenia on postganglionic sympathetic nerve fibers and adrenoreceptors was studied.

The studies were conducted in the Laboratory of Pharmacology and Histopathology in accordance with the rules for keeping and handling animals, as set out in the European Community directive (86/609/EC).

In experiments on an isolated rat vas deferens, the effect of three chemical compounds (VT, $HAuCl_4$ and CVT), on postganglionic sympathetic nerve fibers and adrenoreceptors, was studied.

The effect of compounds on organ contractions caused by transmural electrical stimulation (0.1 *msec*, 80 *imp*/*sec*, supramaximal voltage for 3 sec every 1.5 *min*) and norepinephrine at a concentration of $1 \cdot 10^{-6}$ *g*/*ml* was studied. Compounds were tested at a final concentration of 0.05 *μmol*/*ml*.

The effect of each compound was tested in experiments on two ducts and the arithmetic mean was determined.

Studies have shown that the tested compounds have a weak sympatholytic and adrenomimetic effect (Table).

Table

The sympatholytic and adrenomimetic effect of $HAuCl_4$, CT and CVT compounds

Number of experiments	Compound	Sympatholytic action: reduction of the amplitude of duct contractions caused by transmural electrical stimulation in % of control		Adrenomimetic effect: a decrease in the amplitude of duct contractions caused by 1 • 10-6 *g*/*ml* in % of control	
		10 *min*	60 *min*	10 *min*	60 *min*
2	$HAuCl_4$	27,5	7,5	7,5	15
2	VT	15	31	17*	17
2	CVT	30	29	15	52

* increase in the amplitude of contractions (adrenomimetic effect).

Experimental Section

The IR spectra were recorded on a spectrometer "Termo Nicoletion Nexus" in vaseline oil. The ^{1}H and ^{13}C NMR spectra were measured on a Varian "Mercury-300VX" spectrometer in DMSO-d_6-CCl_4 (1:3) using TMS as internal standard. Elemental analysis was performed on a Eurovector "EA 3000" instrument. Thermogravimetric and chromatography-mass spectral analyses were performed on a "TG/MS NETZSCH STA 449 (TG) QSM403 (MS), Germany" derivatograph, heating rate 5 deg/min, temperature range 20-500°C. As starting materials, 1,2,4-triazole and $HAuCl_4$ manufactured by "Sigma-Aldrich" were used.

1-Vinyl-1,2,4-triazole (VT) was obtained according to the method [18]. IR spectrum, ν, cm^{-1}: 1509.6 (ring), 1653.4 (C=C). ^{1}H NMR spectrum, δ, ppm, Hz: 4.99 dd (1H, $=CH_2$, *J*=8.8 and 0.8), 5.76 dd (1H, $=CH_2$, *J*=15.5 and 0.8), 7.28 ddd (1H, =CH, *J*=15.5, 8.8 and 0.7), 7.84 br.s (1H, 5-H), 8.59 s (1H, 3-H). ^{13}C NMR spectrum, δ, ppm: 102.4 (CH_2), 129.3 (CH-CH_2), 142.7 (CH), 151.2 (CH), bp 58°C/10 *mm* Hg, n_D^{20} 1.5120.

Synthesis of the complex (CVT). 0.5 *g* (1.5 *mmol*) of $HAuCl_4$ was dissolved in 50 *ml* of dry ether, then 0.15 *g* (1.6 *mmol*) of VT was added. The resulting yellow crystals were filtered and dried, mp 85-125°C. The yield was 0.32 *g* (47%). IR spectrum, ν, cm^{-1}: 1519.8 (ring), 1654.3 (C=C). ^{1}H NMR spectrum, δ, ppm, Hz: 5.09 dd (1H, $=CH_2$, J = 8.8 and 0.8), 5.74 dd (1H, $=CH_2$, J=15.5 and 0.8), 7.37 dd (1H, =CH, J=15.5 and 8.8), 8.12 s (1H, 5-H), 8.83 s (1H, 3-H). Found, %: C 11.25; H 1.18; N 9.85. $C_4H_6N_3Cl_4Au$. Calculated, %: C 11.03; H 1.37; N 9.65.

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ՈՍԿՈՒ ՔԼՈՐԻԴՈՎ 1-ՎԻՆԻԼ-1,2,4-ՏՐԻԱԶՈԼԻ ԿՈՄՊԼԵՔՍԻ ՍՏԱՑՈՒՄԸ ԵՎ ՆՐԱ ՋԵՐՄԱՅԻՆ ԵՎ ԿԵՆՍԱԲԱՆԱԿԱՆ ՀԱՏԿՈՒԹՅՈՒՆՆԵՐԻ ՈՒՍՈՒՄՆԱՍԻՐՈՒԹՅՈՒՆԸ

Ա. Ղ. ՀԱՍՐԱԹՅԱՆ

Սինթեզվել է 1-վինիլ-1,2,4-տրիազոլի (ՎՏ) կոմպլեքսը $HAuCl_4$-ի (ԿՎՏ) հետ, որոշվել են նրա ֆիզիկոքիմիական հատկությունները: Ցույց է տրվել, որ կոմպլեքսի առաջացումը տեղի է ունենում տրիազոլային օղակում N4 ազոտի ատոմի միջոցով: Թերմոգրավիմետրիկ և էլեմենտ անալիզների օգնությամբ պարզվել է, որ անկախ ելանյութերի մոլային հարաբերակցությունից (ՎՏ: HAuCl4 – 1:1, 1:2, 2:1) առաջանում է 1:1 բաղադրությամբ կոմպլեքսը: Ուսումնասիրվել է ՎՏ, $HAuCl_4$ և ԿՎՏ միացությունների ազդեցությունը հետազնդիոնային սիմպաթիկ նյարդային մանրաթելերի և ադրենոռեցեպտորների վրա: Հայտնաբերվել է, որ փորձարկված միացություններն ունեն թույլ սիմպաթոլիտիկ և ադրենոմիմետիկ ազդեցություն:

ПОЛУЧЕНИЕ КОМПЛЕКСА 1-ВИНИЛ-1,2,4-ТРИАЗОЛА С ХЛОРИДОМ ЗОЛОТА И ИЗУЧЕНИЕ ЕГО ТЕРМИЧЕСКИХ И БИОЛОГИЧЕСКИХ СВОЙСТВ

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Синтезирован комплекс (КВТ) 1-винил-1,2,4-триазола (ВТ) с $HAuCl_4$, определены его физико-химические характеристики. Показано, что образование комплекса происходит через триазольный атом азота N4. При помощи результатов термогравиметрического и элементного анализов установлено, что независимо от мольного соотношения исходных компонентов (ВТ: $HAuCl_4$ – 1:1, 1:2, 2:1) образуется комплекс состава 1:1. Исследовано действие соединений ВТ, $HAuCl_4$ и КВТ на постганглионарные симпатические нервные волокна и адренорецепторы. Установлено, что испытуемые соединения обладают слабым симпатолитическим и адреномиметическим действием.

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ՀԱՅԱՍՏԱՆԻ ՀԱՆՐԱՊԵՏՈՒԹՅԱՆ ԳԻՏՈՒԹՅՈՒՆՆԵՐԻ
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НАЦИОНАЛЬНАЯ АКАДЕМИЯ НАУК РЕСПУБЛИКИ АРМЕНИЯ
NATIONAL ACADEMY OF SCIENCES OF THE REPUBLIC OF ARMENIA

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SYNTHESIS AND SOME PROPERTIES OF 3-ETHYL-2-THIOXO-2,3-DIHYDRO-1H-SPIRO[BENZO[h]QUINAZOLINE-5,1'-CYCLOHEPTANE]-4(6H)-ONE

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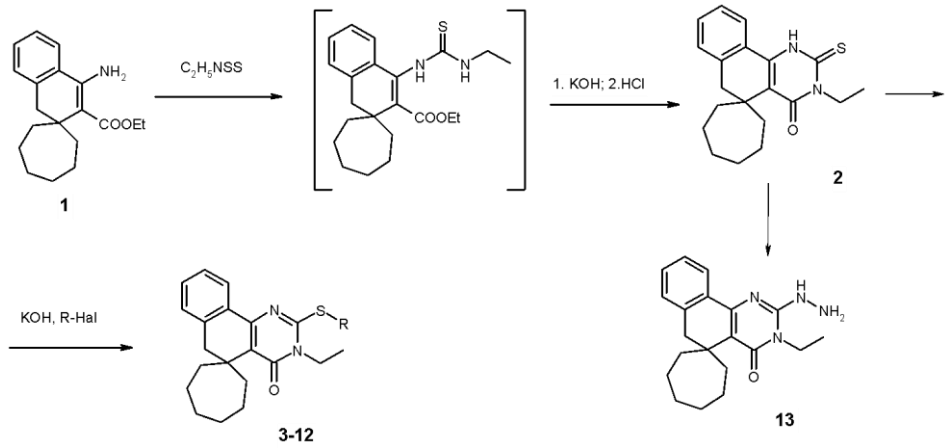
Based on 4'-amino-1'H-spiro[cycloheptane-1,2'-naphthalene]-3'-carboxylate, a synthesis method was developed for 3-ethyl-2-thioxo-2,3-dihydro-1H-spiro[benzo[h]quinazoline-5,1'-cycloheptane]-4(6H)-one, which was converted into 2-sulfanyl-substituted 3-ethyl-3H-spiro[benzo[h]quinazoline-5,1'-cycloheptane]-4(6H)-ones and 3-ethyl-2-hydrazinyl-3H-spiro[benzo[h]quinazoline-5,1'-cycloheptane]-4(6H)-one. By transformations of the latter, 3-ethyl-2-[2-(propan-2-ylidene)hydrazinyl]-3H-spiro[benzo[h]quinazoline-5,1'-cycloheptane]-4(6H)-one, N'-(3-ethyl-4-oxo-4,6-dihydro-3H-spiro[benzo[h]quinazoline-5,1'-cycloheptane]-2-yl) benzohydrazide, N-[2-(3-ethyl-4-oxo-4,6-dihydro-3H-spiro[benzo[h]quinazoline-5,1'-cycloheptane]-2-yl]hydrazinecarbonothioyl)benzamide, 3-ethyl-3H-spiro[benzo[h]quinazoline-5,1'-cycloheptane]-4(6H)-one, 4-ethyl-4H-spiro[benzo[h][1,2,4]triazolo[4,3-a]quinazoline-6,1'-cycloheptane]-5(7H)-one, 4-ethyl-1-mercapto-4H-spiro[benzo[h]-[1,2,4]triazolo[4,3-a]quinazoline-6,1'-cycloheptane]-5(7H)-one and 1-sulfanylsubstituted 4-ethyl-4H-spiro-[benzo[h][1,2,4]triazolo[4,3-a]quinazoline-6,1'-cycloheptane]-5(7H)-ones were synthesized.

References 17.

The work carried out during the recent years in the field of benzo[h]quinazoline series shows that the compounds of this heterocyclic series have valuable biological properties [1-13], which indicates the topicality of such studies. Benzo[h]quinazolines spiro-condensed in the fifth position with a cycloheptane cycle are still poorly studied and there are only a few reports available in the literature [14–17]. This report presents data on the synthesis of derivatives of 3-ethyl-spiro[benzo[h]quinazoline-5,1'-cycloheptane].

By reacting the ethyl 4'-amino-1'H-spiro[cycloheptane-1,2'-naphthalene]-3'-carboxylate (aminoester) (**1**) [17] with ethylisothiocyanate corresponding thioureido derivative was obtained, which, without isolation from the reaction medium, was subjected to cyclization, leading to the synthesis of ethyl 3-ethyl-

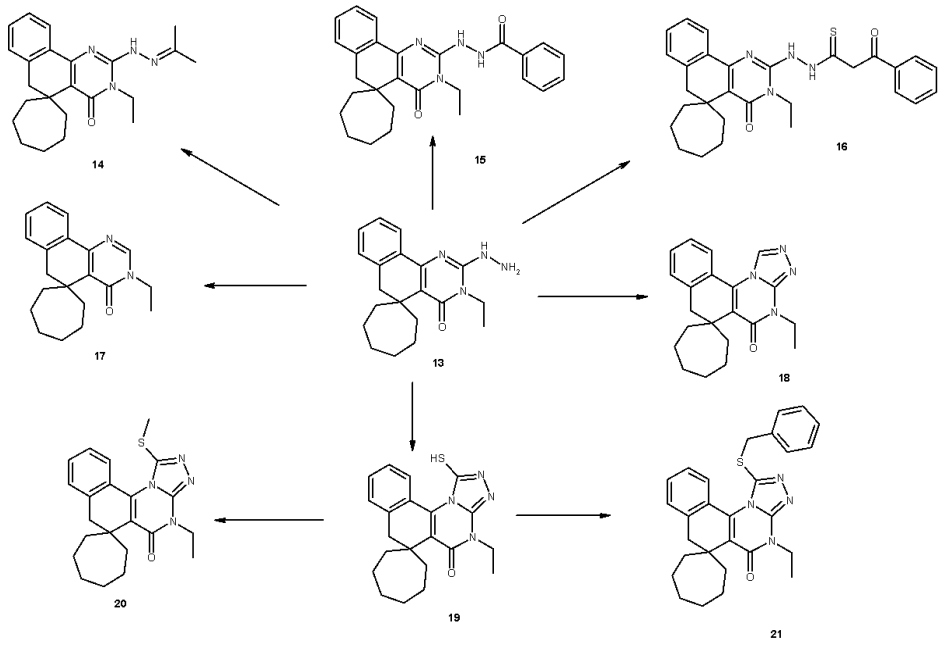
2-thioxo-2,3-dihydro-1H-spiro[benzo[h]quinazoline-5,1'-cycloheptane]-4(6H)-one (**2**). The latter in the presence of potassium hydroxide was reacted with halides of various structures, as a result of which 2-sulfanyl-substituted 3-ethyl-3H-spiro[benzo[h]quinazoline-5,1'-cycloheptane]-4(6H)-ones (**3-12**) were obtained. By condensation of 2-thioxobenzo[h]quinazoline **2** with hydrazine hydrate, 3-ethyl-2-hydrazinyl-3H-spiro[benzo[h]quinazoline-5,1'-cycloheptane]-4(6H)-one (**13**) was synthesized according to the Scheme:



R=CH_3 (**3**), C_2H_5 (**4**), C_3H_7 (**5**), i-C_3H_7 (**6**), $CH_2CH{=}CH_2$ (**7**), C_4H_9 (**8**), CH_2COOEt (**9**), $CH_2C_6H_5$ (**10**), 4-$ClC_6H_4CH_2$(**11**), 4-$CH_3C_6H_4CH_2$(**12**)

Some transformations of 3-ethyl-2-hydrazinyl-3H-spiro[benzo[h]quinazoline-5,1'-cycloheptane]-4(6H)-one (**13**) have been studied, in particular, its interaction with acetone, benzoyl chloride and benzoylisothiocyanate, resulting in 3-ethyl-2-[2-(propan-2-ylidene)hydrazinyl]-3H-spiro[benzo[h]-quinazoline-5,1'-cycloheptane]-4(6H)-one (14), N'-(3-ethyl-4-oxo-4,6-dihydro-3H-spiro [benzo[h]-quinazoline-5,1'-cycloheptane]-2-yl)benzohydrazide (**15**) and N-[2-(3-ethyl-4-oxo-4,6-dihydro-3H-spiro[benzo[h]quinazoline-5,1'-cycloheptane]-2-yl)hydrazinecarbonothioyl]benzamide (**16**) respecti-vely. It is shown that the specified hydrazinobenzo[h]quinazoline in the presence of a base undergoes dehydrazination to afford 3-ethyl-3H-spiro[benzo[h]quinazoline-5,1'-cycloheptane]-4(6H)-one (**17**).

By condensation of 2-hydrazinobenzo[h]quinazoline and ethyl ether of orthoformic acid and carbon disulfide, 4-ethyl-4H spiro[benzo[h][1,2,4] triazolo[4,3-a]quinazoline-6,1'-cycloheptane]-5(7H)-one (**18**) and 4-ethyl-1-mercapto-4H-spiro[benzo[h][1,2,4]triazolo[4,3-a]quinazoline-6,1'-cycloheptane]-5(7H)-one (**19**) were obtained respectively. The latter, in the presence of KOH, was put into interaction with methyl iodide and benzylchloride, which led to the production of the corresponding 1-sulfanylsubstituted 4-ethyl-4H-spiro[benzo[h][1,2,4]triazolo[4,3-a]quinazoline-6,1'-cycloheptane]-5(7H)-ones (**20, 21**) according to the Scheme:



Experimental part

The IR spectra were recorded on a Thermo "Nicolet Nexus FTIR" spectrometer from samples dispersed in mineral oil. The ^{1}H and ^{13}C NMR spectra were recorded on a Varian "Mercury-300VX" instrument from solutions in DMSO-d_6-CCl_4 (1:3); the chemical shifts were measured relative to tetramethylsilane or hexamethyldisiloxane as internal standard. Silufol plates were used for analytical TLC; spots were visualized by treatment with iodine vapor.

3-Ethyl-2-thioxo-2,3-dihydro-1H-spiro[benzo[h]quinazoline-5,1'-cycloheptane]-4(6H)-one (2). The reaction mixture of 29.9 *g* (0.1 *mol*) of ethyl 4'-amino-1'H-spiro[cycloheptane-1,2'-naphthalene]-3'-carboxylate (**1**), 8.7 *g* (0.1 *mol*) of ethyl isothiocyanate and 15 *ml* of ethanol was refluxed for 20 *hrs*, then a solution of 11.2 *g* (0.2 *mol*) of KOH in 70 *ml* of H_2O was added and the mixture was boiled for additional 3 *hrs*. After cooling, the mixture was acidified with a solution of 10% hydrochloric acid. The precipitated crystals were filtered, washed with water, and recrystallized from ethanol. Yield 22.7 *g* (67%) of **2,** mp 212-213°C, R_f 0.78 (ethyl acetate-heptane, 1:1). IR spectrum, ν, cm^{-1}: 1616 (C=C arom); 1676 (C=O); 3221 (NH). ^{1}H NMR spectrum (300 MHz, DMSO-d_6-CCl_4 1/3), δ, ppm: 1.26-1.36 (m, 2H, CH_2 cycloheptane), 1.29 (t, 3H, J=7.0, N-CH_2-$\underline{CH_3}$), 1.43-1.70 (m, 6H, 3×CH_2 cycloheptane), 1.71-1.85 (m, 2H, CH_2 cycloheptane), 2.17-2.28 (m, 2H, CH_2 cycloheptane), 2.85 (s, 2H, C6H_2), 4.42 (q, 2H, J=7.0, N-$\underline{CH_2}$-CH_3), 7.18-7.39 (m, 3H, 3×CH Ar),7.88-7.93 (m, 1H, CH Ar), 11.94 (s, 1H, NH). ^{13}C NMR spectrum (75 MHz, DMSO-d_6-CCl_4 1/3), δ, ppm: 11.41 (N-CH_2-$\underline{CH_3}$), 23.86 (2×CH_2 cycloheptane), 29.50 (2×CH_2

cycloheptane), 35.33 (2×CH_2 cycloheptane), 39.28 (C*5*), 40.28 (N-$\underline{CH_2}$-CH_3), 40.89 (C*6*H_2), 119.51 (C*4*$_a$), 124.58 (CH Ar), 125.35 (C Ar), 126.03 (CH Ar), 127.59 (CH Ar), 130.36 (CH Ar), 136.44 (C Ar), 142.38 (C*10*$_b$), 158.70 (C*4*), 174.88 (C*2*). Found, %: C 70.38; H 7.25; N 8.08; S 9.54. $C_{20}H_{24}N_2OS$. Calculated, %: C 70.55; H 7.10; N 8.23; S 9.42.

2-Alkylthio-ethyl-3H-spiro[benzo[h]quinazoline-5,1'-cycloheptane]-4(6H)-ones (3-12) (General method). A mixture of 1.7 *g* (5 *mmol*) of **3**, 0.4 *g* (7 *mmol*) of KOH and 30 *ml* of absolute ethanol was placed into a round-bottom flask and boiled for 30 *min*. Then 7 *mmol* of halogenide was added and boiling continued for 12 *hrs*. The reaction mixture was cooled and 20 *ml* of water was added. The precipitate was filtered off and recrystallized from ethanol.

3-Ethyl-2-(methylthio)-3H-spiro[benzo[h]quinazoline-5,1'-cycloheptane]-4(6H)-one (**3**). Yield 1.7 *g* (96%) of **3,** mp 163-164°C, R_f 0.76 (ethyl acetate-benzene, 1:10). IR spectrum, ν, cm^{-1}: 1600 (C=C arom); 1644 (C=O).^{1}H NMR spectrum (300 MHz, DMSO-d_6-CCl_4 1/3), δ, ppm: 1.33-1.43 (m, 2H, CH_2 cycloheptane), 1.34 (t, 3H, J=7.0, N-CH_2-$\underline{CH_3}$), 1.46-1.70 (m, 6H, 3×CH_2 cycloheptane), 1.72-1.86 (m, 2H, CH_2 cycloheptane), 2.24-2.35 (m, 2H, CH_2 cycloheptane), 2.68 (s, 3H, S-CH_3), 2.87 (s, 2H, C*6*H_2), 4.04 (q, 2H, J=7.0, N-$\underline{CH_2}$-CH_3), 7.11-7.17 (m, 1H, CH Ar), 7.20-7.32 (m, 2H, 2×CH Ar), 8.00-8.06 (m, 1H, CH Ar). ^{13}C NMR spectrum (75 MHz, DMSO-d_6-CCl_4 1/3), δ, ppm: 12.41 (N-CH_2-$\underline{CH_3}$), 14.09 (S-CH_3), 23.87 (2×CH_2 cycloheptane), 29.63 (2×CH_2 cycloheptane), 35.67 (2×CH_2 cycloheptane), 38.88 (N-$\underline{CH_2}$-CH_3), 39.57 (C*5*), 40.10 (C*6*H_2), 122.89 (C*4*$_a$), 124.63 (CH Ar), 125.86 (CH Ar), 127.15 (CH Ar), 129.41 (CH Ar), 132.06 (C Ar), 136.23 (C Ar), 150.56 (C*10*$_b$), 157.82 (C*2*), 159.76 (C*4*). Found, %: C 70.98; H 7.25; N 7.78; S 9.21. $C_{21}H_{26}N_2OS$. Calculated, %: C 71.15; H 7.39; N 7.90; S 9.04.

3-Ethyl-2-(ethylthio)-3H-spiro[benzo[h]quinazoline-5,1'-cycloheptane]-4(6H)-one (**4**). Yield 1.7 *g* (92%) of **4,** mp 130-131°C, R_f 0.73 (ethyl acetate-benzene, 1:10). IR spectrum, ν, cm^{-1}: 1605 (C=C arom); 1652 (C=O); 1742 (C=O). ^{1}H NMR spectrum (300 MHz, DMSO-d_6-CCl_4 1/3), δ, ppm: 1.32-1.43 (m, 2H, CH_2 cycloheptane), 1.33 (t, 3H, J=7.0, N-CH_2-$\underline{CH_3}$), 1.45-1.70 (m, 6H, 3×CH_2 cycloheptane), 1.49 (t, 3H, J=7.3, S-CH_2-$\underline{CH_3}$), 1.72-1.86 (m, 2H, CH_2 cycloheptane), 2.24-2.35 (m, 2H, CH_2 cycloheptane), 2.87 (s, 2H, C*6*H_2), 3.30 (q, 2H, J=7.3, S-$\underline{CH_2}$-CH_3), 4.03 (q, 2H, J=7.0, N-$\underline{CH_2}$-CH_3), 7.12-7.17 (m, 1H, CH Ar), 7.20-7.32 (m, 2H, 2×CH Ar), 7.95-8.00 (m, 1H, CH Ar). ^{13}C NMR spectrum (75 MHz, DMSO-d_6-CCl_4 1/3), δ, ppm: 12.41 (N-CH_2-$\underline{CH_3}$), 13.75 (S-CH_2-$\underline{CH_3}$), 23.88 (2×CH_2 cycloheptane), 25.52 (S-$\underline{CH_2}$-CH_3), 29.64 (2×CH_2 cycloheptane), 35.69 (2×CH_2 cycloheptane), 38.82 (N-$\underline{CH_2}$-CH_3), 39.59 (C*5*), 40.14 (C*6*H_2), 122.95 (C*4*$_a$), 124.45 (CH Ar), 125.90 (CH Ar), 127.18 (CH Ar), 129.30 (CH Ar), 132.10 (C Ar), 136.27 (C Ar), 150.61(C*10*$_b$), 157.39 (C*2*), 159.82 (C*4*). Found, %: C 71.62; H 7.78; N 7.52; S 8.84. $C_{22}H_{28}N_2OS$. Calculated, %: C 71.70; H 7.66; N 7.60; S 8.70.

3-Ethyl-2-(propylthio)-3H-spiro[benzo[h]quinazoline-5,1'-cycloheptane]-4(6H)-one (**5**). Yield 1.24 *g* (65%) of **5,** mp 70-72°C, R_f 0.67 (ethyl acetate-benzene, 1:10). IR spectrum, ν, cm^{-1}: 1600 (C=C arom); 1663 (C=O). ^{1}H NMR spectrum (300 MHz, DMSO-d_6-CCl_4 1/3), δ, ppm: 1.11 (t, 3H, J=7.3, S-CH_2-CH_2-$\underline{CH_3}$), 1.32-1.43 (m, 2H, CH_2 cycloheptane), 1.33 (t, 3H, J=7.0, N-CH_2-$\underline{CH_3}$), 1.46-1.70 (m, 6H, 3×CH_2 cycloheptane), 1.71-1.93 (m, 4H, CH_2 cycloheptane, S-CH_2-$\underline{CH_2}$-CH_3), 2.23-2.35 (m, 2H, CH_2 cycloheptane), 2.87 (s, 2H, C*6*H_2), 3.27 (t, 2H, J=7.1, S-$\underline{CH_2}$-CH_2-CH_3), 4.04 (q, 2H, J=7.0, N-$\underline{CH_2}$-CH_3), 7.11-7.17 (m, 1H, CH Ar), 7.20-7.32 (m, 2H, 2×CH Ar), 7.94-7.99 (m, 1H, CH Ar). ^{13}C NMR spectrum (75 MHz, DMSO-d_6-CCl_4 1/3), δ, ppm: 12.43 (N-CH_2-$\underline{CH_3}$), 12.97 (S-CH_2-CH_2-$\underline{CH_3}$), 21.74 (S-CH_2-$\underline{CH_2}$-CH_3), 23.87 (2×CH_2 cycloheptane), 29.63 (2×CH_2 cycloheptane), 33.02 (S-$\underline{CH_2}$-CH_2-CH_3), 35.67 (2×CH_2 cycloheptane), 38.84 (N-$\underline{CH_2}$-CH_3), 39.58 (C*5*), 40.13 (C*6*H_2), 122.91 (C4_a), 124.39 (CH Ar), 125.90 (CH Ar), 127.21 (CH Ar), 129.30 (CH Ar), 132.08 (C Ar), 136.27 (C Ar), 150.57 (C10_b), 157.49 (C*2*), 159.84 (C*4*). Found, %: C 72.36; H 7.75; N 7.18; S 8.54. $C_{23}H_{30}N_2OS$. Calculated, %: C 72.21; H 7.90; N 7.32; S 8.38.

3-Ethyl-2-(isopropylthio)-3H-spiro[benzo[h]quinazoline-5,1'-cycloheptane]-4(6H)-one (**6**). Yield 1.19 *g* (62%) of **6,** mp 108-110°C, R_f 0.75 (ethyl acetate-benzene, 1:10). IR spectrum, ν, cm^{-1}: 1603 (C=C arom); 1659 (C=O). ^{1}H NMR spectrum (300 MHz, DMSO-d_6-CCl_4 1/3), δ, ppm: 1.32 (t, 3H, J=7.0, N-CH_2-$\underline{CH_3}$), 1.33-1.43 (m, 2H, CH_2 cycloheptane), 1.47-1.69 (m, 6H, 3×CH_2 cycloheptane), 1.52 (d, 6H, J=6.8, S-CH-($\underline{CH_3}$)$_2$), 1.71-1.86 (m, 2H, CH_2 cycloheptane), 2.23-2.35 (m, 2H, CH_2 cycloheptane), 2.88 (s, 2H, C*6*H_2), 4.00 (q, 2H, J=7.0, N-$\underline{CH_2}$-CH_3), 4.13 (sp, 1H, J=6.8, S-$\underline{CH}$-(CH_3)$_2$), 7.12-7.17 (m, 1H, CH Ar), 7.20-7.32 (m, 2H, 2×CH Ar), 7.92-7.98 (m, 1H, CH Ar). ^{13}C NMR spectrum (75 MHz, DMSO-d_6-CCl_4 1/3), δ, ppm: 12.41 (N-CH_2-$\underline{CH_3}$), 22.27 (S-CH-($\underline{CH_3}$)$_2$), 23.88 (2×CH_2 cycloheptane), 29.65 (2×CH_2 cycloheptane), 35.70 (2×CH_2 cycloheptane), 36.83 (S-$\underline{CH}$-(CH_3)$_2$), 38.80 (N-$\underline{CH_2}$-CH_3), 39.59 (C*5*), 40.16 (C*6*H_2), 122.93 (C4_a), 124.40 (CH Ar), 125.94 (CH Ar), 127.22 (CH Ar), 129.40 (CH Ar), 132.12 (C Ar), 136.29 (C Ar), 150.69 (C10_b), 157.49 (C*2*), 159.80 (C*4*). Found, %: C 72.40; H 7.84; N 7.20; S 8.48. $C_{23}H_{30}N_2OS$. Calculated, %: C 72.21; H 7.90; N 7.32; S 8.38.

2-(Allylthio)-3-ethyl-3H-spiro[benzo[h]quinazoline-5,1'-cycloheptane]-4(6H)-one (**7**). Yield 1.8 *g* (94%) of **7,** mp 104-106°C, R_f 0.74 (ethyl acetate-benzene, 1:10). IR spectrum, ν, cm^{-1}: 1615 (C=C arom); 1661 (C=O). ^{1}H NMR spectrum (300 MHz, DMSO-d_6-CCl_4 1/3), δ, ppm: 1.32-1.43 (m, 2H, CH_2 cycloheptane), 1.34 (t, 3H, J=7.0, N-CH_2-$\underline{CH_3}$), 1.46-1.70 (m, 6H, 3×CH_2 cycloheptane), 1.72-1.86 (m, 2H, CH_2 cycloheptane), 2.24-2.35 (m, 2H, CH_2 cycloheptane), 2.87 (s, 2H, C*6*H_2), 3.97 (dt, 2H, J=6.9, 1.2, S-$\underline{CH_2}$-CH=CH_2), 4.04 (q, 2H, J=7.0, N-$\underline{CH_2}$-CH_3), 5.18 (dq, 1H, J=10.1, 1.2, S-CH_2-CH=$\underline{CH_2}$), 5.37 (dq, 1H, J=17.0, 1.2, S-CH_2-CH=$\underline{CH_2}$), 6.02 (ddt, 1H, J=17.0, 10.1, 6.9, S-CH_2-$\underline{CH}$=CH_2), 7.12-7.17 (m, 1H, CH Ar), 7.21-7.32 (m, 2H, 2×CH Ar), 7.96-

8.01 (m, 1H, CH Ar). ^{13}C NMR spectrum (75 MHz, DMSO-d_6-CCl_4 1/3), δ, ppm: 12.45 (N-CH_2-$\underline{CH_3}$), 23.87 (2×CH_2 cycloheptane), 29.63 (2×CH_2 cycloheptane), 33.82 (S-$\underline{CH_2}$-CH_2-CH_3), 35.65 (2×CH_2 cycloheptane), 38.93 (N-$\underline{CH_2}$-CH_3), 39.60 (C*5*), 40.09 (C*6*H_2), 118.11 (CH_2-CH=$\underline{CH_2}$), 123.08 (C4_a), 124.50 (CH Ar), 125.93 (CH Ar), 127.20 (CH Ar), 129.45 (CH Ar), 131.98 (C Ar), 132.26 (S-CH_2-$\underline{CH}$=CH_2), 136.26 (C Ar), 150.59 (C10_b), 156.88 (C*2*), 159.76 (C*4*). Found, %: C 72.66; H 7.55; N 7.48; S 8.24. $C_{23}H_{28}N_2OS$. Calculated, %: C 72.59; H 7.42; N 7.36; S 8.43.

2-(Butylthio)-3-ethyl-3H-spiro[benzo[h]quinazoline-5,1'-cycloheptane]-4(6H)-one (**8**). Yield 1.45 *g* (73%) of **8,** mp 83-85°C, R_f 0.75 (ethyl acetate-benzene, 1:10). IR spectrum, ν, cm^{-1}: 1604 (C=C arom); 1661 (C=O). ^{1}H NMR spectrum (300 MHz, DMSO-d_6-CCl_4 1/3), δ, ppm: 1.00 (t, 3H, J=7.3, S-CH_2-CH_2-CH_2-$\underline{CH_3}$), 1.32-1.43 (m, 2H, CH_2 cycloheptane), 1.33 (t, 3H, J=7.0, N-CH_2-$\underline{CH_3}$), 1.45-1.69 (m, 8H, 3×CH_2 cycloheptane, S-CH_2-CH_2-$\underline{CH_2}$-CH_3), 1.72-1.86 (m, 4H, CH_2 cycloheptane, S-CH_2-$\underline{CH_2}$-CH_2-CH_3), 2.23-2.35 (m, 2H, CH_2 cycloheptane), 2.87 (s, 2H, C*6*H_2), 3.29 (t, 2H, J=7.1, S-$\underline{CH_2}$-CH_2-CH_2-CH_3), 4.03 (q, 2H, J=7.0, N-$\underline{CH_2}$-CH_3), 7.11-7.17 (m, 1H, CH Ar), 7.20-7.32 (m, 2H, 2×CH Ar), 7.94-7.99 (m, 1H, CH Ar). ^{13}C NMR spectrum (75 MHz, DMSO-d_6-CCl_4 1/3), δ, ppm: 12.43 (N-CH_2-$\underline{CH_3}$), 13.15 (S-CH_2-CH_2-CH_2-$\underline{CH_3}$), 21.41 (S-CH_2-CH_2-$\underline{CH_2}$-CH_3), 23.87 (2×CH_2 cycloheptane), 29.63 (2×CH_2 cycloheptane), 30.38 (S-CH_2-$\underline{CH_2}$-CH_2-CH_3), 30.81 (S-$\underline{CH_2}$-CH_2-CH_2-CH_3), 35.67 (2×CH_2 cycloheptane), 38.82 (N-$\underline{CH_2}$-CH_3), 39.60 (C*5*), 40.12 (C*6*H_2), 122.90 (C4_a), 124.40 (CH Ar), 125.86 (CH Ar), 127.21 (CH Ar), 129.39 (CH Ar), 132.09 (C Ar), 136.28 (C Ar), 150.58 (C10_b), 157.50 (C*2*), 159.84 (C*4*). Found, %: C 72.54; H 8.32; N 7.16; S 7.94. $C_{24}H_{32}N_2OS$. Calculated, %: C 72.68; H 8.13; N 7.06; S 8.09.

Ethyl 2-((3-ethyl-4-oxo-4,6-dihydro-3H-spiro[benzo[h]quinazoline-5,1'-cycloheptane]-2-yl)thio)acetate (**9**). Yield 1.4 *g* (66%) of **9,** mp 104-105°C, R_f 0.75 (ethyl acetate-benzene, 1:10). IR spectrum, ν, cm^{-1}: 1604 (C=C arom); 1657 (C=O): 1747 (C=O ester). ^{1}H NMR spectrum (300 MHz, DMSO-d_6-CCl_4 1/3), δ, ppm: 1.26 (t, 3H, J=7.1, O-CH_2-$\underline{CH_3}$), 1.32-1.43 (m, 2H, CH_2 cycloheptane), 1.38 (t, 3H, J=7.0, N-CH_2-$\underline{CH_3}$), 1.45-1.69 (m, 6H, 3×CH_2 cycloheptane), 1.71-1.85 (m, 2H, CH_2 cycloheptane), 2.23-2.34 (m, 2H, CH_2 cycloheptane), 2.87 (s, 2H, C*6*H_2), 4.03 (s, 2H, S-CH_2), 4.07 (q, 2H, J=7.0, N-$\underline{CH_2}$-CH_3), 4.14 (q, 2H, J=7.1, O-$\underline{CH_2}$-CH_3), 7.11-7.16 (m, 1H, CH Ar), 7.20-7.32 (m, 2H, 2×CH Ar), 7.94-7.99 (m, 1H, CH Ar). ^{13}C NMR spectrum (75 MHz, DMSO-d_6-CCl_4 1/3), δ, ppm, 12.46 (N-CH_2-$\underline{CH_3}$), 13.64 (O-CH_2-$\underline{CH_3}$), 23.88 (2×CH_2 cycloheptane), 29.64 (2×CH_2 cycloheptane), 33.38 (S-CH_2), 35.64 (2×CH_2 cycloheptane), 39.22 (N-$\underline{CH_2}$-CH_3), 39.61 (C*5*), 40.05 (C*6*H_2), 60.68 (O-$\underline{CH_2}$-CH_3), 123.27 (C4_a), 124.76 (CH Ar), 125.82 (CH Ar), 127.15 (CH Ar), 129.51 (CH Ar), 131.78 (C Ar), 36.25 (C Ar), 150.67(C10_b), 156.50 (C*2*), 159.63 (C*4*), 167.08 ($\underline{C(O)}$-O-CH_2-CH_3). Found, %: C 67.69; H 6.95; N 6.48; S 7.67. $C_{24}H_{30}N_2O_3S$. Calculated, %: C 67.58; H 7.09; N 6.57; S 7.52.

2-(Benzylthio)-3-ethyl-3H-spiro[benzo[h]quinazoline-5,1'-cycloheptane]-4(6H)-one (**10**). Yield 1.9 *g* (90%) of **10,** mp 123-125°C, R_f 0.76 (ethyl acetate-benzene, 1:10). IR spectrum, ν, cm^{-1}: 1604 (C=C arom); 1648 (C=O). ^{1}H NMR spectrum (300 MHz, DMSO-d_6-CCl_4 1/3), δ, ppm: 1.33 (t, 3H, J=7.0, N-CH_2-$\underline{CH_3}$), 1.35-1.44 (m, 2H, CH_2 cycloheptane), 1.46-1.70 (m, 6H, 3×CH_2 cyclo-heptane), 1.72-1.87 (m, 2H, CH_2 cycloheptane), 2.24-2.36 (m, 2H, CH_2 cycloheptane), 2.88 (s, 2H, C_6H_2), 4.03 (q, 2H, J=7.0, N-$\underline{CH_2}$-CH_3), 4.57 (s, 2H, S-$\underline{CH_2}$-Ph), 7.13-7.18 (m, 1H, CH Ar), 7.20-7.34 (m, 5H, 5×CH Ar), 7.39-7.45 (m, 2H, 2×CH Ar), 8.00-8.05 (m, 1H, CH Ar). ^{13}C NMR spectrum (75 MHz, DMSO-d_6-CCl_4 1/3), δ, ppm: 12.48 (N-CH_2-$\underline{CH_3}$), 23.88 (2×CH_2 cycloheptane), 29.63 (2×CH_2 cycloheptane), 35.58 (S-$\underline{CH_2}$-Ph), 35.65 (2×CH_2 cycloheptane), 38.94 (N-$\underline{CH_2}$-CH_3), 39.64 (C*5*), 40.10 (C*6*H_2), 123.20 (C4_a), 124.64 (CH Ar), 125.94 (CH Ar), 126.94 (CH Ar), 127.22 (CH Ar), 128.00 (2×CH Ar), 128.56 (2×CH Ar), 129.47 (CH Ar), 131.98 (C Ar), 135.58 (C Ar), 136.27 (C Ar), 150.62 (C10_b), 157.25 (C*2*), 159.74 (C*4*). Found, %: C 75.48; H 7.15; N 6.68; S 7.64. $C_{27}H_{30}N_2OS$. Calculated, %: C 75.31; H 7.02; N 6.51; S 7.45.

2-(4-Chlorobenzylthio)-3-ethyl-3H-spiro[benzo[h]quinazoline-5,1'-cycloheptane]-4(6H)-one (**11**). Yield 1.93 *g* (83%) of **11,** mp 148-149°C, R_f 0.75 (ethyl acetate-benzene, 1:10). IR spectrum, ν, cm^{-1}: 1600 (C=C arom); 1673 (C=O). ^{1}H NMR spectrum (300 MHz, DMSO-d_6-CCl_4 1/3), δ, ppm: 1.32 (t, 3H, J=7.0, N-CH_2-$\underline{CH_3}$), 1.34-1.43 (m, 2H, CH_2 cycloheptane), 1.46-1.70 (m, 6H, 3×CH_2 cycloheptane), 1.71-1.87 (m, 2H, CH_2 cycloheptane), 2.23-2.35 (m, 2H, CH_2 cycloheptane), 2.89 (s, 2H, C*6*H_2), 4.02 (q, 2H, J=7.0, N-$\underline{CH_2}$-CH_3), 4.56 (s, 2H, S-$\underline{CH_2}$-Ph), 7.13-7.19 (m, 1H, CH Ar), 7.21-7.33 (m, 4H, 4×CH Ar), 7.39-7.5 (m, 2H, 2×CH Ar), 7.97-8.02 (m, 1H, CH Ar). ^{13}C NMR spectrum (75 MHz, DMSO-d_6-CCl_4 1/3), δ, ppm: 12.48 (N-CH_2-$\underline{CH_3}$), 23.87 (2×CH_2 cycloheptane), 29.62 (2×CH_2 cycloheptane), 34.57 (S-$\underline{CH_2}$-Ph), 35.62 (2×CH_2 cycloheptane), 39.00 (N-$\underline{CH_2}$-CH_3), 39.65 (C*5*), 40.07 (C*6*H_2), 123.30 (C4_a), 124.56 (CH Ar), 125.98 (CH Ar), 127.29 (CH Ar), 128.07 (2×CH Ar), 129.54 (CH Ar), 130.09 (2×CH Ar), 131.9 (C Ar), 132.43 (C Ar), 134.83 (C Ar), 136.30 (C Ar), 150.60 (C10_b), 156.92 (C*2*), 159.71 (C*4*). Found, %: C 73.88; H 6.16; N 6.17; S 6.65. $C_{27}H_{29}ClN_2OS$. Calculated, %: C 69.73; H 6.29; N 6.02; S 6.89.

3-Ethyl-2-((4-methylbenzyl)thio)-3H-spiro[benzo[h]quinazoline-5,1'-cycloheptane]-4(6H)-one (**12**). Yield 1.90 *g* (85%) of **12,** mp 172-174°C, R_f 0.74 (ethyl acetate-benzene, 1:10). IR spectrum, ν, cm^{-1}: 1603 (C=C arom); 1659 (C=O). ^{1}H NMR spectrum (300 MHz, DMSO-d_6-CCl_4 1/3), δ, ppm: 1.32 (t, 3H, J=7.0, N-CH_2-$\underline{CH_3}$), 1.34-1.43 (m, 2H, CH_2 cycloheptane), 1.46-1.70 (m, 6H, 3×CH_2 cycloheptane), 1.71-1.87 (m, 2H, CH_2 cycloheptane), 2.23-2.35 (m, 2H, CH_2 cycloheptane), 2.33 (s, 3H, $\underline{CH_3}$-Ph), 2.89 (s, 2H, C_6H_2), 4.02 (q, 2H, J=7.0, N-$\underline{CH_2}$-CH_3), 4.52 (s, 2H, S-$\underline{CH_2}$-Ph), 7.05-7.33 (m, 7H, 7×CH Ar), 8.01-8.06 (m, 1H, CH Ar). ^{13}C NMR spectrum (75 MHz, DMSO-d_6-CCl_4 1/3), δ, ppm: 12.48 (N-CH_2-$\underline{CH_3}$), 20.55 ($\underline{CH_3}$-Ph), 23.90 (2×CH_2 cycloheptane), 29.65

(2×CH_2 cycloheptane), 35.43 (S-$\underline{CH_2}$-Ph), 35.67 (2×CH_2 cycloheptane), 38.95 (N-$\underline{CH_2}$-CH_3), 39.65 (C*5*), 40.12 (C*6*H_2), 123.16 (C4_a), 124.67 (CH Ar), 125.94 (CH Ar), 127.23 (CH Ar), 128.51 (2×CH Ar), 128.67 (2×CH Ar), 129.48 (CH Ar), 132.01 (C Ar), 132.39 (C Ar), 136.24 (C Ar), 136.28 (C Ar), 50.63 (C10_b), 157.38 (C*2*), 159.76 (C*4*). Found, %: C 75.49; H 7.08; N 6.48; S 7.09. $C_{28}H_{32}N_2OS$. Calculated, %: C 75.64; H 7.25; N 6.30; S 7.21.

3-Ethyl-2-hydrazinyl-3H-spiro[benzo[h]quinazoline-5,1'-cycloheptane]-4(6H)-one (**13**). The mixture of 25.0 *g* (0.073 *mol)* of 2-thioxoquinazoline **2** and 125 *ml* of hydrazine hydrate was boiled for 3 *hrs* in a reaction flask with a backflow condenser. Then 120 *ml* of water was added, the precipitate was filtered, washed with water and recrystallized from butanol. Yield 15.8 *g* (64%) of **13,** mp 207-209°C, R_f 0.73 (methanol-benzene, 1:10). IR spectrum, ν, cm^{-1}: 1604 (C=C arom); 1656 (C=O); 3150-3290 ($NHNH_2$). ^{1}H NMR spectrum (300 MHz, DMSO-d_6-CCl_4 1/3), δ, ppm: 1.20 (t, 3H, J=7.0, N-CH_2-$\underline{CH_3}$), 1.28-1.39 (m, 2H, CH_2 cycloheptane), 1.43-1.69 (m, 6H, 3×CH_2 cycloheptane), 1.70-1.85 (m, 2H, CH_2 cycloheptane), 2.23-2.35 (m, 2H, CH_2 cycloheptane), 2.82 (s, 2H, C*6*H_2), 3.93 (q, 2H, J=7.0, N-$\underline{CH_2}$-CH_3), 4.17 (s, 2H, NH_2), 7.07-7.14 (m, 1H, CH Ar), 7.17-7.27 (m, 2H, 2×CH Ar), 8.05-8.12 (m, 1H, CH Ar), 8.16 (s, 1H, NH). ^{13}C NMR spectrum (75 MHz, DMSO-d_6-CCl_4 1/3), δ, ppm: 12.30 (N-CH_2-$\underline{CH_3}$), 24.00 (2×CH_2 cycloheptane), 29.73 (2×CH_2 cycloheptane), 34.39 (N-$\underline{CH_2}$-CH_3), 36.23 (2×CH_2 cycloheptane), 39.32 (C*5*), 40.67 (C*6*H_2), 117.32 (C4_a), 124.76 (CH Ar), 125.55 (CH Ar), 126.89 (CH Ar), 128.77 (CH Ar), 132.96 (C Ar), 136.45 (C Ar), 151.23 (C10_b), 153.47 (C*2*), 160.42 (C*4*). Found, %: C 73.17; H 8.18; N 14.66. $C_{23}H_{30}N_4O$. Calculated, %: C 72.98; H 7.99; N 14.80.

3-Ethyl-2-(2-(propan-2-ylidene)hydrazinyl)-3H-spiro[benzo[h]quinazoline-5,1'-cyclo-heptane]-4(6H)-one (**14**). The mixture of 2.0 *g* (0.006 *mol*) of 3-ethyl-2-hydrazinyl-3H-spiro-[benzo[h]quinazoline-5,1'-cycloheptane]-4(6H)-one (**13**), 3 *ml* of acetone and 25 *ml* of ethanol was boiled for 5 *hrs* in a reaction flask with a backflow condenser. After the solvent distillation, the precipitate was recrystallized from ethanol. Yield 1.3 *g* (57%) of **14,** mp 169-171 °C, R_f 0.78 (ethyl acetate-benzene, 1:1). IR spectrum, ν, cm^{-1}: 1604 (C=C arom); 1642 (C=N); 1663 (C=O); 3318 (NH). ^{1}H NMR spectrum (300 MHz, DMSO-d_6-CCl_4 1/3), δ, ppm: 1.23 (t, 3H, J=7.0, N-CH_2-$\underline{CH_3}$), 1.27-1.39 (m, 2H, CH_2 cycloheptane), 1.42-1.70 (m, 6H, 3×CH_2 cycloheptane), 1.71-1.85 (m, 2H, CH_2 cycloheptane), 2.05 (s, 6H, N=C($\underline{CH_3}$)$_2$), 2.21-2.33 (m, 2H, CH_2 cycloheptane), 2.85 (s, 2H, C*6*H_2), 4.00 (q, 2H, J=7.0, N-$\underline{CH_2}$-CH_3), 7.23-7.29 (m, 1H, CH Ar), 7.33-7.43 (m, 3H, 3×CH Ar), 9.37 (s, 1H, NH). ^{13}C NMR spectrum (75 MHz, DMSO-d_6-CCl_4 1/3), δ, ppm: 11.73 (N-CH_2-$\underline{CH_3}$), 17.38 (N=C($\underline{CH_3}$)$_2$), 23.93 (2×CH_2 cycloheptane), 24.72 (N=C($\underline{CH_3}$)$_2$), 29.60 (2×CH_2 cycloheptane), 34.53 (N-$\underline{CH_2}$-CH_3), 36.18 (2×CH_2 cycloheptane), 38.82 (C*5*), 40.61 (C*6*H_2), 113.41 (C4_a), 120.39 (CH Ar), 126.41 (C Ar), 126.46 (CH Ar), 128.23 (CH Ar), 130.13 (CH Ar), 136.80 (C Ar), 138.94 (C10_b), 147.60 (N=$\underline{C}$(CH_3)$_2$), 157.69 (C*2*),

160.04 (C*4*). Found, %: C 73.17; H 7.81; N 14.78. $C_{23}H_{30}N_4O$. Calculated, %: C 72.98; H 7.99; N 14.80.

N'-(3-ethyl-4-oxo-4,6-dihydro-3H-spiro[benzo[h]quinazoline-5,1'-cycloheptane]-2-yl)- benzohydrazide (**15**). The mixture of 2.0 *g* (0.006 *mol*) of 3-ethyl-2-hydrazinyl-3H-spiro-[benzo[h]quinazoline-5,1'-cycloheptane]-4(6H)-one (**13**), 1.4 *g* (0.01 *mol*) of benzoil chloride and 25 *ml* of benzene was boiled for 10 *hrs* in a reaction flask with a backflow condenser. After the solvent distillation, the precipitate was recrystallized from butanol. Yield 2.1 *g* (49%) of **15,** mp 190-191°C, R_f 0.55 (ethyl acetate-benzene, 1:1). IR spectrum, ν, cm^{-1}: 1600 (C=C arom); 1625 (C=N); 1640 (C=O); 16773 (C=Oamid); 3150-3250 (NH). ^{1}H NMR spectrum (300 MHz, DMSO-d_6-CCl_4 1/3), δ, ppm: 1.30-1.41 (m, 2H, CH_2 cycloheptane), 1.34 (t, 3H, J=7.0, N-CH_2-$\underline{CH_3}$), 1.44-1.70 (m, 6H, 3×CH_2 cycloheptane), 1.71-1.86 (m, 2H, CH_2 cycloheptane), 2.26-2.38 (m, 2H, CH_2 cycloheptane), 2.82 (s, 2H, C*6*H_2), 4.11 (q, 2H, J=7.0, N-$\underline{CH_2}$-CH_3), 7.02-7.11 (m, 2H, 2×CH Ar), 7.15-7.22 (m, 1H, CH Ar), 7.45-7.57 (m, 3H, 3×CH Ar), 7.78-7.83 (m, 1H, CH Ar), 7.97-8.03 (m, 2H, 2×CH Ar), 9.02 (s, 1H, NH), 10.25 (s, 1H, NH). ^{13}C NMR spectrum (75 MHz, DMSO-d_6-CCl_4 1/3), δ, ppm: 12.64 (N-CH_2-$\underline{CH_3}$), 24.04 (2×CH_2 cycloheptane), 29.78 (2×CH_2 cycloheptane), 35.16 (N-$\underline{CH_2}$-CH_3), 36.20 (2×CH_2 cycloheptane), 39.48 (C*5*), 40.63 (C*6*H_2), 118.58 (C4_a), 124.80 (CH Ar), 125.67 (CH Ar), 126.97 (CH Ar), 127.37 (2×CH Ar), 127.82 (2×CH Ar), 128.93 (CH Ar), 130.94 (CH Ar), 132.85 (C Ar), 133.05 (C Ar), 136.46 (C Ar), 151.58 (C10_b), 152.05 (C*2*), 160.42 (C*4*), 166.44 (C(O)-NH). Found, %: C 73.41; H 6.72; N 12.48. $C_{27}H_{30}N_4O_2$. Calculated, %: C 73.28; H 6.83; N 12.66.

N-(2-(3-ethyl-4-oxo-4,6-dihydro-3H-spiro[benzo[h]quinazoline-5,1'-cycloheptane]-2-yl)-hydrazinecarbonothioyl)benzamide (**16**). The mixture of 3.3 *g* (0.01 *mol)* of 3-ethyl-2-hydrazinyl-3H-spiro[benzo[h]quinazoline-5,1'-cycloheptane]-4(6H)-one (**13**), 1.63 *g* (0.01 *mol*) of benzoylisothiocyanate and 30 *ml* of ethanol was boiled for 10 *hrs* with a backflow condenser. Then it was cooled and 10 *ml* of water was added. The precipitate was filtered, washed with 70% ethanol. Yield 3.20 *g* (64%) of **16,** mp 215-217°C, R_f 0.45 (ethyl acetate-benzene, 1:1). IR spectrum, ν, cm^{-1}: 1603 (C=C arom); 1662 (C=O); 3214 (NH). ^{1}H NMR spectrum (300 MHz, DMSO-d_6-CCl_4 1/3), δ, ppm: 1.30-1.86 (m, 10H, 5×CH_2 cycloheptane), 1.42 (t, 3H, J=7.0, N-CH_2-$\underline{CH_3}$), 2.24-2.36 (m, 2H, CH_2 cycloheptane), 2.86 (s, 2H, C*6*H_2), 4.10 (q, 2H, J=7.0, N-$\underline{CH_2}$-CH_3), 7.08-7.14 (m, 1H, CH Ar), 7.21-7.28 (m, 2H, 2×CH Ar), 7.46-7.54 (m, 2H, 2×CH Ar), 7.57-7.64 (m, 1H, CH Ar), 8.09-8.15 (m, 2H, 2×CH Ar), 8.17-8.24 (m, 1H, CH Ar), 9.53 (s, 1H, NH), 11.56 (s, 1H, NH), 13.24 (br.s, 1H, NH). ^{13}C NMR spectrum (75 MHz, DMSO-d_6-CCl_4 1/3), δ, ppm: 12.33 (N-CH_2-$\underline{CH_3}$), 23.99 (2×CH_2 cycloheptane), 29.75 (2×CH_2 cycloheptane), 35.33 (N-$\underline{CH_2}$-CH_3), 36.09 (2×CH_2 cycloheptane), 39.48 (C*5*), 40.51 (C*6*H_2), 119.65 (C4_a), 125.28 (CH Ar), 126.01 (CH Ar), 126.86 (CH Ar), 127.72 (2×CH Ar), 128.53 (2×CH Ar), 129.19 (CH Ar), 131.65 (C Ar), 132.23 (CH Ar), 132.29 (C Ar), 136.30 (C Ar),

148.89 (C*10*$_b$), 151.20 (C*2*), 159.96 (C*4*), 167.45 (C(O)-NH), 175.60 (C=S). Found, %: C 66.88; H 6.40; N 14.12; S 6.58. $C_{28}H_{31}N_5O_2S$. Calculated, %: C 67.04; H 6.23; N 13.96; S 6.39.

3-Ethyl-3H-spiro[benzo[h]quinazoline-5,1'-cycloheptane]-4(6H)-one (**17**). The mixture of 2.0 *g* (0.006 *mol*) of 3-ethyl-2-hydrazinyl-3H-spiro[benzo[h]quinazoline-5,1'-cycloheptane]-4(6H)-one (**13**), 0.56 *g* (0.001 *mol*) of KOH and 25 *ml* of 90 % ethanol was boiled for 10 *hrs* in a reaction flask with a backflow condenser. After the solvent distillation, the precipitate was recrystallized from ethanol. Yield 1.2 *g* (65%) of **17,** mp 140-142 ^{o}C, R_f 0.63 (ethyl acetate-benzene, 1:1). IR spectrum, ν, cm^{-1}: 1599 (C=C arom); 1625 (C-N); 1668 (C=O). ^{1}H NMR spectrum (300 MHz, DMSO-d_6-CCl_4 1/3), δ, ppm: 1.33-1.44 (m, 2H, CH_2 cycloheptane), 1.37 (t, 3H, J=7.0, N-CH_2-$\underline{CH_3}$), 1.46-1.72 (m, 6H, 3×CH_2 cycloheptane), 1.73-1.88 (m, 2H, CH_2 cycloheptane), 2.26-2.38 (m, 2H, CH_2 cycloheptane), 2.88 (s, 2H, C*6*H_2), 3.95 (q, 2H, J=7.0, N-$\underline{CH_2}$-CH_3), 7.11-7.18 (m, 1H, CH Ar), 7.20-7.31 (m, 2H, 2×CH Ar), 7.98-8.04 (m, 1H, CH Ar), 8.16 (s, 1H, C*2*H).^{13}C NMR spectrum (75 MHz, DMSO-d_6-CCl_4 1/3), δ, ppm: 14.37 (N-CH_2-$\underline{CH_3}$), 23.90 (2×CH_2 cycloheptane), 29.63 (2×CH_2 cycloheptane), 35.47 (2×CH_2 cycloheptane), 39.91 (C*5*), 40.03 (N-$\underline{CH_2}$-CH_3), 41.13 (C*6*H_2), 124.91 (CH Ar), 125.90 (CH Ar), 127.04 (CH Ar), 127.81 (C*4*$_a$), 129.33 (CH Ar), 132.06 (C Ar), 135.90 (C Ar), 148.40 (C*2*H), 152.22 (C*10*$_b$), 159.22 (C*4*). Found, %: C 77.93; H 7.796; N 77.71. $C_{20}H_{24}N_2O$. Calculated, %: C 77.89; H 7.84;

4-Ethyl-4H-spiro[benzo[h][1,2,4]triazolo[4,3-a]quinazoline-6,1'-cycloheptane]-5(7H)-one (**18**). The mixture of 2.20 *g* (0.0065 *mol*) of 3-ethyl-2-hydrazinyl-3H-spiro[benzo[h]quinazoline-5,1'-cycloheptane]-4(6H)-one (**13**) and 15 *ml* of ethylorthoformate was boiled for 15 *hrs* with a backflow condenser. After distillation of the excess of ethylorthoformate, the precipitate was recrystallized from absolute ethanol. Yield 1.0 *g* (44%) of **18,** mp 178-179^{o}C, R_f 0.40 (ethyl acetate-benzene, 1:1). IR spectrum, ν, cm^{-1}: 1590 (C=C arom); 1617 C=N); 1669 (C=O). ^{1}H NMR spectrum (300 MHz, DMSO-d_6-CCl_4 1/3), δ, ppm: 1.24-1.33 (m, 2H, CH_2 cycloheptane), 1.40 (t, 3H, J=7.0, N-CH_2-$\underline{CH_3}$), 1.45-1.72 (m, 6H, 3×CH_2 cycloheptane), 1.73-1.88 (m, 2H, CH_2 cycloheptane), 2.23-2.35 (m, 2H, CH_2 cycloheptane), 2.92 (s, 2H, C*7*H_2), 4.25 (q, 2H, J=7.0, N-$\underline{CH_2}$-CH_3), 7.32-7.50 (m, 3H, 3×CH Ar), 7.81-7.87 (m, 1H, CH Ar), 8.98 (s, 1H, C*1*H). ^{13}C NMR spectrum (75 MHz, DMSO-d_6-CCl_4 1/3), δ, ppm: 12.06 (N-CH_2-$\underline{CH_3}$), 24.03 (2×CH_2 cycloheptane), 29.32 (2×CH_2 cycloheptane), 34.54 (2×CH_2 cycloheptane), 37.44 (C*7*H_2), 40.29 (N-$\underline{CH_2}$-CH_3), 40.50 (C*6*), 124.29 (CH Ar), 124.33 (C*5*$_a$), 125.28 (C Ar), 126.75 (CH Ar), 128.25 (CH Ar), 130.62 (CH Ar), 135.10 (C*1*H), 136.07 (C Ar), 136.71 (C*11*$_b$), 147.86 (C*3a*), 157.22 (C*5*). Found, %: C 72.56; H 7.12; N 16.26 $C_{21}H_{24}N_4O$. Calculated, %: C 72.39; H 6.94; N 16.08.

4-Ethyl-1-mercapto-4H-spiro[benzo[h][1,2,4]triazolo[4,3-a]quinazoline-6,1'-cycloheptane]-5(7H)-one (**19**). The mixture of 2.2 *g* (0.0065 *mol*) of 3-

ethyl-2-hydrazinyl-3H-spiro[benzo[h]-quinazoline-5,1'-cycloheptane]-4(6H)-one (**13**), 15 *ml* of carbon disulfide and 15 *ml* of pyridine was boiled for 20 *hrs* with a backflow condenser. Then the mixture was cooled and acidified by chlorhydric acid up to pH=3.0-3.5. The precipitate was filtered and recrystallized from butanol. Yield 1.80 *g* (75%) of **19,** mp 240-241°C, R_f 0.60 (ethyl acetate-benzene, 1:1). IR spectrum, ν, cm^{-1}: 1585 (C=C arom); 1632 (C=N); 1672 (C=O). ^{1}H NMR spectrum (300 MHz, DMSO-d_6-CCl_4 1/3), δ, ppm: 0.80-2.20 (br.m, 11H, 11×CH cycloheptane), 1.35 (t, 3H, J=7.0, N-CH_2-$\underline{CH_3}$), 2.56-3.10 (br.m, 3H, CH cycloheptane, C*7*H_2), 4.08 (q, 2H, J=7.0, N-$\underline{CH_2}$-CH_3), 7.14-7.22 (m, 2H, 2×CH Ar), 7.28-7.35 (m, 1H, CH Ar), 7.52-7.57 (m, 1H, CH Ar), 13.79 (s, 1H, SH). ^{13}C NMR spectrum (75 MHz, DMSO-d_6-CCl_4 1/3), δ, ppm: 11.78 (N-CH_2-$\underline{CH_3}$), 24.01 (2×CH_2 cycloheptane), 28.93 (2×CH_2 cycloheptane), 29.23 (2×CH_2 cycloheptane), 36.99 (C*7*H_2), 40.15 (N-$\underline{CH_2}$-CH_3), 41.30 (C*6*), 123.64 (CH Ar), 123.99 (C5_a), 126.45 (CH Ar), 129.08 (C Ar), 129.28 (CH Ar), 129.71 (CH Ar), 134.79 (C*1*), 138.96 (C Ar), 145.48 (C11_b), 156.69 (C*3a*), 162.34 (C*5*). Found, %: C 66.12; H 6.45; N 14.78; S 8.60. $C_{21}H_{24}N_4OS$. Calculated, %: C 66.29; H 6.36; N 14.72; S, 8.43.

4-Ethyl-1-(methylthio)-4H-spiro[benzo[h]imidazo[1,2-a]quinazoline-6,1'-cycloheptane]-5(7H)-one (**20**). In a round bottom flask with a backflow condenser a mixture of 3.4 *g* (0.01 *mol*) of 4-ethyl-1-mercapto-4H-spiro[benzo[h][1,2,4]triazolo[4,3-a]quinazoline-6,1'-cycloheptane]-5(7H)-one (**19**), 0.56 *g* (0.01 *mol*) of KOH, 30 *ml* of absolute ethanol was placed and boiled for 30 *min*. Then 1.41 *g* (0.01 *mol*) of methyl iodide was added and boiling continued for another 10 *hrs*. The reaction mixture was cooled and 20 *ml* of water was added. The precipitate was filtered and recrystallized from ethanol. Yield 3.1 *g* (79%) of **20,** mp 203-205°C, R_f 0.54 (ethyl acetate-benzene, 1:1). IR spectrum, ν, cm^{-1}: 1614 (C=C arom); 1660 (C=O). ^{1}H NMR spectrum (300 MHz, DMSO-d_6-CCl_4 1/3), δ, ppm: 0.80-2.20 (br.m, 11H, 11×CH cycloheptane), 1.39 (t, 3H, J=7.0, N-CH_2-$\underline{CH_3}$), 2.61 (s, 3H, S-CH_3), 2.56-3.10 (br.m, 3H, CH cycloheptane, C*7*H_2), 4.21 (br.q, 2H, J=7.0, N-$\underline{CH_2}$-CH_3), 7.28-7.46 (m, 4H, 4×CH Ar). ^{13}C NMR spectrum (75 MHz, DMSO-d_6-CCl_4 1/3), δ, ppm: 12.01 (N-CH_2-$\underline{CH_3}$), 16.62 (S-CH_3), 23.95 (2×CH_2 cycloheptane), 28.67 (2×CH_2 cycloheptane), 29.33 (2×CH_2 cycloheptane), 37.35 (C*7*H_2), 40.12 (N-$\underline{CH_2}$-CH_3), 41.37 (C*6*), 124.92 (C5_a), 125.21 (CH Ar), 125.28 (CH Ar), 126.70 (C Ar), 127.61 (CH Ar), 130.54 (CH Ar), 135.64 (C*1*), 136.93 (C Ar), 143.63 (C11_b), 149.53 (C*3a*), 156.79 (C*5*). Found, %: C 70.02; H 6.75; N 10.85; S 8.30. $C_{23}H_{27}N_3OS$. Calculated, %: C 70.19; H 6.92; N 10.68; S 8.15.

1-(Benzylthio)-4-ethyl-4H-spiro[benzo[h][1,2,4]triazolo[4,3-a]quinazoline-6,1'-cycloheptane]-5(7H)-one (21). Similarly, from 3.4 *g* (0.01 *mol*) of 4-ethyl-1-mercapto-4H-spiro[benzo[h]-[1,2,4]triazolo[4,3-a]quinazoline-6,1'-cycloheptane]-5(7H)-one (**19**), 0.56 *g* (0.01 *mol*) of KOH and 1.27 *g* (0.01 *mol*) of benzyl chloride, 3.7 *g* (78%) of **21** was obtained**,** mp 135-137 °C, R_f 0.67 (ethyl acetate-benzene, 1:1). IR spectrum, ν, cm^{-1}: 1616 (C=C arom); 1654

(C=O). ^{1}H NMR spectrum (300 MHz, DMSO-d_6-CCl_4 1/3), δ, ppm: 0.80-2.20 (br.m, 11H, 11×CH cycloheptane), 1.39 (t, 3H, J=7.0, N-CH_2-$\underline{CH_3}$), 2.56-3.10 (br.m, 3H, CH cycloheptane, C7H_2), 4.21 (br.q, 2H, J=7.0, N-$\underline{CH_2}$-CH_3), 4.24-4.33 (br.s, 2H, CH_2-Ph), 7.12-7.43 (m, 9H, 9×CH Ar). ^{13}C NMR spectrum (75 MHz, DMSO-d_6-CCl_4 1/3), δ, ppm: 11.97 (N-CH_2-$\underline{CH_3}$), 23.96 (2×CH_2 cycloheptane), 28.74 (2×CH_2 cycloheptane), 29.23 (2×CH_2 cycloheptane), 29.86 (CH_2-Ph), 37.30 (C7H_2), 39.90 (N-$\underline{CH_2}$-CH_3), 41.17 (C6), 125.02 (C5$_a$), 125.18 (CH Ar), 125.23 (CH Ar), 126.69 (C Ar), 126.95 (CH Ar), 127.59 (CH Ar), 127.82 (2×CH Ar), 128.52 (2×CH Ar), 130.50 (CH Ar), 135.50 (C1), 135.84 (C Ar), 136.90 (C Ar), 142.29 (C11$_b$), 149.40 (C3a), 156.72 (C5). Found, %: C 71.63; H 6.35; N 11.78; S 6.94. $C_{28}H_{30}N_4OS$. Calculated, %: C 71.46; H 6.43; N 11.90; S 6.81.

3-ԷԹԻԼ-2-ԹԻՕՔՍՈ-2,3-ԴԻՀԻԴՐՈՍՊԻՐՈ [ԲԵՆԶՕ[h]ԽԻՆԱԶՈԼԻՆ-5,1'-ՑԻԿԼՈՀԵՊՏԱՆ]-4(6H)-ՈՆԻ ՍԻՆԹԵԶԸ ԵՎ ՈՐՈՇ ՀԱՏԿՈՒԹՅՈՒՆՆԵՐԸ

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Էթիլ 4'-ամինո-'H-սպիրո[ցիկլոհեպտան-1,2'-նավթալին]-3'-կարբօքսիլատի և էթիլ-իզոթիոցիանատի փոխազդեցությունից ստացված թիոուրեիդոածանցյալն, առանց ռեակցիոն միջավայրից անջատելու, ենթարկվել է ցիկլման, ինչը բերել է 3-էթիլ-2-թիօքսո-2,3-դիհիդրոսպիրո[բենզո[h]խինազոլին-5,1'-ցիկլոհեպտան]-4(6H)-ոնի ստացմանը: Վերջինս հիմքի ներկայությամբ կոնդենսվել է հալոգենիդների հետ, որի արդյունքում ստացվել են 2-սուլֆանիլտեղակալված 3-էթիլ-3H-սպիրո[բենզո[h]խինազոլին-5,1'-ցիկլոհեպտան]-4(6H)-ոններ: Վերոհիշյալ 2-թիօքսոբենզո[h]խինազոլինից անցում է կատարվել 3-էթիլ-2-հիդրազինիլ-3H-սպիրո[բենզո[h]խինազոլին-5,1'-ցիկլոհեպտան]-4(6H)-ոնի: Վերջինս փոխազդեցության մեջ է դրվել ացետոնի, բենզոիլքլորիդի և բենզոիլիզոթիոցիանատի հետ, որի արդյունքում ստացվել են համապատասխանաբար 3-էթիլ-2-[2-(պրոպան-2-իլիդեն)հիդ–րազինիլ]-3H-սպիրո[բենզո[h]խինազոլին-5,1'-ցիկլո-հեպտան]-4(6H)-ոն, N'-(3-էթիլ-4-օքսո-4,6-դիհիդրո-3H-սպիրո[բենզո[h]խինազոլին-5,1'-ցիկլոհեպտան]-2-իլ)բենզոհիդրազիդ և N-[2-(3-էթիլ-4-օքսո-4,6-դիհիդրո-3H-սպիրո[բենզո[h]խինազոլին-5,1'-ցիկլոհեպտան]-2-իլ)հիդրազինոկարբոնոթիոիլ]բենզամիդ Ցույց է տրվել, որ նշված հիդրազինոբենզո[h]խինազոլինը հիմքի ներկայությամբ ենթարկվում է դեհիդրազինացման, առաջացնելով 3-էթիլ-3H-սպիրո[բենզո[h]խինազոլին-5,1'-ցիկլոհեպտան]-4(6H)-ոն: Հիդրազինոբենզո[h]խինազոլինի և օրթոմրջնաթթվի էթիլ էսթերի կամ ծծմբաածխածնի կոնդենսման արդյունքում սինթեզվել են համապատասխանաբար 4-էթիլ-4H-սպիրո[բենզո[h][1,2,4]տրիազոլո[4,3-a]խինազոլին-6,1'-ցիկլո-հեպտան]-5(7H)-ոն և 1-մերկապտո-4-էթիլ-4H-սպիրո[բենզո[h][1,2,4]տրիազոլո[4,3-a]խինազոլին-6,1'-ցիկլոհեպտան]-5(7H)-ոն: Վերջինից անցում է կատարվել 1-մեթիլթիո- և 1-բենզիլթիո-4-էթիլ-4H-սպիրո[բենզո[h][1,2,4]տրիազոլո[4,3-a]խինազոլին-6,1'-ցիկլոհեպտան]-5(7H)-ոնների:

СИНТЕЗ И НЕКОТОРЫЕ СВОЙСТВА 3-ЭТИЛ-2-ТИОКСО-2,3-ДИГИДРОСПИРО [БЕНЗО[h]ХИНАЗОЛИН-5,1'-ЦИКЛОГЕПТАН]-4(6H)-ОНА

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Тиоуреидопроизводное, полученное взаимодействием этил 4'-амино-'H-спиро[циклогептан-1,2'-нафталин]-3'-карбоксилата и этилизотиоцианата без выделения из реакционной среды, подвергнуто циклизации, приведшей к 3-этил-2-тиоксо-2,3-дигидроспиро[бензо[h]хиназолин-5,1'-циклопентан]-4(6H)-онам. Последний в присутствии оснований конденсирован с галогенидами, в результате чего получены 2-сульфанилзамещенные 3-этил-3H-спиро[бензо[h]хиназолин-5,1'-циклопентан]-4(6H)-оны. От вышеуказанного 2-тиоксобензо[h]хиназолина совершен переход к 3-этил-2-гидразинил-3H-спиро[бензо[h]хиназолин-5,1'-циклогептан]-4(6H)-ону. Последний поставлен во взаимодействие с ацетоном, бензоилхлоридом и бензоилизотиоцианатом, в результате чего получены соответственно 3-этил-2-[2-(пропан-2-илиден)гидразинил]-3H-спиро[бензо[h]хиназолин-5,1'-циклопентан]-4(6H)-он, N'-(3-этил-4-оксо-4,6-дигидро-3H-спиро[бензо[h]хиназолин-5,1'-циклопентан]-2-ил)бензгидразид и N-[2-(3-этил-4-оксо-4,6-дигидро-3H-спиро[бензо[h]хиназолин-5,1'-циклогептан]-2-ил)гидразинокарбонотиоил]бензамид. Показано, что указанный гидразинобензо[h]хиназолин в присутствии основания подвергается дегидразинированию, образуя 3-этил-3H-спиро[бензо[h]хиназолин-5,1'-циклогептан]-4(6H)-он. Конденсацией 2-гидразинобензо[h]хиназолина и этилового эфира ортомуравьиной кислоты или сероуглерода синтезированы соответственно 4-этил-4H-спиро[бензо[h][1,2,4]триазоло[4,3-a]хиназолин-6,1'-циклогептан]-5(7H)-он и 1-меркапто-4-этил-4H-спиро[бензо[h][1,2,4]триазоло[4,3-a]хиназолин-6,1'-циклогептан]-5(7H)-он. От последнего совершен переход к 1-метилтио- и 1-бензилтио-4-этил-4H-спиро[бензо[h][1,2,4]триазоло[4,3-a]хиназолин-6,1'-циклогептан]-5(7H)-онам.

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ՀԱՅԱՍՏԱՆԻ ՀԱՆՐԱՊԵՏՈՒԹՅԱՆ ԳԻՏՈՒԹՅՈՒՆՆԵՐԻ
ԱԶԳԱՅԻՆ ԱԿԱԴԵՄԻԱ
НАЦИОНАЛЬНАЯ АКАДЕМИЯ НАУК РЕСПУБЛИКИ АРМЕНИЯ
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SYNTHESIS OF AZAANALOGUES OF BIOLOGICALLY ACTIVE 3-[(1H-PYRROL-2-YL)METHYLENE]-1-METHYLINDOLIN-2-ONES

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By the interaction of isatin and its 1-substituted derivatives with 2-hydrazino-4,5-dihydro-1H-imidazole iodohydrate, 3-(2-(1H-imidazol-2-yl)hydrazylidene)indolin-2-ones were synthesized.

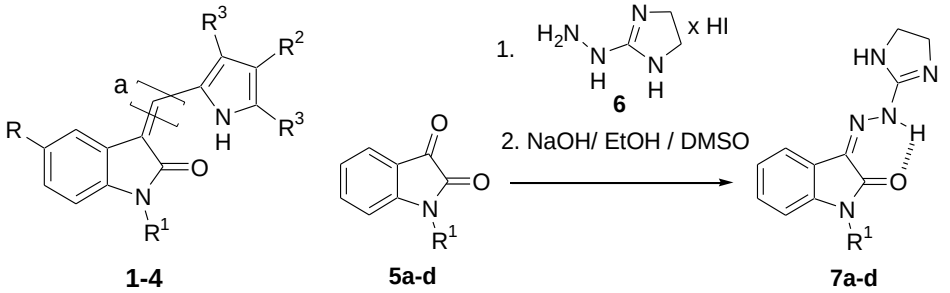
The compounds obtained are the simplest analogues of biologically active 3-substituted indolin-2-ones.

References 2.

It is known that various indolin-2-one derivatives exhibit pronounced antitumor activity due to inhibitory properties against a variety of cellular tyrosine kinase receptors (RTKs) by inhibiting ligand-dependent autophosphorylation of kinases in submicromolar doses [1]. Among well-known drugs are 3-substituted indolin-2-one **1** (Semaxanib, SU5416), which has shown high antikinase activity against the receptor for vascular endothelial growth factor (VEGFR-1) and (VEGFR-2), an antitumor drug Sunitinib **2** (Sunitinib, SU 11248), a multiple kinase inhibitor (VEGFR)-1, VEGFR-2, PDGFRb, fms-like tyrosine kinase-3), as well as piperidin-1-ylmethyl derivative **3** (drug Z24) angiogenesis inhibitor and 3-(dimethylamino)propyl derivative **4** (preparation TMP-20) with pronounced antitumor activity *in vivo*. Since the main structural elements responsible for the biological activity of the class of compounds under discussion are the fragments of indolin-2-one and pyrrole linked by a linker (**a**), in the present study by the interaction of isatin and its 1-substituted derivatives **5a-d** with 2-hydrazino-4,5-dihydro-1H-imidazole **6**, 3-(2-(1H-imidazol-2-yl)hydrazylidene)indolin-2-ones **7a-d** were synthesized, two of which were prepared and characterized as bases. In the synthesized compounds, a fragment

of indolin-2-one and 4,5-dihydroimidazole are linked by a hydrazine residue, which allows to trace the influence of the nature of the five-membered nitrogen heterocycle and the linking chain on the biological activity. The synthesis of target compounds is presented in the Scheme:

Scheme



1-4 **5a-d** **7a-d**

1: R, R^1, R^2, R^3 = H, H, H, Me; **2**: H, H, $Et_2N(CH_2)_2NHCO$), Me; **3**: H, $CH_2N(CH_2)_5$, H, H; **4**: Cl, $Me_2N(CH_2)_3$, H, H; **5a-d, 7a-d**: R^1 = H (**a**), Bn (**b**), *n*-pentyl (**c**), Ac (**d**).

Since on the basis of physicochemical data we have not yet been able to establish the exact geometric structure of derivatives **7a-d**, a preliminary choice of the configuration of synthesized compounds was made in favor of (*Z*)-isomers in which the formation of an energetically favorable intramolecular N-H-O-hydrogen connection with the formation of a six-membered cycle took place.

The toxicity and antitumor activity of compounds **7a** and **7d** were studied. In the study of acute toxicity, it was found that LD_{100} of compounds was 1750 *mg*/*kg*, and MTD was 900 *mg*/*kg*.

In chemotherapeutic experiments *in vivo*, these compounds were administered intraperitoneally daily for 6 *days* at a dose of 150 *mg*/*kg*. It was found that imidazolines **7a** and **7d** exhibited weak antitumor activity against sarcoma 180 of mice, inhibiting tumor growth by 28.4% (compound **7a**) and 40.3% (compound **7d**) and both compounds were inactive in the Ehrlich ascites carcinoma model.

Experimental part

IR spectra were recorded on a "Nicolet Avatar 330" in vaseline oil. ^1H and ^{13}C NMR spectra were obtained on a Varian "Mercury-300 VX" instrument with a frequency of 300.8 *MHz* and 75.46 *MHz*, in a DMSO-d_6 – CCl_4, 1:3 mixture, and the internal standard was TMS. TLC was performed on "Silufol UV-254" plates in the system water - methanol - ethyl acetate, 1: 2: 10), visualization – in UV light.

1-Substituted indolin-2-ones 7a-d. An equimolar mixture of 0.0055 *mol* of 1-substituted isatin **5a-d** and 2-hydrazino-4,5-dihydroimidazole iodohydrate **6**

[2] in 15 *ml* of absolute methanol was boiled for 2*hr* and left overnight. The precipitated iodine hydrate of the compound was filtered off and dried. To obtain the bases of the synthesized compounds, the obtained salt was dissolved in DMSO, neutralized with a 20% alcohol solution of NaOH, poured into water; the precipitate formed was filtered off, dried and recrystallized from ethanol.

(*Z*)-3-[2-(4,5-Dihydro-1H-imidazol-2-yl)hydrazylidene]indolin-2-one iodohydrate (7a) was obtained by the interaction of indoline-2,3-dione with 2-hydrazino-4,5-dihydro-1H-imidazole iodohydrate **(6).** The yield 63.5%, mp > 320 °C (base yield 78.6%, mp 242-244°C, R_f 0.63). IR spectrum, ν, *cm*$^{-1}$: 3460, 3392, 3161 (NH_2^+, NH), 1712 (CO), 1650, 1612 (C=C–C=N). ^{1}H NMR spectrum, δ, ppm, *Hz*: 3.91 br.s (4H, 2·NCH_2); 6.93 br.d (1H, J = 7.8, C_6H_4); 7.05 td (1H, J = 7.6, 0.8 C_6H_4); 7.32 td (1H, J = 7.7, 1.2, C_6H_4); 7.63 br.d (1H, J = 7.4, C_6H_4); 9.10 br.s (2H, 2·NH); 11.18 br.s (1H, NH); 12.78 br.s (1H, NH). ^{13}C NMR spectrum, δ, ppm: 43.1 (2·NCH); 110.9 (CH); 119.0 (CH); 121.4 (CH); 122.1 (CH); 131.7; 138.0; 142.7; 158.2; 161.5. Found, %: C 57.47; H 5.04; N 30.27. $C_{11}H_{11}N_5O$. Calculated, %: C 57.63; H 4.84; N, 30.55.

(*Z*)-1-Benzyl-3-(2-(4,5-dihydro-1H-imidazol-2-yl)hydrazylidene]indolin-2-one (7b) was prepared by reacting 1-benzylindoline-2,3-dione with 2-hydrazino-4,5-dihydro-1H-imidazole iodohydrate **(6).** Yield 67.7%, mp 294-295 °C, R_f 0.67. IR spectrum, ν, *cm*$^{-1}$: 3448, 3200 (NH), 1704 (CO), 1614 (C=C–C=N). ^{1}H NMR spectrum, δ, ppm, *Hz*: 3.62 br.s (4H, 2·NCH_2); 4.91 br.s (2H, CH_2Ph); 6.65 br.s (1H, J = 7.7, C_6H_4); 6.90 br.s (1H, J = 7.4, C_6H_4); 7.04 br.s (1H, J = 7.5, C_6H_4); 7.60 br.s (1H, J = 7.3, C_6H_4); 7.16-7.32 m (5H, C_6H_4); 7.85 br.s (2H, 2·NH). ^{13}C NMR spectrum, δ, ppm: 41.9 (CH_2), 42.1 (2·NCH_2), 108.2 (CH), 118.3 (CH), 121.1 (CH), 123.3, 127.10 (CH), 127.12 (2·CH), 128.5 (2.CH), 132.3, 137.2, 139.9, 156.5, 169.1. Found, %: C 67.83; H 5.15; N 21.77. $C_{18}H_{17}N_5O$. Calculated, %: C 67.70; H 5.37; N 21.93.

(*Z*)-1-Pentyl-3-(2-(4,5-dihydro-1H-imidazol-2-yl)hydrazylidene]indolin-2-one (7c) was prepared by reacting 1-pentylindoline-2,3-dione with 2-hydrazino-4,5-dihydro-1H-imidazole iodohydrate **(6).** Yield 75.7%, mp 130-132°C, R_f 0.64. IR spectrum, ν, *cm*$^{-1}$: 3385, 3127 (NH), 1691 (CO), 1650, 1611 (C=C–C=N). ^{1}H NMR spectrum, δ, ppm, *Hz*: 0.91t (3H, J = 6.6, CH_3), 1.29-1.43 m (4H, 2·CH_2), 1.61-1.72 m (2H, CH_2), 3.71 t (2H, J = 7.1, NCH_2), 3.87 s (4H, 2·NCH_2), 6.91 br.s (1H, J = 7.8, C_6H_4), 7.03 br.d (1H, J = 7.5, C_6H_4), 7.27 br.d (1H, J = 7.8, 7.4, C_6H_4), 7.65 br.d (1H, J = 7.4, C_6H_4), 9.34 br.s (2H, 2·NH). Found, %: C 64.41; H 7.25; N 23.44. $C_{16}H_{21}N_5O$. Calculated, %: C 64.19; H 7.07; N 23.39.

(*Z*)-1-Acetyl-3-(2-(4,5-dihydro-1H-imidazol-2-yl)hydrazylidene]indolin-2-one iodo-hydrate (7d) was prepared by reacting 1-acetylindoline-2,3-dione with 2-hydrazino-4,5-dihydro-1H-imidazole iodohydrate **(6).** Yield 59.9%, mp 235-237°C, $R_f$base 0.57. IR spectrum, ν, *cm*$^{-1}$: 3240, 3120 (NH_2^+, NH), 1729, 1710 (CO), 1647, 1610 (C=C–C=N). ^{1}H NMR spectrum, δ, ppm, *Hz*: 2.68 s (3H, CH_3), 3.96 s (4H, 2.N·CH_2), 7.32 td (1H, J = 7.6, 0.8, C_6H_4), 7.48 ddd (1H, J =

8.1, 7.6, 1.4, C_6H_4), 7.88 br.s (1H, J = 7.5, C_6H_4), 8.19 br.s (1H, J = 8.1, C_6H_4), 9.04 br.s (2H, NH·HI), 12.78 br.s (1H, NH). Found, %: C 57.38; H 5.03; N 25.60. $C_{16}H_{21}N_5O$. Calculated, %: C 57.56; H 4.83; N 25.82.

ԿԵՆՍԱԲԱՆՈՐԵՆ ԱԿՏԻՎ 3-[(1-Հ-ՊԻՐՈԼ-2-ԻԼ)ՄԵԹԻԼԵՆ]-1-ՄԵԹԻԼԻՆԴՈԼԻՆ-2-ՈՆԵՐԻ ԱԶԱՆՄԱՆԱԿՆԵՐԻ ՍԻՆԹԵԶԸ

Մ. Ա. ԻՐԱԴՅԱՆ, Ն. Ս. ԻՐԱԴՅԱՆ, Հ. Մ. ՍՏԵՓԱՆՅԱՆ և Ա. Ա. ՀԱՐՈՒԹՅՈՒՆՅԱՆ

Իզատինի և նրա 1-տեղակալված ածանցյալների և 2-հիդրազինո-4,5-դիհիդրո-1Հ-իմիդազոլի յոդհիդրատի փոխազդեցությամբ սինթեզվել են 3-(2-(1Հ-իմիդազոլ-2-իլ)հիդրազիլիդեն)ինդոլին-2-ոններ: Ստացված միացությունները կենսաբանորեն ակտիվ 3-տեղակալված ինդոլին-2-ոնների պարզագույն նմանակներն են:

СИНТЕЗ АЗААНАЛОГОВ БИОЛОГИЧЕСКИ АКТИВНЫХ 3-[(1-*Н*-ПИРРОЛ-2-ИЛ)МЕТИЛЕН]-1-МЕТИЛИНДОЛИН-2-ОНОВ

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Взаимодействием изатина и его1-замещенных производных с йодгидратом 2-гидразино-4,5-дигидро-1*Н*-имидазола синтезированы 3-(2-(1Н-имидазол-2-ил)гидразилиден)индолин-2-оны.

Полученные соединения представляют собой простейшие аналоги биологически активных 3-замещенных индолин-2-онов.

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ՀԱՅԱՍՏԱՆԻ ՀԱՆՐԱՊԵՏՈՒԹՅԱՆ ԳԻՏՈՒԹՅՈՒՆՆԵՐԻ
ԱԶԳԱՅԻՆ ԱԿԱԴԵՄԻԱ
НАЦИОНАЛЬНАЯ АКАДЕМИЯ НАУК РЕСПУБЛИКИ АРМЕНИЯ
NATIONAL ACADEMY OF SCIENCES OF THE REPUBLIC OF ARMENIA

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SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF NEW 4-(2-PHENYL-4-QUINOLYLCARBAMOYL)BENZOIC ACID DERIVATIVES

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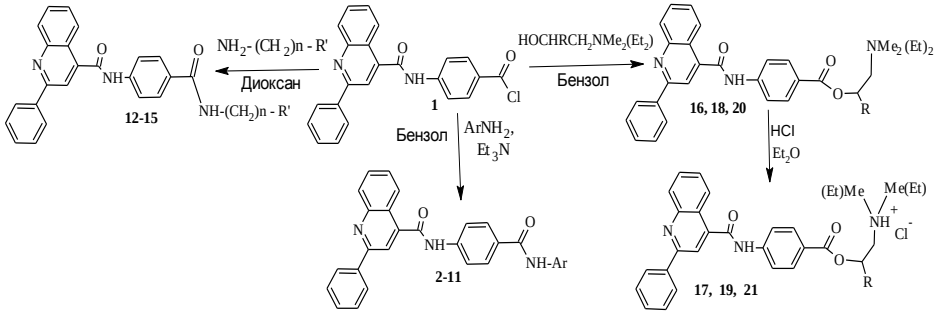
As a result of the N-acylation reaction of some primary aromatic amines and substituted alkylamines by 4-(2-phenyl-4-quinolylcarbamoyl)benzoic acid chloride, new benzamides - N1-(substituted phenyl)-4-(2-phenyl-4-quinolylcarbamoyl)-, N1-(substituted alkyl)-4-(2-phenyl-4-quinolylcarbamoyl) benzamides were obtained. O-acylation yielded 2-dialkylaminoalkyl-4-(2-phenyl-4-quinolyl-carbamoyl)benzoates and N,N-dialkyl-2-[(4-{2-phenyl-4-quinolylbenzamido}benzoyl) oxy]ethane-, propane-1-ammonium chlorides. The antibacterial properties of the compounds with respect to gram-positive staphylococci and gram-negative rods were studied. It was found that the products of N-acylation exhibited weak antimicrobial activity against all strains used (d = 10-14 mm). When replacing the benzamide group with dialkylaminoalkyl, the activity of compounds significantly increased (d = 16-22 mm).

References 8.

Due to the developing resistance to many antibiotics, doctors face infections for which there is no effective therapy. Therefore, there is a high demand for new drugs for the treatment of bacterial infections, especially caused by resistant bacterial strains [1-5]. The aim of this work is the synthesis of new antibacterial agents in a series of derivatives of 4-(2-phenyl-4-quinolylcarbamoyl)benzoic acid in the N- and O-acylation reactions of various primary aromatic amines, substituted alkylamines and aminoalkanols. The acylating reagent in the presented syntheses is 4-(2-phenyl-4-quinolylcarbamoyl)benzoic acid chloride **1**. As a result of the N-acylation reaction of some primary aromatic amines and substituted alkylamines, new benzamides were obtained – N1-(substituted phenyl)-4-(2-phenyl-4-quinolylcarbamoyl)- and N1-(substituted alkyl)-4-(2-phenyl-4-quinolylcarbamoyl)benamides **2-15**.

O-acylated compounds **16, 18, 20** – 2-dialkylaminoalkyl-4-(2-phenyl-4-quinolylcarbamoyl)benzoates were obtained by heating a mixture of the corresponding substrates with 4-(2-phenyl-4-quinolyl-carbamoyl)benzoic acid chloride in dry benzene. Then, by exposure to an ethereal solution of hydrogen chloride, the corresponding N,N-dialkyl-2-[(4-{2-phenyl-4-quinolyl benzamido} benzoyl)oxy]ethane-, propane-1-ammonium chlorides **17, 19, 21** were obtained. The initial starting compound, which is the pharmaceutical preparation of atofan - 2-phenyl-4-quinolinecarboxylic acid, was obtained by the well-known Pfitzinger reaction [6] and converted to the acid chloride.

Scheme



2 - 11: Ar = 4-Br-C_6H_4 (**2**), 3-NO_2-C_6H_4 **(3)**, 4-NO_2-C_6H_4 (**4**), 2-CH_3-C_6H_4 (**5**), 3-CH_3-C_6H_4 (**6**), 4-C H_3-C_6H_4 (**7**), 2-CH_3O-C_6H_4 **(8)**, 3-CH_3O-C_6H_4 (**19**), 4-CH_3O-C_6H_4 (**10**), 6-methyl-2-pyridyl (**11**). **12 - 15:** n = 2, R' = NMe_2 (**12**), NEt_2 (**13**); C_6H_5 (**14**), n = 3, R' = OCH_3 (**15**); **16, 18, 20:** R = H, NMe_2 (**16**), NEt_2 (**18**); R = CH_3, NMe_2 (**20**); R = H, NMe_2·HCI (**17**), NEt_2·HCI (**19**); R = CH_3, NMe_2·HCI (**21**).

The structure of the obtained compounds was confirmed by the data of IR, ^{1}H NMR spectroscopy, the composition – by elemental analysis. In the IR spectra of all benzamides **2-11** and aminoamides **12-15**, intense absorption bands of amide groups were found at 3348-3208 cm^{-1} (NH) and 1668-1597 cm^{-1} (C = O). In the IR spectra of compounds **16, 18, 20** strong absorption bands were observed for the stretching vibrations of carbonyl groups of COO at 1718-1711 cm^{-1}, of ether C-O in the region of 1100-1170 cm^{-1}.

The antibacterial activity of compounds **2-21** was studied according to the procedure [7] with a bacterial load of 20 *million* microbial bodies per 1 *ml* of medium. Gram-positive staphylococci (*Staphylococcus aureus* 209p, 1) and gram-negative bacilli (*Sh. Fleaneri* 6858, *E.coli* 0-55) were used in the experiments. Compounds were tested at a 1:20 dilution prepared in DMSO. On Petri dishes with crops of the above strains of microorganisms, solutions of the tested substances in a volume of 0.1 *ml* were applied. The results were taken into account according to the diameter (d, mm) of the zones of the absence of microorganism growth at the place of application of the substances after daily

cultivation of test cultures in a thermostat at 37°C. The known drug furazolidone was used as a positive control [8].

It was found that N-acylation products **2-15** exhibited weak antimicrobial activity against all strains used (d = 10-14 *mm*). When replacing a benzamide moiety with a dialkylaminoalkyl group **16-21**, the activity of the compounds increased significantly (d = 16-22*mm*), however, it was slightly inferior to the control drug furazolidone (d = 24-25*mm*).

Experimental part

IR spectra were recorded on a "Nicolet Avatar 330 FT-IR" spectrometer. ^{1}H NMR spectra were recorded on a "Mercury 300-VX" spectrometer with a resonant frequency of 300.08 *MHz*, in a DMSO + CF_3COOD solution; internal standard - TMS. The melting point of the obtained substances was determined on a Boetius instrument. The individuality of substances was monitored by TLC on "Silufol-254" plates in the system butanol – ethanol – acetic acid – water (8 : 2: 1: 3), and the developer was iodine pairs.

N-(2, 3, 4-Substituted phenyl)-4-(2-phenyl-4-quinolylcarbamoyl) benzamides (2-11). (General methodology). 0.01 *mol* of the corresponding amine and 1.0 *g* (0.01 *mol*) of Et_3N in 20 *ml* of dry benzene are added to (0.01 *mol*) of the acid chloride of the corresponding acid. The reaction mixture is boiled for 3 hours, then benzene is distilled off, cooled and 25 *ml* of water are added. Precipitation is observed. The contents are left overnight at room temperature, then the precipitate is filtered off, washed with water. The obtained crystalline products are recrystallized from ethanol – DMF (2 : 0.5).

N1-(4-Bromophenyl)-4-(2-phenyl-4-quinolylcarbamoyl)benzamide (2). Yield 86%, mp 358-359 ^{o}C, Rf 0.64. IR spectrum, υ, cm^{-1}: 3315 (NH), 1645 (NHC = O). ^{1}H NMR spectrum, d, ppm: 7.39-7.44 m (2H, C_6H_4); 7.45-7.64m (4H, C_6H_4), 7.76-7.83 m (3H, C_6H_4); 7.94-8.05 m (4H, C_6H_4); 8.13-8.18 m (1H, C_6H_4); 8.25 s (1H, = CH); 8.28-8.37 m (3H, C_6H_4); 10.09 s (1H, NH); 10.88 s (1H, NH). Found, %: C 66.64; H 3.18; N 8.01; Br 15.28. $C_{29}H_{20}BrN_3O_2$. Calculated, %: C 66.68; H 3.86; N 8.04; Br 15.30.

N1-(3-Nitrophenyl)-4-(2-phenyl-4-quinolylcarbamoyl)benzamide (3). Yield 71%, mp 241-243°C, Rf 0.63. IR spectrum, υ, cm^{-1}: 3260 (NH), 1668 (NHC = O). ^{1}H NMR spectrum, d, ppm: 7.48-7.60 m (4H, C_6H_4); 7.62-7.68 m (1H, C_6H_4), 7.7 9-7.85 m (1H, C_6H_4); 7.89 dd (1H, J1 8.2., J2 2.2, J3 0.9 Hz, H arom); 7.93-8.03 and 8.06-8.11 m (2H and 2H, C_6H_4); 8.24-8.28 m (1H, C_6H_4); 8.30 s (1H, = CH); 8.31-8.40 m (4H, C_6H_4); 8.81 t (1H, J1 2.2 Hz, C_6H_4); 10.46 s (1H, NH); 10.99 s (1H, NH). Found, %: C 66.63; H 3.81; N 8.01; Br 15.28. $C_{29}H_{20}N_4O_4$. Calculated, %: C 66.68; H 3.86; N 8.04; Br 15.30.

N1-(4-Nitrophenyl)-4-(2-phenyl-4-quinolylcarbamoyl)benzamide (4). Yield 73%, mp. 239-241°C, Rf 0.61. IR spectrum, υ, cm^{-1}: 3326 (NH), 1661 (NHC = O). ^{1}H NMR spectrum, d, ppm: 7.45-7.64 m (4H, C_6H_4); 7.76-7.82m

(1H, C_6H_4), 7.97-8.09 m (4H, C_6H_4); 8.10-8.23 m (5H, C_6H_5); 8.25 s (1H, = CH); 8.28- 8.37 m (3H, C_6H_4); 10.53 s (1H, NH); 10.91 s (1H, NH). Found, %: C 66.64; H 3.82; N 8.01; Br 15.26. $C_{29}H_{20}N_4O_4$. Calculated, %: C 66.68; H 3.86; N 8.04; Br 15.30.

N1-(2-Tolyl)-4-(2-phenyl-4-quinolylcarbamoyl)benzamide (5). Yield 75%, mp 182-183°C, Rf 0.61. IR spectrum, υ, cm^{-1}: 3268 (NH), 1650 (NHC = O). ^{1}H NMR spectrum, d, ppm: 2.32 s (3H, CH_3); 7.08-7.24 m (3H, $C_6H_4CH_3$); 7.40 m (5H, C_6H_4 CH_3); 7.75-7.82 m (1H, H arom); 7.93-8.07 m (4H, C_6H_4); 8.13 -8.18 m (1H, C_6H_4); 8.25 s (1H, = CH); 8.28-8.37 m (3H, C_6H_4) 9.54 s (1H, NH); 10.84 s (1H, NH). Found, %: C 78.74; H 5.04; N 9.15. $C_{30}H_{23}N_3O_2$. Calculated, %: C 78.76; H 5.07; N 9.18.

N1-(3-Tolyl-4-(2-phenyl-4-quinolylcarbamoyl)benzamide (6). Yield 71%, mp 192-194°C, Rf 0.61. IR spectrum, υ, cm^{-1}: 3270 (NH), 1650 (NHC = O). ^{1}H NMR spectrum, d, ppm: 2.38 s (3H, CH3); 6.84 br.s (1H, J 7.5, Hz, $C_6H_4CH_3$); 7.16 t (1H, J 7.8 Hz, $C_6H_4CH_3$); 7.48-7.69 m (6H, H arom); 7.80-7.86 m (1H, C_6H_4); 7.94-8.06 m (4H, C_6H_4); 8.26-8.41 m (4H, C_6H_4); 8.30 s (1H, = CH); 9.86 s (1H, NH); 10.96 s (1H, NH). Found, %: C 78.73; H 5.05; N 9.16. $C_{30}H_{23}N_3O_2$. Calculated, %: C 78.76; H 5.07; N 9.18.

N1-(4-Tolyl)-4-(2-phenyl-4-quinolylcarbamoyl)benzamide (7). Yield 73%, mp 197-199 °C, Rf 0.61. IR spectrum, υ, cm^{-1}: 3226 (NH), 1644 (NHC = O). ^{1}H NMR, d, ppm: 2.34 s (3H, CH_3); 7.06 -7.11 m (2H, C_6H_4); 7.45-7.69 m (6H, C_6H_4); 7.75-7.82 m (1H, H arom); 7.93-8.05 m (4H, C_6H_4); 8.14-8.19 m (1H, C_6H_4); 8.25 s (1H, = CH); 8.29 - 8.38 m (3H, C_6H_4); 9.86 s (1H, NH); 10.85 s (1H, NH). Found, %: C 78.72; H 5.02; N 9.17. $C_{30}H_{23}N_3O_2$. Calculated, %: C 78.76; H 5.07; N 9.18.

N1-(2-Methoxyphenyl)-4-(2-phenyl-4-quinolylcarbamoyl)benzamide (8). Yield 79%, mp 182-183°C, Rf 0.58. IR spectrum, υ, cm^{-1}: 3280 (NH), 1650 (NHC = O). ^{1}H NMR spectrum, d, ppm: 3.97 s (3H, OCH_3); 6.92-7.10 m (3H, N arom); 7.45-7.65 m (4H, H arom); 7.76-7.82 m (1H, H arom); 7.93-8.03 m. (4H, C_6H_4); 8.14-8.19 m (1H, C_6H_4); 8.24 dd (1H, J1 7.8, J2 1.7 Hz, C_6H_4); 8.25 s (1H, = CH);); 8.28 - 8.32 m (1H, C_6H_4); 8.33-8.37 m (2H, C_6H_4); 8.85 s (1H, NH); 10.88 s (1H, NH). Found, %: C 76.08; H 4.89; N 8.85. $C_{30}H_{23}N_3O_3$. Calculated, %: C 76.09; H 4.90; N 8.87.

N1-(3-Methoxyphenyl)-4-(2-phenyl-4-quinolylcarbamoyl)benzamide (9). Yield 77%, mp 191-193 °C, Rf 0.57. IR spectrum, υ, cm^{-1}: 3296 (NH), 1649 (NHC = O). ^{1}H NMR spectrum, d, ppm: 3.96 s (3H, OCH_3); 6.92-7.10 m (3H, N arom); 7.45-7.64 m (4H, H arom); 7.75-7.82 m (1H, H arom); 7.93-8.03 m. (4H, C_6H_4); 8.13-8.17 m (1H, C_6H_4); 8.21-8.25 m (1H, C_6H_4); 8.25 s (1H, = CH); 8.27 - 8.31 m (1H, C_6H_4); 8.31-8.37 m (2H, C_6H_4); 8.86 s (1H, NH); 10.88 s (1H, NH). Found,: C 76.06; H 4.87; N 8.86. $C_{30}H_{23}N_3O_3$. Calculated, %: C 76.09; H 4.90; N 8.87.

N1-(4-Methoxyphenyl)-4-(2-phenyl-4-quinolylcarbamoyl)benzamide (10). Yield 81%, mp 194-195 °C, Rf 0.58. IR spectrum, υ, cm^{-1}: 3306 (NH),

1639 (NHC = O). ^{1}H NMR spectrum, d, ppm: 3.79 s (3H, OCH_3); 6.81-6.86 m (3H, N arom); 7.45-7.64 m (3H, H arom); 7.67-7.73 m (2H, C_6H_4); 7.75-7.81 m (1H, C_6H_4); 7.92-8.04 m (4H, C_6H_4); 8.13-8.17 m (1H, C_6H_4); 8.25 s (1H, = CH); 8.29-8.37 m (3H, C_6H_4); 9.82c (1H, NH); 10.83 s (1H, NH). Found,: C 76.06; H 4.87; N 8.86. $C_{30}H_{23}N_3O_3$. Calculated: C 76.09; H 4.90; N 8.87.

N1-(6-Methyl-2-pyridyl)-4-(2-phenyl-4-quinolylcarbamoyl)benzamide (11). Yield 74%, mp 236-237°C, Rf 0.54. IR spectrum, υ, *cm*$^{-1}$: 3330 (NH), 1645 (NHC = O). ^{1}H NMR spectrum, d, ppm: 2.50 s (3H, OCH_3); 6.91 d (1H, J 7.5 Hz, C_6H_4); 7.45-7.67 m (5H, H arom); 7.75-7.82 m (1H, C_6H_4); 7.93-7.99 m (2H, C_6H_4); 8.07-8.18 m (4H, C_6H_4); 8.25 s (1H, = CH); 8.28-8.38 m (3H, C_6H_4); 10.10 s (1H, NH); 10.85 s (1H, NH). Found, %: C 76.06; H 4.87; N 8.86. $C_{29}H_{22}N_4O_2$. Calculated, %: C 75.97; H 4.84; N 12.22.

N1-(3-Diethylaminoethyl)-4-(2-phenyl-4-quinolylcarbamoyl)benzamide (13). Yield 75%, mp 240-241°C, Rf 0. 55. IR spectrum, υ, *cm*$^{-1}$: 3292 (NH), 1653, 1636 (NHC = O). ^{1}H NMR spectrum, d, ppm: 1.06 t [6H, J 7.2 Hz, N (CH_2CH_3)] 2; 2.56 q [4H, J 7.2 Hz, N (CH_2CH_3)] 2; 2.47 t (2H, J 6.7 Hz, NCH_2); 3.36 - 3.43 m (2H, $NHCH_2$); 7.44-7.63 m (4H, C_6H_4); 7.75-7.81 m (1H, C_6H_4); 7.81-7.96m (5H, C_6H_4 and NH); 8.12-8.18 m (1H, C_6H_4); 8.23 s (1H, = CH); 8.26-8.30 m (1H, C_6H_4); 8.32-8.36 m (2H, C_6H_4); 10.76 s (1H, NH). Found, %: C 74.63; H 6.45; N 12.00. $C_{29}H_{30}N_4O_2$. Calculated, %: C 74.65; H 6.48; N 12.01.

N1-Phenethyl-4-(2-phenyl-4-quinolylcarbamoyl)benzamide (14). Yield 80%, mp 275-276°C, Rf 0.56. IR spectrum, υ, *cm*$^{-1}$: 3323 (NH), 1653, 1632 (NHC = O). ^{1}H NMR spectrum, d, pp m: 2.88-2.94 m (2H, CH_2); 3.49-3.57m (2H, NCH_2); 7.13-7.29 m (5H, C_6H_5); 7.45-7.64 m (4H, C_6H_4); 7.75-7.81 m (1H, C_6H_4); 7.84-7.93 m (4H, C_6H_4); 8.13-8.17 m (1H, C_6H_4); 8.23 s (1H, = CH); 8.24 t (1H, J 5.6 Hz, $NHCH_2$); 8.28-8.32 m (1H, C_6H_4); 8.33-8.37 m (2H, C_6H_4); 10.79 s (1H, NH). Found,: C 78.93; H 5.31; N 8.90. $C_{31}H_{25}N_3O_2$. Calculated, %: C 78.96; H 5.34; N 8.91.

N1-(3-Methoxypropyl)-4-(2-phenyl-4-quinolylcarbamoyl)benzamide (15). Yield 80%, mp 228-230°C, Rf 0.57. IR spectrum, υ, *cm*$^{-1}$: 3291 (NH), 1654 (NHC = O). ^{1}H NMR spectrum, d, ppm: 1.78-1.87 m (2H, CH2); 3.32 s (3H, OCH3); 3.32-3.39 m (2H, NCH_2); 3.44 t (2H., J 6.2 Hz, OCH_2); 7.44-7.63 m (4H, C_6H_4); 7.75-7.81 m (1H, C_6H_4); 7.83-7.91 m (4H, C_6H_4); 8.10 t (1H, J 5.7 Hz, NH); 8.13-8.17 m (1H, C_6H_4); 8.23 s (1H, = CH); 8.27-8.31 m (1H, C_6H_4); 8.32-8.37 m (2H, C_6H_4); 10.77 s (1H, NH). Found, %: C 73.76; H 5.74; N 9.53. $C_{27}H_{25}N_3O_3$. Calculated, %: C 73.79; H 5.73; N 9.56.

General procedure for the preparation of 4-(2-phenyl-4-quinolylcarbamoyl)benzoates (16-21). In a flask with a capacity of 150 *ml*, a solution of acid chloride (0.046 *mol*) in 35 *ml* of dry benzene is placed. Then, with cooling, 0.061 *mol* of aminopropanol dissolved in 35 *ml* of dry benzene is gradually added dropwise. Next, the mixture is boiled in a water bath for 6-7 *hours*, after cooling, it is treated with a saturated solution of potassium

carbonate. The benzene layer is separated, and the aqueous is extracted with benzene (3×50 *ml)*. The combined extracts are dried over sodium sulfate. Benzene is distilled off, the residue is an oily substance, crystallizes, recrystallized from a mixture of absolute ethanol and DMF (15: 5).

2-Dimethylaminoethyl-4-(2-phenyl-4-quinolylbenzamido)benzoate (16). Yield 69%, mp 173-175 °C, Rf 0.51. IR spectrum, ν, cm^{-1}: 3215 (NH); 1640 (NHC = O); 1711 (C = O). ^{1}H NMR spectrum, ppm: 1.00 t (6H, J 7.1 Hz, N[(CH_3)2]; 2.78 t (2H,, J 6.3 Hz, NCH_2); 4.31 t (2H, J 6.3 Hz, OCH_2) ; 7.44-7.61 m (4H, C_6H_4); 7.74-7.80m (1H, C_6H_4); 7.93-8.02 m (4H, C_6H_4); 8.12-8.16 m (2H, C_6H_4); 8.22 s (1H, = CH); 8.26-.8.31 m (1H, C_6H_4); 8.31-8.35 m (2H, C_6H_4); 10.88 s (1H, NH). Found, %: C 73.93; H 5.95; N 12.77. $C_{27}H_{25}N_3O_3$. Calculated, %: C 73.79; H 5.73; N 9.56.

N,N-Dimethyl-2-[(4-{2-phenyl-4-quinolylbenzamido}benzoyl)oxy] ethane-1-ammonium chloride (17). Yield 82%, mp 193-194°C, Rf 0.45. IR spectrum, ν, cm^{-1}: 1713 (C = O), 2365 (NH +). Found, %: C 68.11; H 5.44; N 8.81. $C_{27}H_{26}CIN_3O_3$. Calculated, %: C 68.13; H 5.46; N 8.83.

2-Diethylaminoethyl-4-(2-phenyl-4-quinolylbenzamido)benzoate (18). Yield 68%, mp 169-170°C, Rf 0.52. IR spectrum, ν, cm^{-1}: 3172 (NH); 1679 (NHC = O); 1716 (C = O). ^{1}H NMR spectrum, ppm: 1.06 t (6H, J 7.1 Hz, N [(CH_2CH_3)2]; 2.60 k (4H, J 7.1 Hz, N [(CH_2CH_3) 2]; 2.79 t (2H, J 6.3 Hz, NCH_2); 4.30 t (2H, J 6.3 Hz, OCH_2); 7.45-7.63 m (4H, C_6H_4); 7.75-7.81m (1H, C_6H_4); 7.94-8.01 m (4H, C_6H_4); 8.13- 8.17 m (2H, C_6H_4); 8.22 s (1H, = CH); 8.26-8.30 m (1H, C_6H_4); 8.32-8.36 m (2H, C_6H_4); 10.89 s (1H, NH). Found, %: C 73.93; H 5.95; N 12.77. $C_{29}H_{29}N_3O_3$. Calculated, %: C 74.50; H 6.25; N 8.99.

N,N-Diethyl-2-[(4-{2-phenyl-4-quinolylbenzamido}benzoyl)oxy]ethane-1-ammonium chloride (19). Yield 84%, mp. 197-199°C, Rf 0.55. IR spectrum, ν, cm^{-1}: 1722 (C = O), 2345 (NH +). Found, %: C 69.87; H 7.81; N 6.78. $C_{29}H_{30}CIN_3O_3$. Calculated,: C 69.88; H 7.82; N 6.79.

2-Dimethylamino-1-methylethyl-4-(2-phenyl-4-quinolylbenzamido)benzoate (20). Yield 71%, mp 163-165 °C, Rf 0.53. IR spectrum, ν, cm^{-1}: 3172 (NH); 1682 (NHC = O); 1776 (C = O). ^{1}H NMR spectrum, ppm: 1.54 d (3H, CH_3 CH, J 6.3 Hz); 2.88-2.89 both d (3H each, N (CH_3) 2, J 3.0 Hz); 3.47 dd (1H, CH_2, J1 14.0, J2 6.7, J3 2.3 Hz); 3.66 dd (1H, CH_2, J1 14.0, J2 9.2, J3 3.5 Hz); 4.16 dc (1H, OCH, J1 9.7, J2 6.3, J3 2.6 Hz); 7.44-7.61 m (4H, C_6H_4); 7.74-7.80 m (1H, C_6H_4); 7.93-8.02 m (4H, C_6H_4); 8.12-8.16 m (2H, C_6H_4); 8.22 s (1H, = CH); 8.26-8.8.31 m (1H, C_6H_4); 8.31-.8.35 m (2H, C_6H_4); 10.87 s (1H, NH). Found, %: C 74.11; H 6.01; N 9.21. $C_{28}H_{27}N_3O_3$. Calculated, %: C 74.15; H 6.00; N 9.26.

N,N-Dimethyl-2-[(4-{2-phenyl-4-quinolylbenzamido}benzoyl)oxy]propane-1-ammonium chloride (21). Yield 87%, mp 193-194°C, Rf 0.45. IR spectrum, ν, cm^{-1}: 1723 (C = O), 2345 (NH +). Found, %: C 68.62; H 5.71; N 8.56. $C_{28}H_{28}CIN_3O_3$. Calculated, %: C 68.64; H 5.72; N 8.58.

4-(2-ՖԵՆԻԼ-4-ՔԻՆՈԼԻԼԿԱՐԲԱՄՈԻԼ)ԲԵՆԶՈՅԱԿԱՆ ԹԹՎԻ ՆՈՐ ԱԾԱՆՑՅԱԼՆԵՐԻ ՍԻՆԹԵԶԸ ԵՎ ՀԱԿԱՄԱՆՐԷԱՅԻՆ ԱԿՏԻՎՈՒԹՅՈՒՆԸ

Ա. Ն. ԻՍԱԽԱՆՅԱՆ, Ա. Ա. ՀԱՐՈՒԹՅՈՒՆՅԱՆ, Ն. Ս. ՀԱՐՈՒԹՅՈՒՆՅԱՆ, Ա. Գ. ԱՌԱՔԵԼՅԱՆ, Ա. Ս. ՍԱՖԱՐՅԱՆ և Ա. Ա. ՇԱԽԱՏՈՒՆԻ

Որոշ առաջնային արոմատիկ ամինների և տեղակալված ալկիլամինների N-ացիլացման ռեակցիայի արդյունքում 4-(2-ֆենիլ)-4-(քինոլիլկարբամոյիլ)բենզոյական թթվի քլորանհիդրիդով սինթեզվել են նոր բենզամիդներ՝ N1-(տեղակալված ֆենիլ)-4-(2-ֆենիլ-4-քինոլիլկարբամոյիլ)-, N1-(տեղակալված ալկիլ)-4-(2-ֆենիլ-4-քինոլիլկարբամոյիլ)բենզամիդներ: O-Ացիլացմամբ սինթեզվել են 2-դիալկիլամինոալկիլ-4-(2-ֆենիլ-4-քինոլիլկարբամոյիլ)բենզոատներ և N,N-դիալկիլ-2-[(4-{2-ֆենիլ-4-քինոլիլբենզամիդո}բենզոյիլ)օքսի]էթան-, պրոպան-1-ամոնիումի քլորիդներ: Ուսումնասիրվել են միացությունների հակամանրէային ակտիվությունները գրամդրական ստաֆիլակոկկերի և գրամբացասական ցուպիկների նկատմամբ: Պարզվել է, որ N-ացիլացման արգասիքները թույլ հակամանրէային ակտիվություն են ցուցաբերում օգտագործված բոլոր շտամների նկատմամբ (d=10-14մմ): Երբ միացություններում բենզամի դային խումբը փոխարինվում է դիալկիլամինաալկիլային խմբով, հակամանրէային ակտի վությունը զգալիորեն մեծանում է (d = 16-22 մմ).

СИНТЕЗ И АНТИБАКТЕРИАЛЬНАЯ АКТИВНОСТЬ НОВЫХ ПРОИЗВОДНЫХ 4-(2-ФЕНИЛ-4-ХИНОЛИЛКАРБАМОИЛ)БЕНЗОЙНОЙ КИСЛОТЫ

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В результате реакции N-ацилирования хлорангидридом 4-(2-фенил-4-хинолилкарбамоил)бензойной кислоты некоторых первичных ароматических аминов и замещенных алкиламинов получены новые бензамиды – N1-(замещенные фенил)-4-(2-фенил-4-хинолилкарбамоил), N1-(замещенные алкил)-4-(2-фенил-4-хинолилкарбамоил)бензамиды. О-Ацилированием получены 2-диалкил аминоалкил-4-(2-фенил-4-хинолилкарбамоил)бензоаты и N,N-диалкил-2-[(4-{2-фенил-4-хинолил бензамидо}бензоил)окси]этан-, пропан-1-аммониум хлориды. Установлено, что продукты N-ацилирования проявляют слабую противомикробную активность в отношении всех использованных штаммов(d=10-14 *мм*). При замене бензамидной группировки на диалкиламиноалкильную активность соединений значительно повышается (d=16-22 *мм*).

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ՀԱՅԱՍՏԱՆԻ ՀԱՆՐԱՊԵՏՈՒԹՅԱՆ ԳԻՏՈՒԹՅՈՒՆՆԵՐԻ
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SYNTHESIS OF N-TERT-BUTYLOXYCARBONYLGLYCYL-(*S*)-β-[4-ALLYL-3-PROPYL-5-THIOXO-1,2,4-TRIAZOL-1-YL]-α-ALANINE DIPEPTIDE AND STUDY OF ITS ANTIFUNGAL EFFECT

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A new undescribed in the literature N-t-butyloxycarbonylglycyl-(*S*)-β-[4-allyl-3-propyl-5-thioxo-1,2,4-triazol-1-yl]-α-alanine dipeptide has been synthesized by the method of activated esters.

To obtain comparative data on antifungal effect, the synthesized dipeptide and the initial amino acids (*S*)-β-[4-allyl-3-propyl-5-thioxo-1,2,4-triazol-1-yl]-α-alanine and glycine were studied *in vitro*. 3 Fungi strains were selected for the study: *Aspergillus fumigatus* MDC 8403, *Aspergillus candidus* MDC 10556, *Penicillium chrysogenum* MDC 8281. They were provided by the Microbial Depository Center of the Scinetific and Production Center "Armbiotechnology" of NAS RA.

The study showed that the initial protein and non-protein amino acids did not exhibit antifungal effect, while the synthesized dipeptide suppressed the growth of the selected strains. Concentration-dependent subsequent experiments showed that with the increase in peptide concentration the inhibitory effect enhanced.

Figs. 3, references 6.

Despite the fact that peptides have been studied in various fields of chemistry and medicine for decades, interest in peptides remains topical today.

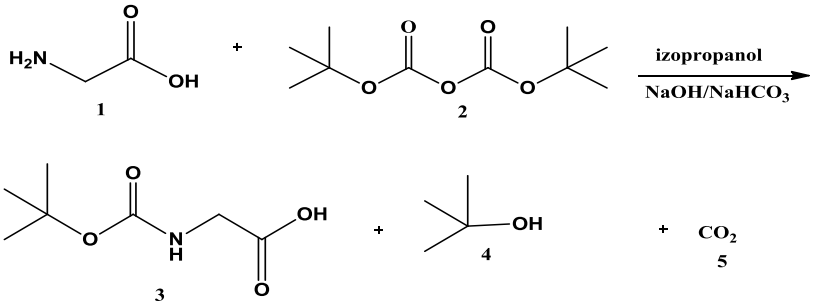
Peptides are pharmacologically active compounds used in the treatment of various diseases starting from diabetes to tumors [1-2].

It is worth mentioning that the number of peptides containing non-protein amino acids is high among both well-known drugs and new tested compounds [3].

However, there are almost no data on peptide-nature drugs with antifungal effect. Thus, taking into account the efficacy [4] of the triazole ring containing compounds among antifungal drugs, a new undescribed in the literature N-t-butyloxycarbonylglycyl-(*S*)-β-[4-allyl-3-propyl-5-thioxo-1,2,4-triazol-1-yl]-α-alanine dipeptide, which contains a triazole ring in its structure, has been synthesized by us. We have also studied the antifungal effect of the synthesized dipeptide.

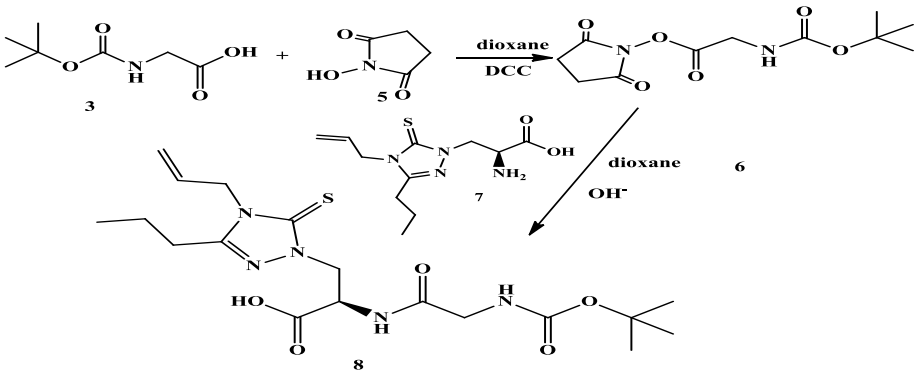
The peptide synthesis was carried out by the method of activated esters in a solution. The method is distinguished by its simplicity and possibility to obtain final products with good yields and high purity [5]. At the first stage, N-t-butyloxycarbonylglycine was obtained using di-tert-butyl pyrocarbonate in an alkaline aqueous-organic medium (Scheme 1).

Scheme 1



At the next stage, from N-t-butyloxycarbonylglycine (3) using dicyclohexylcarbodiimide, succinimide ester (6) was obtained, which by condensation with a non-protein amino acid in an alkaline aqueous-organic medium was converted to the corresponding dipeptide – N-t-butyloxycarbonylglycyl-(*S*)-β-[4-allyl-3-propyl-5-thioxo-1,2,4-triazol-1-yl]-α-alanine (8) (Scheme 2).

Scheme 2



The next stage related to study of the effects of the initial amino acids, including glycine, (*S*)-β-[4-allyl-3-propyl-5-thioxo-1,2,4-triazol-1-yl]-α-alanine and that of the synthesized dipeptide N-t-butyloxycarbonylglycyl-(*S*)-β-[4-allyl-3-propyl-5-thioxo-1,2,4-triazol-1-yl]-α-alanine.

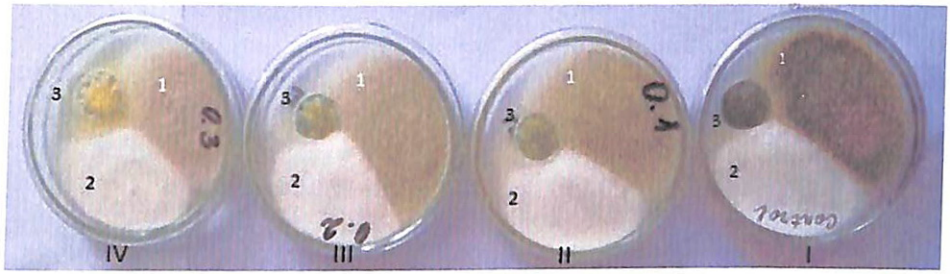


Fig. 1. I-control, II-0.1 ml, III-0.2 ml, IV-0.2 ml solution of N-t-butyloxycarbonylglycyl-(*S*)-β-[4-allyl-3-propyl-5-thioxo-1,2,4-triazol-1-yl]-α-alanine. 1- *Aspergillus fumigatus* MDC 8403, 2- *Aspergillus candidus* MDC 10556, 3- *Penicillium chrysogenum* MDC 8281.

The objects of the study were 3 strains of fungi from the National Culture Collection of Microorganisms of MDC: *Aspergillus fumigatus* MDC 8403, *Aspergillus candidus* MDC 10556, *Penicillium chrysogenum* MDC 8281.

The study has shown that the synthesized dipeptide suppresses the growth of strains, whereas the initial amino acids do not affect the growth of strains.

At the next stage, different concentrations of the synthesized dipeptide were tested, the results are shown in Fig. 1.

As follows from the Figure, when adding the studied dipeptide to the nutrient medium, suppression of sporulation and partial growth are observed in test fungi compared with the control, strengthening with the increase in concentration of dipeptide.

Experimental Part

^{1}H NMR spectra were recorded on Varian "Mercury 300VX" with an operating frequency of 300.08 *MHz* in a DMSO-D_6/CCl_4 1/3 solution using the method of double resonance. TLC was performed on "Silufol UV-254" plates in a mixture of chloroform-ethyl acetate-methanol (4:4:1), and the developer was chlorotoluidine. The elemental analysis was performed on an elemental CNS-O "Euro EA3000" analyzer.

HPLC analysis of the dipeptide was carried out on a "Waters 2695 Separations Module" liquid chromatographer (USA) with a "Waters 2487" ultraviolet detector using a stationary phase "AltimaC 18", 5 μm, 250×4.6 *mm*; elution was performed in an isocratic mode; as a mobile phase A: 0.15% TFA + H2O; B: 0.13% TFA + MeCN was used, the flow rate was 1 ml/min, detection was carried out at a wavelength of 210 *nm*, column temperature was 25°C, injection volume was 10 μl. Chemicals and eluents from "Sigma-Aldrich" were used with a purity of > 99.9% (gradient grade for HPLC).

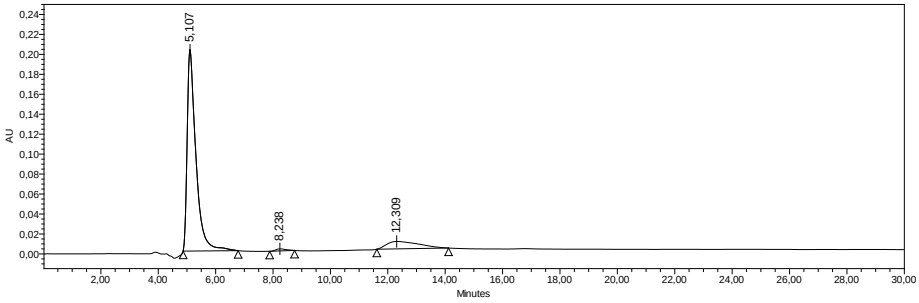
An optically pure non-protein amino acid was provided by the researchers of the Laboratory of Asymmetric Synthesis.

Obtaining of N-t-butyloxycarbonylglycine (3) was carried out by the method of **[6]**. TLC analysis was in the chloroform-ethyl acetate-methanol system – 2:4:1. Yield of product **3** – 70%, mp – 95-96^{o}C.

Synthesis of N-t-butyloxycarbonylglycyl-(S)-β-[4-allyl-3-propyl-5-thioxo-1,2,4-triazol-1-yl]-α-alanine dipeptide (8). 0.48 *g* (2.32 *mmol*) of dicyclohexyl-carbodiimide, previously dissolved in 32 *ml* of dioxane was added to a solution of 0.35 *g* (2 *mmol*) of N-t-butyloxy-carbonylglycine and 0.25 *g* (2.2 *mmol*) of N-hydroxysuccinimide in a mixture of 5.4 *ml* of dioxane and 2 *ml* of methylene chloride at 0°C. The reaction mixture was stirred for ~2 *hrs* at 0°C and left in the refrigerator overnight. TLC analysis [SiO_2, $CHCl_3$/ethyl acetate/CH_3OH (2:4:1), developer chlorotoluidine]. The residue formed was filtered off, the solvent was distilled off on a rotary evaporator, and the precipitate was crystallized from isopropyl alcohol. Yield 0.38 *g* (71%). The obtained succinimide ester was used at the next stage for the synthesis of N-t butyloxycarbonyl tripeptide.

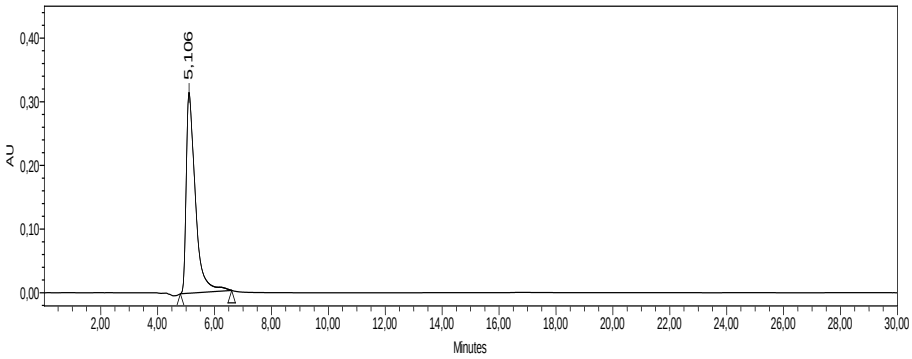
In a flat-bottomed flask with a magnetic stirrer, 0.381 *g* (1.41 *mmol*) of (*S*)-β-[4-allyl-3-propyl-5-thioxo-1,2,4-triazol-1-yl]-α-alanine, 2.8 *ml* (1.4 *mmol*) of 0.5M sodium hydroxide solution (NaOH) and 0.089 *g* (1.07 *mmol*) of baking soda ($NaHCO_3$) were mixed. At room temperature, 0.365 *g* (1.34 *mmol*) of N-t-butyloxycarbonylglycine succinimide in 4 ml of dioxane was added, the reaction mixture was stirred for 6 *hrs* and left overnight. The next day, 10 *ml* of ethyl acetate and 3 *ml* of 10% citric acid were added to the contents of the flask. After vigorous stirring, the organic layer was separated, and the aqueous layer was twice extracted with ethyl acetate (6 *ml* each). The organic layer was dried with anhydrous sodium sulfate, then the solvent was evaporated to dryness. The viscous residue was dissolved by heating in a mixture of 10 *ml* of hexane and 3 *ml* of ethyl acetate and left overnight. The white precipitate was filtered off on a nutsche filter, washed successively with 2 *ml* of ethyl acetate, after which the peptide was dried at a temperature of 65°C. TLC analysis [SiO_2, $CHCl_3$/ethyl acetate/CH_3OH (2:4:1), developer – chlorotoluidine]. Product yield 0.4 g (70%). Found, %: C 50.11; H 6.75; N 16.31. $C_{18}H_{29}N_5O_6S$. Calculated, %: C 50.57; H 6.84; N 16.38. ^{1}H NMR Spectrum, δ, ppm Hz: 1.00 (3H, t, J=7.4, $\underline{CH_3}$), 1.41 (9H, s, Me_3), 1.73 (2H, sx, J=7.4, $\underline{CH_2}CH_3$), 2.57 (2H, t, J=7.4, $\underline{CH_2}C_2H_5$), 3.54 (2H, br.d, J=5.5, $\underline{CH_2}NH$), 4.30 (1H, dd, J=13.6, 8.3, $\underline{CH_2}CH$), 4.52 (1H, dd, J=13.6, 4.8, $\underline{CH_2}CH$), 4.62 (2H, dt, J=5.1, 1.5, CH_2All), 4.72 (1H, td, J=8.3, 4.8, $\underline{CH}CH_2$), 5.08 (1H, dtd, J=17.2, 1.5, 1.0, $=CH_2$), 5.19 (1H, dtd, J=10.5 1.5, 1.0, $=CH_2$), 5.86 (1H, ddt, J=17.2 10.5, 5.1, =CH), 6.28 (1H, br.t, J=5.5, $NHCH_2$), 7.79 (1H, br.d, J=8.3, NHCH).

The chemical purity of the synthesized dipeptide was also studied by HPLC. The chromatograms are shown below in Figures 3, 4.



Name	Retention Time	Area	% Area	Height
N-t-Boc-Gly-(*S*)-β-[4-allyl-3-propyl-5-thioxo-1,2,4-triazol-1-yl]-α-Ala	5,107	4277543	87,15	202276
N-t-Boc-Gly-OSu	8,238	51141	1,04	2090
N-t-Boc-Gly	12,309	579505	11,81	7456

Fig. 2. Chromatogram of N-t-Boc-Gly-(*S*)-β-[4-allyl-3-propyl-5-thioxo-1,2,4-triazol-1-yl]-α-Ala dipeptide after crystallization.



Name	Retention Time	Area	% Area	Height
N-t-Boc-Gly-(*S*)-β-[4-allyl-3-propyl-5-thioxo-1,2,4-triazol-1-yl]-α-Ala	5,106	7151078	100,00	315864

Fig. 3. Chromatogram of N-t-Boc-Gly-(*S*)-β-[4-allyl-3-propyl-5-thioxo-1,2,4-triazol-1-yl]-α-Ala dipeptide after final crystallization.

As follows from the graphs, the dipeptide synthesized at the first stage after crystallization contained side compounds, the peaks of which corresponded to N-t-butyloxy-carbonylglycine and N-t-BOC-glycyl-succinimide ester peaks. This was proved by the HPLC analysis of the mentioned compounds. Subsequent recrystallization made it possible to purify the target peptide.

Study of antifungal effect. The objects of the study were 3 strains of fungi from the National Culture Collection of Microorganisms of MDC: *Aspergillus fumigatus* MDC 8403, *Aspergillus candidus* MDC 10556, *Penicillium chrysogenum* MDC 8281.

For the study, an aqueous suspension of fungal spores, obtained after 14 days of growth, was used. Suspensions were added to a 40°C Chapek agar medium and poured into Petri dishes.

0.1M solution of the dipeptide dissolved in DMSO was added per 0.1, 0.2, 0.3 *ml* to 20 *ml* Chapek agar medium cooled to 37-38^{o}C and poured into Petri dishes. After cooling, test fungi were inoculated with an injection. The control was fungi inoculated on a dipeptide-free Chapek agar medium in the presence of DMSO.

To evaluate antifungal activity, the studied compound was applied to a solid nutrient Chapek medium with a fungi culture. Dishes were incubated at a temperature of 28°C for 5-7 days.

The research results were expressed by visual assessment of the inhibition of fungal growth by amino acids. The control was the growth of fungi without adding amino acids.

This study was supported by the ISTC A-2209.

N-ՏՐԵՏԲՈՒՏՕՔՍԻԿԱՐԲՈՆԻԼԳԼԻՑԻԼ-(S)-β-[4-ԱԼԻԼ-3-ՊՐՈՊԻԼ-5-ԹԻՕՔՍՈ-1,2,4-ՏՐԻԱԶՈԼ-1-ԻԼ]-α-ԱԼԱՆԻՆԻ ԴԻՊԵՊՏԻԴԻ ՍԻՆԹԵԶԸ ԵՎ ՀԱԿԱՄԱՆԿԱՅԻՆ ԱԶԴԵՑՈՒԹՅԱՆ ՀԵՏԱԶՈՏՈՒՄԸ

Տ. Հ. ՍԱՐԳՍՅԱՆ, Յու. Մ. ԴԱՆՂՅԱՆ, Ս. Մ. ՋԱՄԳԱՐՅԱՆ, Է. Ա. ԳՅՈՒԼՈՒՄՅԱՆ, Ն. Ս. ԽԱՉԱՏՈՒՐՅԱՆ, Ս. Ա. ԳԵՎՈՐԳԱՅԱՆ, Հ. Ի. ՀԱԿՈԲՅԱՆ, Զ. Զ. ՄԱՐԴԻՅԱՆ և Ա. Ս. ՍԱՂՅԱՆ

Սինթեզվել է N-տրետբուտօքսիկարբոնիլգլիցիլ-(S)-β-[4-ալիլ-3-պրոպիլ-5-թիօքսո-1,2,4-տրիազոլ-1-իլ]-α-ալանին նոր, գրականության մեջ չնկարագրված, դիպեպտիդ՝ կիրառելով ակտիվացված էսթերների եղանակը:

Իրականցվել է սինթեզված դիպեպտիդի և համեմատական տվյալներ ստանալու ակնկալիքով ելային ամինաթթուների (S)-β-[4-ալիլ-3-պրոպիլ-5-թիօքսո-1,2,4-տրիազոլ-1-իլ]-α-ալանինի և գլիցինի հակասնկային ազդեցության in vitro հետազոտում: Ուսումնասիրման համար ընտրվել են 3 սնկային շտամները՝ Aspergillus fumigatus MDC 8403, Aspergillus candidus MDC 10556, Penicillium chrysogenum MDC 8281, որոնք ձեռք են բերվել Հայաստանի մանրէների ավանդադրման կենտրոնից:

Հետազոտության արդյունքում բացահայտվել է, որ ելային ամինաթթուները չեն ցուցաբերել հակասնկային ազդեցություն, իսկ սինթեզված դիպեպտիդը ճնշել է ընտրված շտամերի աճը: Հետագա փորձարկումները կախված կոնցենտրացիայից ցույց են տվել, որ պեպտիդի կոնցենտրացիայի մեծացումը բերում է արգելակիչ ազդեցության մեծացմանը:

СИНТЕЗ N-ТРЕТБУТИЛОКСИКАРБОНИЛ-(S)-β-[4-АЛЛИЛ-3-ПРОПИЛ-5-ТИОКСО-1,2,4-ТРИАЗОЛ-1-ИЛ]-α-АЛАНИН ДИПЕПТИДА И ИССЛЕДОВАНИЕ ЕГО АНТИГРИБКОВОГО ДЕЙСТВИЯ

Т. О. САРГСЯН, Ю. М. ДАНГЯН, С. М. ДЖАМГАРЯН, Э. А. ГЮЛУМЯН, Н. А. ХАЧАТУРЯН, С. А. ГЕВОРГЯН, Е. И АКОПЯН, З.З. МАРДИЯН и А. С. САГЯН

Методом активированных эфиров синтезирован не описанный в литературе дипептид N-трет-бутилоксикарбонилглицил-(*S*)-β-[4-аллил-3-пропил-5-токсо-1,2,4-триазол-1-ил]-α-аланина.

Осуществлено исследование *in vitro* антигрибкового действия синтезированого дипептида и исходных аминокислот (*S*)-β-[4-аллил-3-пропил-5-токсо-1,2,4-триазол-1-ил]-α-аланина и глицина.

Объектами исследования служили 3 штамма грибов из Национальной коллекции культур микроорганизмов Армении; *Aspergillus fumigatus* MDC 8403, *Aspergillus candidus* MDC 10556, *Penicillium chrysogenum* MDC 8281.

Результаты исследования выявили, что исходные аминокислоты не проявляют антигрибкового действия, а синтезированный дипептид подавляет рост выделенных штаммов по сравнению с контролем. Было также отмечено подавление спороношения и частично роста грибков, усиливающееся с повышением концентрации дипептида в питательной среде.

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ՀԱՅԱՍՏԱՆԻ ՀԱՆՐԱՊԵՏՈՒԹՅԱՆ ԳԻՏՈՒԹՅՈՒՆՆԵՐԻ
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НАЦИОНАЛЬНАЯ АКАДЕМИЯ НАУК РЕСПУБЛИКИ АРМЕНИЯ
NATIONAL ACADEMY OF SCIENCES OF THE REPUBLIC OF ARMENIA

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INTERACTION OF ACETOACETIC ACID ARYLAMIDES WITH ETHOXYMETHYLIDENEMALONONITRILE. SYNTHESIS OF 5-ACETYL-1-ARYL-2-AMINO-6-OXO-1,6-DIHYDROPYRIDINE-3-CARBONITRILES

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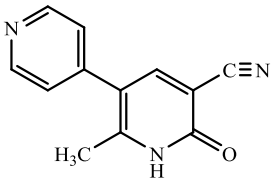
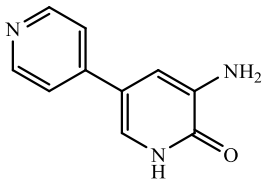
It has been shown that the interaction of acetoacetic acid arylamides with ethoxymethylidenemalononitrile proceeds in absolute ethanol in the presence of triethylamine at room temperature, and according to NMR and IR spectroscopy, affords 5-acetyl-1-aryl-2-amino-1,6-dihydropyridine-3-carbonitriles in 57-78% yields.

References 9.

The intensive development of chemistry of pyridones and their analogues led to the creation of numerous derivatives interesting from the point of view of synthetic organic chemistry. Among pyridine derivatives, cyano- and amino derivatives, which possess a wide spectrum of biological activity, occupy a special place. Thus, Milrinon, Amrinon [1] and their analogs [2-4] are cardiotonic agents for the treatment of cardiac insufficiency. Some 2-pyridones have been reported to have antitumor [5] and antibacterial [6] activities.



Milrinone WIN47203

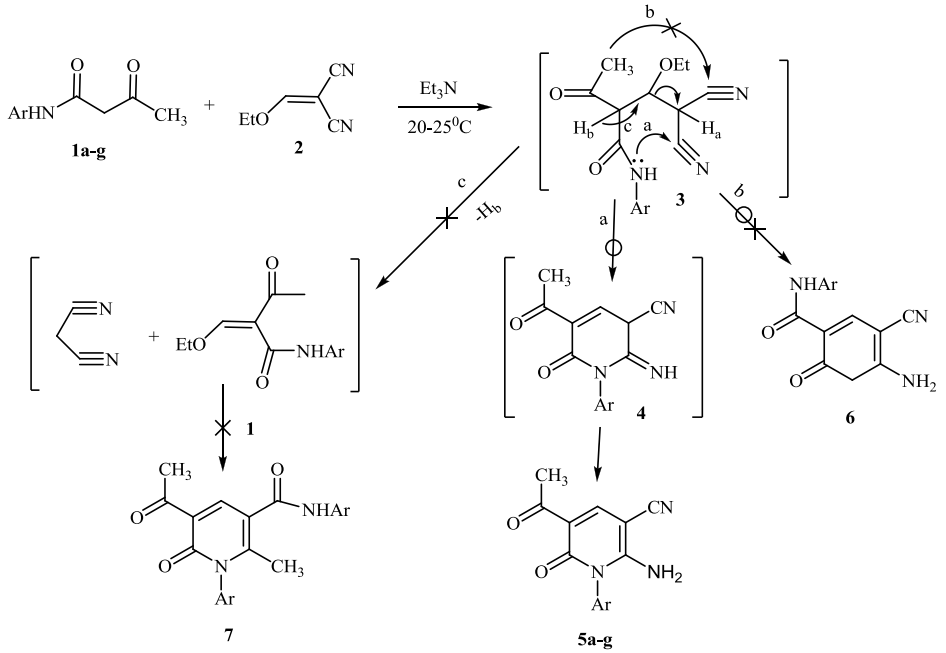


Amrinone WIN 40680

Recently, we have established that the interaction of ethoxymethylidene-cyanoacetic ester with arylamides of acetoacetic acid proceeds in the presence of triethylamine or sodium ethoxide. At the same time, the resulting Michael intermediate adduct undergoes azacyclization involving mainly the cyano group, forming ethyl 5-acetyl-1-aryl-6-hydroxy-2-imino-1,2-dihydropyridine-3-carboxylates [7].

In this work, we studied the interaction of acetoacetic acid arylamides **1** with ethoxymethylidenemalononitrile **2** in order to detect the regioselectivity of intramolecular cyclization of the intermediate Michael reaction adduct, that is, to find which of the functional groups, amide- (path **a**) or acetyl- (path **b**) will participate in cyclization as a nucleophile. It should be noted that this adduct, in addition to cyclization, can theoretically undergo the retro-Michael reaction [8] (path **c**, Scheme).

Scheme



Ar=C_6H_5 (**a**), 4-$CH_3C_6H_4$ (**b**), 4-$NO_2C_6H_4$ (**c**), 2-$CH_3C_6H_4$ (**d**), 3-$CH_3C_6H_4$ (**e**), 4-$CH_3OC_6H_4$ (**f**), 2-$CH_3OC_6H_4$ (**g**).

Experiments have shown that this interaction occurs in the presence of triethylamine at room temperature, and the resulting intermediate adduct (**3**), according to NMR and IR spectroscopy, undergoes azacyclization (path **a**), forming 5-acetyl-1-aryl-2-amino-6-oxo-1,6-dihydropyridine-3-carbonitriles (**5a-g**), with yields of 57-78%. It should be noted that no compounds which could be formed via paths **b** and **c** were found in the reaction products.

The antibacterial activity of the synthesized compounds **5b-f** was studied by the agar diffusion with a bacterial load of 20 million microbial cells per 1 ml of medium on gram-positive staphylococci (Staphylococcus aureus 209p., Bacilus

subtilis) and gram-negative bacilli (Sh. Flexnezi; 6858, E. Coli subure); 55) [9]. Studies have shown that compounds **5b-f** exhibit weak activity.

Thus, we have found a new efficient method for the synthesis of previously unknown 5-acetyl-1-aryl-2-amino-6-oxo-1,6-dihydropyridine-3-carbonitriles by reacting acetoacetic acid arylamides with ethoxymethylidenemalononitrile in the presence of triethylamine at room temperature.

Experimental part

The IR spectra were recorded on a "Nicolet Avatar 330 FT-IR" spectrophotometer in vaseline oil. The ^{1}H and ^{13}C NMR spectra were obtained on a Varian "Mercury 300VX" instrument with operating frequencies of 300.077 and 75 *MHz*, solvent — DMSO-d-CCl_4 (1: 3), internal standard — TMS. Melting points are determined on the "Boëtius" table.

General procedure for the synthesis of 5-acetyl-1-aryl-2-amino-6-oxo-1,6-dihydropyridine-3-carbonitriles 5a-g. An absolute ethanol solution of 1.5 *mmol* of compounds **1** and **2** in the presence of a catalytic amount of triethylamine is left for 3 days at room temperature. The precipitated crystals are filtered off, washed with absolute ether and recrystallized from absolute ethanol.

5-Acetyl-2-amino-6-oxo-1-phenyl-1,6-dihydropyridine-3-carbonitrile (5a). Yield 0.29 *g* (78%), mp 260ºC. IR spectrum, ν, cm^{-1}: 3449, 3196 (NH_2), 2222 (CN), 1686 (CO), 1652 (CON). ^{1}H NMR spectrum, δ, ppm: 2.39 (s, 3H, CH_3); 7.20-7.25 (m, 2H, orto-C_6H_5); 7.36 (m, 2H, NH_2); 7.49-7.62 (m, 3H, meta, para-C_6H_5); 8.17 (s, 1H, =CH). ^{13}C NMR spectrum, δ_C, ppm: 29.8 (CH_3); 73.1 (<u>C</u>CN); 112.9; 116.1 (CN); 128.2 (2·CH, Ph); 129.1 (CH, Ph); 129.8 (2·CH, Ph); 134.2 (Cipso, Ph); 146.2 (CH); 157.4; 159.8, 192.0 (CO). Found, %: C 66.12; H 4.51; N 16.82. $C_{14}H_{11}N_3O_2$. Calculated, %: C 66.40; H 4.38; N 16.59.

5-Acetyl-2-amino-6-oxo-1-*p*-tolyl-1,6-dihydropyridine-3-carbonitrile (5b). Yield 0.29 *g* (68%), mp 259ºC. IR spectrum, ν, cm^{-1}: 3308, 3187 (NH_2), 2212 (C≡N), 1662 (CO), 1640 (CON). ^{1}H NMR spectrum, δ, ppm: 2.39 (s, 3H, $COCH_3$); 2.47 (s, 3H, CH_3); 7.07-7.12 (m, 2H, C_6H_4); 7.28 (m, 2H, NH_2); 7.36-7.41 (m, 2H, C_6H_4); 8.16 (s,1H, =CH). ^{13}C NMR spectrum, δ_C, ppm: 20.8 (CH_3); 29.9 (CO<u>C</u>H_3); 73.1 (<u>C</u>CN); 113.0; 116.1 (CN); 127.9 (2·CH); 130.5 (2·CH); 131.5, 138.7, 146.1 (CH); 157.5, 159.9, 192.2 (CO). Found, %: C 67.05; H 4.72; N 15.91. $C_{15}H_{13}N_3O_2$. Calculated, %: C 67.40; H 4.90; N 15.72.

5-Acetyl-2-amino-1-(4-nitrophenyl)-6-oxo-1,6-dihydropyridine-3-carbonitrile (5c). Yield 0.29 *g* (66%), mp 350ºC. IR spectrum, ν, cm^{-1}: 3417, 3187 (NH_2), 2213 (CN), 1672 (CO), 1632 (CON). ^{1}H NMR spectrum, δ, ppm: 2.39 (s, 3H, CH_3); 7.51-7.56 (m, 2H, C_6H_4); 7.76 (m, 2H, NH_2); 8.18 (s, 1H, =CH); 8.37-8.42 (m, 2H, C_6H_4,). ^{13}C NMR spectrum, δ_C, ppm: 29.8 (CH_3); 73.5 (<u>C</u>CN); 112.5; 115.9 (CN); 125.0 (2·CH); 130.3 (2·CH); 140.3,146.6 (=CH); 148.1, 157.2, 159.7, 191.8 (CO). Found, %: C 56.04; H 3.52; N 18.98. $C_{14}H_{10}N_4O_4$. Calculated, %: C 56.38; H 3.38; N 18.78.

5-Acetyl-2-amino-6-oxo-1-o-tolyl-1,6-dihydropyridine-3-carbonitrile (5d). Yield 0.3 *g* (75%), mp 170ºC. IR spectrum, v, cm^{-1}: 3316, 3187 (NH_2), 2218 (C≡N), 1690 (CO), 1632 (CON). ^{1}H NMR spectrum, δ, ppm: 2.10 (s, 3H, CH_3); 2.40 (s, 3H, $COCH_3$); 7.09-7.15 (m, 1H, C_6H_4); 7.35 (m, 2H, NH_2); 7.35-7.46 (m, 3H, C_6H_4); 8.18 (s,1H, =CH). ^{13}C NMR spectrum, δ_C, ppm: 16.6 (CH_3); 29.8 ($CO\underline{C}H_3$); 73.0 ($\underline{C}CN$); 112.8; 116.0 (CN); 127.4 (CH); 128.1 (CH); 129.3 (CH); 131.3 (CH); 133.2, 135.6, 146.3 (=CH); 157.0, 159.3, 192.0 ($\underline{C}OCH_3$). Found, %: C 67.11; H 4.71; N 15.98. $C_{15}H_{13}N_3O_2$. Calculated, %: C 67.40; H 4.90; N 15.72.

5-Acetyl-2-amino-6-oxo-1-m-tolyl-1,6-dihydropyridine-3-carbonitrile (5e). Yield 0.23 *g* (57%), mp 230ºC. IR spectrum, v, cm^{-1}: 3306, 3189 (NH_2), 2225 (C≡N), 1655 (CO), 1619 (CON). ^{1}H NMR spectrum, δ, ppm, *Hz*: 2.39 (s, 3H, $COCH_3$); 2.45 (br.d, 3H, CH_3); 6.98-7.03 (m, 2H, C_6H_4), (5,6); 7.32 (m, 2H, NH_2); 7.30-7.34 (m, 1H, C_6H_4), (3); 7.46 (td, 1H,J=7.6, 0.6, C_6H_4), (4); 8.15 (s, 1H, =CH). ^{13}C NMR spectrum, δ_C, ppm: 20.8 (CH_3); 29.8 ($CO\underline{C}H_3$); 73.0 ($\underline{C}CN$); 112.9; 116.0 (CN); 125.0 (CH); 128.6 (CH); 129.5 (CH); 129.8 (CH); 134.0, 139.5, 146.1 (=CH); 157.3, 159.8, 192.0 ($\underline{C}OCH_3$). Found, %: C 67.15; H 4.61; N 16.01. $C_{15}H_{13}N_3O_2$. Calculated, %: C 67.40; H 4.90; N 15.72.

5-Acetyl-2-amino-1-(4-methoxyphenyl)-6-oxo-1,6-dihydropyridine-3-carbonitrile (5f). Yield 0.32 *g* (76%), mp 240ºC. IR spectrum, v, cm^{-1}: 3440, 3136 (NH_2), 2214 (C≡N), 1688 (CO), 1661(CON). ^{1}H NMR spectrum, δ, ppm: 2.39 (s, 3H, CH_3); 3.88 (s, 3H, OCH_3); 7.06-7.15 (m, 4H, C_6H_4); 7.32 (m, 2H, NH_2); 8.15 (s, 1H, =CH). ^{13}C NMR spectrum, δ_C, ppm: 29.9 (CH_3); 54.9 (OCH_3); 73.0 ($\underline{C}CN$); 112.9; 115.2 (2·CH); 116.1 (CN); 126.4; 129.3 (2·CH); 146.0 (=CH); 157.8, 159.7, 160.0, 192.2 ($\underline{C}OCH_3$). Found, %: C 63.25; H 4.42; N 15.07. $C_{15}H_{13}N_3O_3$. Calculated, %: C 63.60; H 4.63; N 14.83.

5-Acetyl-2-amino-1-(2-methoxyphenyl)-6-oxo-1,6-dihydropyridine-3-carbonitrile (5g). Yield 0.31 *g* (74%), mp 209ºC. IR spectrum, v, cm^{-1}: 3454, 3176 (NH_2), 2214 (C≡N), 1709 (CO), 1640 (CON). ^{1}H NMR spectrum, δ, ppm, *Hz*: 2.39 (s, 3H, CH_3); 3.83 (s, 3H, OCH_3); 7.08-7.14 (m, 2H, C_6H_4); 7.18 (br.d, d 1H, J=8.4, C_6H_4); 7.36 (m, 2H, NH_2); 7.49 (ddd,1H, J=8.4, 5.5, 3.7, C_6H_4); 8.16 (s, 1H, =CH). ^{13}C NMR spectrum, δ_C, ppm: 29.8 (CH_3); 55.4 (OCH_3); 72.9 ($\underline{C}CN$); 112.7 (CH); 116.2, 121.0 (CH); 122.2, 129.4 (CH); 130.8 (CH); 146.3 (CH); 154.6, 157.4, 159.4, 192.2. Found, %: C 63.25; H 4.49; N 15.13. $C_{15}H_{13}N_3O_3$. Calculated, %: C 63.60; H 4.63; N 14.83.

ԱՑԵՏՕՔՍԱՑԱԽԱԹԹՎԻ ԱՐԻԼԱՄԻԴՆԵՐԻ ՓՈԽԱԶԴԵՑՈՒԹՅՈՒՆԸ ԷԹՕՔՍԻՄԵԹԻԼԻԴԵՆՄԱԼՈՆՈՆԻՏՐԻԼԻ ՀԵՏ: 5-ԱՑԵՏԻԼ-1-ԱՐԻԼ-2-ԱՄԻՆՈ-6-ՕՔՍՈ-1,6-ԴԻՀԻԴՐՈՊԻՐԻԴԻՆ-3-ԿԱՐԲՈՆԻՏՐԻԼՆԵՐԻ ՍԻՆԹԵԶ

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Ցույց է տրվել, որ ացետոքացախաթթվի արիլամիդների փոխազդեցությունը էթօքսիմեթիլիդենմալոնոնիտրիլի հետ ընթանում է բացարձակ էթանոլում, տրիէթիլամինի ներկայությամբ, սենյակային ջերմաստիճանում: Հետևանքով ՄՄՌ և ԻԿ սպեկտրոսկոպիայի տվյալների, առաջացնում են 5-ացետիլ-1-արիլ-2-ամինո-6-օքսո-1,6-դիհիդրոպիրիդին-3-կարբոնիտրիլներ 57-78% ելքով: Վերջիններիս առաջացումը ցույց է տալիս, որ նախ փոխազդեցության ընթացքում գոյացած միջանկյալ ադուկտի ցիկլացման ժամանակ որպես նուկլեոֆիլ հանդես է գալիս միայն ամիդային խմբավորումը: Երկրորդ՝ ցիկլացման ընթացքում գոյացած պիրիդինի իմինային ածանցյալը, ռեակցիայի պայմաններում, վեր է ածվում ենամինային տաուտոմերի: Հարկ է ավելացնել, որ նշված պայմաններում, փոխազդեցության միջանկյալ ադուկտի մասնակցությամբ ընթացող Միքայելի ռետրո-ռեակցիայի արգասիքներ չեն գոյանում:

Հակամանրէային ուսումնասիրությունները ցույց են տվել, որ սինթեզված միացությունները ցուցաբերում են թույլ ակտիվություն:

ВЗАИМОДЕЙСТВИЕ АРИЛАМИДОВ АЦЕТОУКСУСНОЙ КИСЛОТЫ С ЭТОКСИМЕТИЛИДЕНМАЛОНОНИТРИЛОМ. СИНТЕЗ 5-АЦЕТИЛ-1-АРИЛ-2-АМИНО-6-ОКСО-1,6-ДИГИДРОПИРИДИН-3-КАРБОНИТРИЛОВ

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Показано, что взаимодействие ариламидов ацетоуксусной кислоты с этоксиметилиденмалононитрилом протекает в абсолютном этаноле в присутствии триэтиламина при комнатной температуре. Согласно данным ЯМР и ИК спектроскопии, образуются 5-ацетил-1-арил-2-амино-1,6-дигидропиридин-3-карбонитрилы с выходами 57-78%. Образование последних показывает, что при циклизации образующегося промежуточного аддукта в качестве нуклеофила выступает только амидная группа. В процессе циклизации образующееся иминопроизводное пиридина в условиях реакции превращается в енаминный таутомер. Следует добавить, что продукты ретро-реакции Михаэля с участием промежуточного аддукта в данных условиях не образуются.

Исследования показали, что синтезированные соединения проявляют слабую антибактериальную активность.

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ՀԱՅԱՍՏԱՆԻ ՀԱՆՐԱՊԵՏՈՒԹՅԱՆ ԳԻՏՈՒԹՅՈՒՆՆԵՐԻ
ԱԶԳԱՅԻՆ ԱԿԱԴԵՄԻԱ
НАЦИОНАЛЬНАЯ АКАДЕМИЯ НАУК РЕСПУБЛИКИ АРМЕНИЯ
NATIONAL ACADEMY OF SCIENCES OF THE REPUBLIC OF ARMENIA

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SYNTHESIS AND STUDY OF ANTIOXIDANT ACTIVITY OF 5,7-DIALKYLDIAZAADAMANTANES CONTAINING CARBOXYLIC ACID FRAGMENTS

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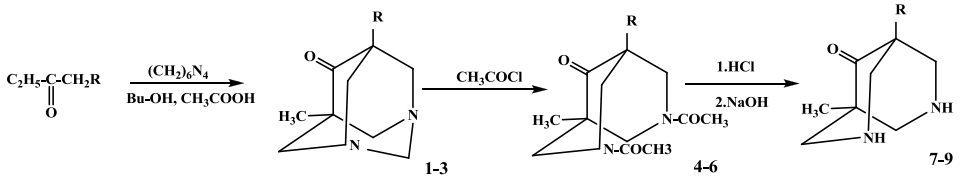
For the first time, 9-oxo-1-methyl-5-ethyl-(5-propyl-, 5-butyl)-3,7-diazabicyclo/3.3.1/-nonanes were synthesized. By condensation of the latter and 9-hydroxy-1,5-(dimethyl-, diethyl-, dipropopyl-, dibutyl)-3,7-diazabicyclo/3.3.1/nonanes with pyruvic or levulinic acid, new 2-substituted diazaadamantanes containing a carboxyl group were obtained. According to the results of biological tests, some compounds of this series have weak antioxidant activity.

References 7.

Our early works were devoted to the synthesis and study of the biological activity of some 2-substituted diazaadamantanes containing aromatic or aliphatic substituents at the 5th and 7th positions of the adamantane ring [1-4]. It was of interest to synthesize diazabicyclononanes with various radicals in these positions, such as methylethyl, methylpropyl and methylbutyl **7-9**. The synthesis was carried out according to Scheme 1.

Scheme 1



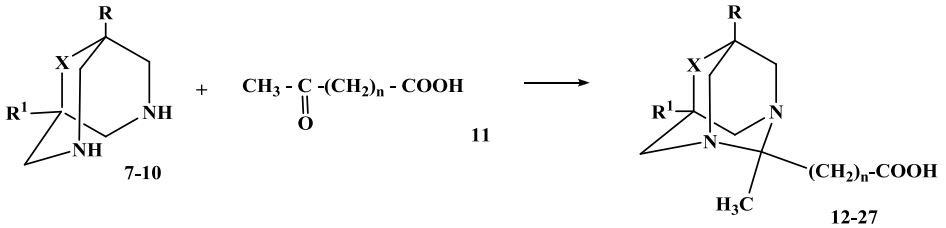
R = C_2H_5, C_3H_7, C_4H_9

Mannich reaction from ethylpropyl, ethylbutyl, ethylpentylketones, urotropine in butanol in the presence of acetic acid gave diazaadamantanes **1-3**, which were further converted by diacetyl chloride to diacetyl derivatives **4-6**. By acid hydrolysis and further alkaline treatment of **4-6,** 1-methyl-5-ethyl-, 1-

methyl-5-propyl-, 1-methyl-5-butyl-9-oxo-3,7-diazabicyclo/3.3.1/- nonanes **7-9** were synthesized**.**

The combination of compounds of the adamantane series with acid fragments is of great interest for the synthesis of new derivatives of various types. The antimicrobial and antibacterial activity of these compounds is known [5]. However, in the literature there are no data on diazadamantane acids. For the synthesis of such compounds, 5,7-dialkyl-substituted diazabicyclononanes **7-10** (compound **10** was obtained by reducing the keto group in the corresponding bicyclononanes with sodium borohydride) were condensed with pyruvic or levulinic acid. As a result, compounds **12-27** containing an acid fragment in the second position of the diazaadamantane ring were obtained (Scheme 2).

Scheme 2



X = O, R = R^1 = CH_3, n = 0 (12); R = R^1 = CH_3, n = 2 (13); R = R^1 = C_2H_5, n = 0 (14); R = R^1 =C_2H_5, n = 2 (15); R = CH_3, R^1 = C_2H_5, n = 2 (16); R = CH_3, R^1 = C_3H_7, n = 2 (17); R = R^1 = C_3H_7, n = 0 (18); R = R^1 = C_3H_7, n = 2 (19); R = CH_3, R^1 = C_4H_9, n = 2 (20); R = R^1 = C_4H_9, n = 2 (21); R = R^1 =iso-C_3H_7, n = 0 (22); X = OH, R = R^1 = CH_3, n = 2 (23); R = R^1 = C_2H_5, n = 0 (24); R = R^1 = C_2H_5, n = 2 (25); R = R^1 = C_3H_7, n = 2 (26); R = R^1 = C_6H_5, n = 2 (27).

The structure of the synthesized compounds was confirmed by elemental analysis, IR, ^1H and ^{13}C NMR spectra.

The antioxidant activity of the synthesized compounds was studied in rat brain tissue homogenates in experiments *in vitro* according to the method [6,7]. Lipid peroxidation was evaluated in a non-enzymatic lipid peroxidation system by the yield of one of the final products of malondialdehyde (MDA), which was determined by the ratio of the density of the studied substances to the control, expressed as a percentage. A sample with induced lipid peroxidation was used as a control.

Studies showed that the studied compounds did not exhibit a noticeable antioxidant effect. The highest activity was detected in compound **27** at a concentration of 10^{-3} M. The degree of influence of the latter led to inhibition of the lipid oxidation process in the form of a decrease in MDA by 28% ($P < 0.05$) compared to the control. A similar, but less pronounced effect was found in compounds **24** and **25** by 14, 18.5%, respectively, at the same concentration. The remaining compounds did not have a significant antioxidant effect. The data obtained indicate that among the studied compounds, only compounds having a

hydroxyl group in the diazaadamantane fragment exhibit a weak antioxidant effect.

Experimental part

IR spectra were recorded on a "Nicolet Avatar 330 FT-IR" spectrometer from samples dispersed in mineral oil. The ^{1}H and ^{13}C NMR spectra were recorded on a Varian "Mercury-300VX" instrument at 303 *K* with a frequency of 300.078 and 75.46 *MHz*, respectively. In the assignment of signals, the methods of double resonance, DEPT and HMQC were used. Chemical shifts are given in ppm relative to the internal TMS for DMSO-d_6/CCl_4 1/3 solutions. The course of the reactions and the purity of the substances were controlled using thin-layer chromatography on "Silufol UV-254" plates using propanol-water (7:3) as eluent, spots were visualized by treatment with iodine vapor.

General procedure for the preparation of 5-methyl-7-ethyl, 5-methyl-7-propyl, 5-methyl-7-butyl-6-oxo-1,3-diazaadamantane (1-3). A mixture of 10 *mmol* of the corresponding ketone, 7.6 *mmol* of urotropine, 30 *ml* of n-butanol and 10 *ml* of acetic acid is boiled for 3 *h*. Butanol is then distilled off, the residue is recrystallized from hexane.

5-Methyl-7-ethyl-6-oxo-1,3-diazaadamantane (1). Yield 1.6 *g* (81%), R_f 0.42, mp 70-71°C. IR-spectrum, ν, cm^{-1}: 1710 (C = O). ^{1}H NMR spectrum, δ, ppm, *Hz*: 0.78-0.88 m (6H, 2×CH_3); 1.28 dd (2H, J = 5.8, 5.9 CH_2CH_3); 2.88 dd (4H, J = 7.0, 1.4, 2×NCH_2); 3.21 dd (4H, J = 13.8, 1.2, 2×NCH_2); 3.98 s (2H, NCH_2). Found, %: C 68.15; H 9.35; N 14.28. $C_{11}H_{18}N_2O$. Calculated, %: C 68.05; H 9.27; N 14.43.

5-Methyl-7-propyl-6-oxo-1,3-diazaadamantane (2). Yield 1.6 *g* (78%), R_f 0.41, mp 74-75°C. IR-spectrum, ν, cm^{-1}: 1710 (C=O). ^{1}H NMR spectrum, δ, ppm, *Hz*: 0.76-0.87 m (6H, 2×CH_3); 1.26 dd (4H, J = 5.9, 7.1 $CH_2CH_2CH_3$); 2.86 dd (4H, J = 7.1, 4.2, 2×NCH_2); 3.25 dd (4H, J = 13.8, 1.2, 2×NCH_2); 4.01 s (2H, NCH_2). Found, %: C 70.98; H 9.16; N 12.61. $C_{12}H_{20}N_2O$. Calculated, %: C 70.90; H 9.09; N 12.72.

5-Methyl-7-butyl-6-oxo-1,3-diazaadamantane (3). Yield 1.6 *g* (80%), R_f 0.47, mp 61°C. IR-spectrum, ν, cm^{-1}: 1708 (C = O). ^{1}H NMR spectrum, δ, ppm, *Hz*: 0.80-0.91 m (6H, 2×CH_3); 1.32 dd (6H, J = 7.1, 2.4, 3×CH_2); 2.84 dd (4H, J = 8.1, 2.4, 2×NCH_2); 3.26 dd (4H, J = 12.5, 2.4, 2×NCH_2); 4.01 s (2H, NCH_2). Found, %: C 70.80; H 9.17; N 12.63. $C_{13}H_{22}N_2O$. Calculated, %: C 70.91; H 9.10; N 12.73.

General procedure for the preparation of 1-methyl-5-ethyl (propyl, butyl)-9-oxo-3,7-diacetyldiazabicyclo/3.3.1/nonanes (4-6). To a solution of 9 *mmol* of the correspondingadamantane 1-3 in a mixture of 50 *ml* of benzene and 20 *ml* of water with stirring, 25 *mmol* of acetyl chloride is added dropwise at room temperature. The benzene layer is separated, washed with water, dried over $MgSO_4$ and distilled off. The residue is recrystallized from acetone.

1-Methyl-5-ethyl-9-oxo-3,7-diacetyldiazabicyclo/3.3.1/nonane (4). Yield 1.8 *g* (68%), R_f 0.61, mp 161°C. IR-spectrum, ν, cm^{-1}: 1637 (N-C = O). 1715 (C

= O). ^{1}H NMR spectrum, δ, ppm, *Hz*: 0.98 dd (6H, J = 6.9, 2.4 2×CH_3); 1.52 q (2H, CH_2); 2.05 s (6H, 2×$COCH_3$); 2.66 br.d (2H, J = 12.5, NCH_2); 3.34 ddd (2H, J = 5.8, 2.4, 1.2, NCH_2); 4.05 dd (2H, J = 5.9, 2.4, NCH_2); 4.96 ddd (2H, J = 5.8, 2.4, 1.2, NCH_2). ^{13}C NMR spectrum, ppm: 7.3 (2×CH_3); 15.9 (CH_2); 20.9 (CH_2); 23.2 (CH_2); 45.2 (CH_2); 47.3 (CH_2); 50.3 (C*); 52.3 (C*); 54.9 (C*); 56.8 (C*); 168.3 (C); 168.4 (C*); 210.7 (C*). Found, %: C 63.27; H 8.41; N 10.38. $C_{14}H_{22}N_3O_3$. Calculated, %: C 63.15; H 8.31; N 10.50.

1-Methyl-5-propyl-9-oxo-3,7-diacetyldiazabicyclo/3.3.1/nonane (5). Yield 2.1 *g* (77.7%), R_f 0.62, mp 168°C. IR-spectrum, ν, cm^{-1}: 1637 (N-C = O). 1715 (C = O). ^{1}H NMR spectrum, δ, ppm, *Hz*: 0.88-096 m (6H, 2×CH_3); 1.54 dd (4H, J = 5.8, 5.9, 2×CH_2); 2.1 s (6H, 2×$COCH_3$); 2.64 d (2H, J = 12.8, NCH_2); 3.32 ddd (2H, J = 5.8, 2.4, 1.2, NCH_2); 4.1 ddd (2H, J = 5.8, 5.9, 1.4, NCH_2); 4.98 ddd (2H, J = 5.8, 2.4, 1.2, 2×NCH_2). Found, %: C 67.72; H 9.20; N 9.68. $C_{16}H_{24}N_2O_3$. Calculated, %: C 67.6; H 9.11; N 9.80.

1-Methyl-5-butyl-9-oxo-3,7-diacetyldiazabicyclo/3.3.1/nonane (6). Yield 2.0 *g* (70.4%), R_f 0.63, mp 168°C (acetone). IR-spectrum, ν, cm^{-1}: 1637 (N-C = O). 1715 (C = O). ^{1}H NMR spectrum, δ, ppm, *Hz*: 0.86-094 m (6H, 2×CH_3); 1.58 dd (6H, J = 5.8, 5.9, 3×CH_2); 2.24 s (6H, 2×$COCH_3$); 2.68 br.d (2H, J = 12.9, NCH_2); 3.31 ddd (2H, J = 5.8, 2.4, 1.2, NCH_2); 4.2 ddd (2H, J = 5.8, 5.9, 1.4, NCH_2); 4.96 ddd (2H, J = 5.8, 2.4, 1.2, NCH_2). Found, %: C 65.42; H 8.96; N 9.38. $C_{16}H_{26}N_3O_3$. Calculated, %: C 65.3; H 8.80; N 9.5.

General procedure for the preparation of 1-methyl-5-(ethyl, propyl, butyl)-9-oxo-3,7-diazabicyclo/ 3.3.1 /nonane (7-9). 5 *mmol* of diacetyl **(4-6)** and 25 *ml* of 4N HCL are boiled for 5 *h*. After cooling, the precipitated crystals are filtered off, dissolved in a small amount of ice water, and neutralized with NaOH to pH 9, after cooling, the precipitate is filtered, washed with a small amount of ice water and recrystallized from ethyl acetate. 1,5-Dimethyl-(dipropyl-, diethyl-, -diphenyl)-9-hydroxy-3,7-diazabicyclo /3.3.1/nonanes **10** were obtained according to the procedure [3].

1-Methyl-5-ethyl-9-oxo-3,7-diazabicyclo/3.3.1/nonane (7). Yield 1.2 *g* (82%), R_f 0.32, mp 40-41°C. IR-spectrum, ν, cm^{-1}: 1715 (C = O), 3354 (NH). ^{1}H NMR spectrum, δ, ppm, *Hz*: 0.78 s (3H, CH_3); 0.82 t (3H, J = 7.1, CH_2CH_3); 1.31 q (2H, CH_2CH_3, J = 8.1, NCH_2); 2.78 br.d (4H, J = 12.5, 2×NCH_2); 3.01 br.s (2H, NH); 3.35 ddd (2H, J = 5.8, 5.9, 1.4, 2×NCH_2). Found, %: C 66.05; H 9.70; N 15.30. $C_{10}H_{18}N_2O$. Calculated, %: C 65.93; H 9.80; N 15.38.

1-Methyl-5-propyl-9-oxo-3,7-diazabicyclo/3.3.1/nonane (8). Yield 1.5 *g* (76.3%), R_f 0.33, mp 71-72°C. IR-spectrum, ν, cm^{-1}: 1697 (C = O), 3354 (NH). ^{1}H NMR spectrum, δ, ppm, *Hz*: 0.74 s (3H, CH_3); 0.88 s (3H, CH_3); 1.22 br.s (4H, 2×CH_3); 2.76 dd (4H, J = 5.9, 2.4, 2×NCH_2); 2.90 br.s (2H, 2×NH); 3.28 br.d (2H, J = 12.5, NCH_2). ^{13}C NMR spectrum, ppm: 14.8 (2×CH_3); 16.0 (CH_2); 17.0 (CH_2); 33.9 (2×C*); 48.8 (CH_2); 51.1 (CH_2); 59.1 (CH_2); 61.2 (CH_2); 213.7 (C*). Found, %: C 67.50; H 10.28; N 14.35. $C_{11}H_{20}N_2O$. Calculated, %: C 67.34; H 10.20; N 14.43.

1-Methyl-5-butyl-9-oxo-3,7-diazabicyclo/3.3.1/nonane (9). Yield 1.4 *g* (67.3%), R_f 0.35, mp 56-58°C. IR-spectrum, ν, cm^{-1}: 1696 (C = O), 3352 (NH). ^{1}H NMR spectrum, δ, ppm, *Hz*: 0.76 s (3H, CH_3); 0.91 s (3H, J = 7.0, CH_3); 1.11-1.36 m (6H, 3×CH_2); 2.77 br.d (2H, J = 12.5, NCH_2); 2.78 br.d (2H, J = 12.5, NCH_2); 2.90 br.s (2H, 2×NH); 3.20 br.d (2H, J = 12.8, NCH_2). 3.28 br.d (2H, J = 12.5, NCH_2). ^{13}C NMR spectrum, ppm: 13.6 (CH_3); 17.0 (CH_2); 23.2 (CH_2); 25.0 (CH_2); 31.3 (C*); 48.8 (2×CH_2); 50.9 (C*); 59.1 (2×CH_2); 61.3 (2×CH_2); 213.8 (C*). Found, %: C 69.31; H 10.64; N 13.40. $C_{14}H_{22}N_2O$. Calculated, %: C 69.23; H 10.57; N 13.46.

General production procedure (12-29). To a water-alcohol solution (1:1) of 5 *mmol* of the corresponding diazabicyclo/3.3.1/nonane **7-9**, a solution of 5 *mmol* of levulinic or pyruvic acid in 10 *ml* of water is added. The mixture is stirred for 1 *h* and left overnight. The solution is evaporated in vacuo, the remaining mass is triturated with ethyl acetate and recrystallized from a mixture of isopropanol:benzene 1:1.

2-Carboxy-2,5,7-trimethyl-6-oxo-1,3-diazaadamanane (12). Yield 1.8 *g* (75.8%), R_f 0.38, mp 232-233°C (isopropanol:benzene 1:1). IR-spectrum, ν, cm^{-1}: 1704 (C = O); 1983 (C = Acid); 3490 (OH Acid). ^{1}H NMR spectrum, δ, ppm, *Hz*: 0.78-1.02 m (6H, 2×CH_3); 1.32 d (2H, J = 5.9, NCH_2); 1.86-2.06 m (2H, NCH_2); 2.68-2.82 m (4H, 2×NCH_2); 3.21-3.48 m (3H, CH_3); 5.62 br.s (1H, COOH). Found, %: C 60.60; H 7.58; N 11.65. $C_{12}H_{18}N_2O_3$. Calculated, %: C 60.50; H 7.50; N 11.76.

2-Carboxyethyl-2,5,7-trimethyl-6-oxo-1,3-diazaadamanane (13). Yield 1.8 *g* (67.7%), R_f 0.41, mp 231-232°C (ethyl acetate). IR-spectrum, ν, cm^{-1}: 1708 (C = O); 1985 (C = Acid); 2490 (OH Acid). ^{1}H NMR spectrum, δ, ppm, *Hz*: 0.82 s (3H, CH_3); 0.83 s (3H, CH_3); 1.47 s (3H, CH_3); 2.16-2.31 m (4H, 2×CH_2); 2.63-2.71 m (4H, NCH_2); 3.59-3.67 m (4H, NCH_2); 11.63 br.s (1H, COOH). Found, %: C 63.26; H, 8.39; N 10.38. $C_{14}H_{22}N_2O_3$. Calculated, %: C 63.15; H 8.27; N 10.52.

2-Carboxy-2-methyl-5,7-diethyl-6-oxo-1,3-diazaadamanane (14). Yield 1.9 *g* (71.4%), R_f 0.43, mp 240-241°C (ethyl acetate). IR-spectrum, ν, cm^{-1}: 1718 (C = O); 3365 (OH acid). ^{1}H NMR spectrum, δ, ppm, *Hz*: 0.82-0.96 m (6H, 2×CH_3); 1.22-1.38 m (4H, 2×NCH_2); 1.62 s (3H, CH_3); 2.78-2.87 m (4H, 2×NCH_2); 3.42 br.d (2H, J = 12.6, NCH_2); 3.58 br.s.d (2H, J = 13.3, NCH_2); 4.46 br.s (1H, COOH). Found, %: C 63.27; H 8.15; N 10.40. $C_{14}H_{22}N_2O_3$. Calculated, %: C 63.15; H 8.2; N 10.51.

2-Carboxyethyl-2-methyl-5,7-diethyl-6-oxo-1,3-diazaadamanane (15). Yield 2.1 *g* (71.5%), R_f 0.43, mp 187-188°C (isopropanol:methanol 1:1). IR-spectrum, ν, cm^{-1}: 1704 (C = O); 2490 (COOH). ^{1}H NMR spectrum, δ, ppm, *Hz*: 0.84 d (6H, J = 7.0, 2×CH_3); 1.22-1.38 m (4H, 2×NCH_2); 1.42 s (3H, CH_3); 2.20 dd (2H, J = 13.9, 2.4, CH_2); 2.28 dd (2H, J = 13.3, 2.4, CH_2); 2.66 dd (4H, J = 8.0, 7.1, NCH_2); 3.62 d (4H, J = 5.9, 2×CH_2); 11.61 br.s (1H, COOH). Found, %: C 65.43; H 8.95; N 9.40. $C_{16}H_{26}N_2O_3$. Calculated, %: C 65.31; H 8.84; N 9.52.

2-Carboxyethyl-2,5-dimethyl-7-ethyl-6-oxo-1,3-diazaadamanane (16). Yield 2 *g* (72.1%), R_f 0.33, mp 188-189°C (ethyl acetate:methanol 1:1). IR-spectrum, ν, *cm* $^{-1}$: 1710 (C = O); 3595 (OH). ^{1}H NMR spectrum, δ, ppm, *Hz*: 0.84-0.98 m (6H, 2×CH_3); 1.32 d (2H, CH_2CH_3); 1.41 s (3H, CH_3); 2.32 dd (4H, J = 13.9, 15.9, 2×CH_2); 2.70 dd (4H, J = 13.8, 12.9, 2×NCH_2); 3.62 dd (4H, J = 12.4, 12.5, 2×NCH_2); 4.36 br.s (1H, COOH). ^{13}C NMR spectrum, ppm: 7.2 (CH_3); 15.6 (CH_3); 21.6 (CH_3); 23.1 (C*); 28.3 (CH_2); 30.7 (C*); 44.4 (CH_2); 45.5 (CH_2); 45.7 (CH_2); 46.6 (CH_2); 56.8 (CH_2); 57.5 and 58.9 (CH_2); 72.2 (C*); 174.2 (COOH); 209.1 (C*). Found, %: C 80.47; H 8.65; N 10.11. $C_{15}H_{24}N_2O_3$. Calculated, %: C 80.35; H 8.57; N 10.0.

2-Carboxyethyl-2,5-dimethyl-6-oxo-7-propyl-1,3-diazaadamanane (17). Yield 2 *g* (68%), R_f 0.38, mp 192-193°C (isopropanol:methanol 1:1). IR-spectrum, ν, *cm*$^{-1}$: 1704, 1983 (C = O); 2490 (OH). ^{1}H NMR spectrum, δ, ppm, *Hz*: 0.82 m (3H, CH_3); 0.91 s (3H, CH_3); 1.36 br.s (4H, 2×CH_2); 1.41 s (3H, CH_3); 2.18-2.31 m (4H, 2×CH_2); 2.61-2.74 m (4H, 2×NCH_2); 5.59-5.67 m (4H, 2×NCH_2); 11.62 br.s (1H, COOH). ^{13}C NMR spectrum, ppm: 14.61 (CH_3); 15.6 (CH_3); 15.7 (CH_3); 21.5 (CH_2); 21.6 (CH_2); 28.3 (C*); 30.6 (C*); 43.7 (CH_2); 44.4 (CH_2); 45.8 (CH_2); 46.7 (CH_2); 57.2 (CH_2); 59.7 (CH_2); 72.1 (C*); 174.5 (COOH); 208.9 (C*). Found, %: C 65.46; H 8.97; N 9.41. $C_{16}H_{26}N_2O_3$. Calculated, %: C 65.32; H 8.84; N 9.52.

2-Carboxy-2-methyl-5,7-dipropyl-6-oxo-1,3-diazaadamanane (18). Yield 2.1 *g* (68.2%), R_f 0.35, mp 202-203°C (ethyl acetate:methanol 1:1). IR-spectrum, ν, *cm*$^{-1}$: 1644, 1718 (C = O); 3365 (OH). ^{1}H NMR spectrum, δ, ppm, *Hz*: 0.81-1.08 m (6H, 2×CH_3); 1.1-1.42 m (9H, 3×CH_2, CH_3); 1.62 s (0.6H) and 1.85 s (1.4H, CH_2); 2.78-2.86 m (4H, 2×NCH_2); 3.25-3.58 m (4H, 2×NCH_2); 6.5 br.s (1H, COOH). Found, %: C 65.50; H 8.98; N 9.43. $C_{16}H_{26}N_2O_3$. Calculated, %: C 65.35; H 8.85; N 9.52.

2-Carboxyethyl-2-methyl-6-oxo-5,7-dipropyl-1,3-diazaadamanane (19). Yield 2.2 *g* (68.3%), R_f 0.34, mp 219-220°C (ethyl acetate:methanol 1:1). IR-spectrum, ν, *cm*$^{-1}$: 1697.1980 (C = O); 3365 (OH acid). ^{1}H NMR spectrum, δ, ppm, *Hz*: 0.96 s (6H, 2×CH_3); 1.18-1.38 m (8H, 4×CH_2); 1.41 s (3H, CH_3); 2.18 dd (2H, J = 13.9, 2.4, CH_2); 2.28 dd (2H, J = 13.3, 2.4, CH_2); 2.66 dd (4H, J = 5.8.5.9, 2×NCH_2); 3.62 d (4H, J = 5.9, 2×NCH_2); 11.62 br.s (1H, COOH). ^{13}C NMR spectrum, ppm: 14.6 (CH_3); 15.6 (CH_3); 15.7 (CH_3); 21.6 (CH_2); 28.2 (C*); 30.6 (C*); 32.9 (CH_2); 38.9 (CH_2); 39.5 (CH_2); 39.9 (CH_2); 40.0 (CH_2); 45.9 (CH_2); 46.8 (CH_2); 57.2 (CH_2); 57.8 (CH_2); 72.3 (C*); 174.1 (COOH); 208.8 (C*). Found, %: C 67.20; H 9.42; N 8.58. $C_{18}H_{30}N_2O_3$. Calculated, %: C 67.08; H 9.31; N 8.69.

2-Carboxyethyl-2,7-dimethyl-5-butyl-6-oxo-1,3-diazaadamanane (20). Yield 2.1 *g* (69.8%), R_f 0.42, m.p. 189-190°C (ethyl acetate:methanol 1:1). IR-spectrum, ν, *cm*$^{-1}$: 1645, 1710 (C = O); 3365 (OH acid). ^{1}H NMR spectrum, δ, ppm, *Hz*: 0.81 s (1.5H) and 0.82 s (1.5H, CH_3); 0.92 t (3H, J = 6.8, CH_3-Bu); 1.21-1.37 m (6H, 3×CH_2-Bu); 1.45 s (1.5H) and 1.46 s (1.5H, CH_3); 2.13-2.31 m (4H, CH_2CH_2); 2.61-2.72 m (4H, 2×NCH_2); 3.58-3.68 m (4H, 2×NCH_2);

11.78 br.s (1H, COOH). ^{13}C NMR spectrum, ppm: 13.6 (CH_3); 15.6 (CH_3); 21.5 (CH_2); 23.0 (CH_2); 24.4 (CH_2); 24.5 (CH_2); 28.2 (CH_2); 28.5 (C*); 30.3 (C*); 30.6 (C*); 44.4 (2×CH_2); 45.6 (CH_2); 57.8 (2×CH_2); 59.8 (2×CH_2); 72.1 (C*); 174.1 (COOH); 208.9 (C*). Found, %: C 69.07; H 9.30; N 7.95. $C_{17}H_{28}N_2O_3$. Calculated, %: C 68.96; H 9.19; N 8.04.

2-Carboxyethyl-2-methyl-6-oxo-5,7-dibutyl-1,3-diazaadamanane (21). Yield 2.4 *g* (69%), R_f 0.40, mp 193-194°C (ethyl acetate:methanol 1:1). IR-spectrum, ν, *cm*$^{-1}$: 1698.1980 (C = O); 3365 (OH acid). ^{1}H NMR spectrum, δ, ppm, *Hz*: 0.88 s (6H, 2×CH_3); 1.18-1.38 m (12H, 6×CH_2); 1.44 s (3H, CH_3); 2.20 dd (2H, J = 13.3, 2.4, CH_2); 2.28 dd (2H, J = 12.6, 2.4, NCH_2); 2.68 dd (4H, J = 5.8.5.9, 2×NCH_2); 3.61 d (4H, J = 5.9, 2×NCH_2); 11.62 br.s (1H, COOH). ^{13}C NMR spectrum, ppm: 13.5 (CH_3); 21.6 (CH_3); 23.0 (CH_3); 24.5 (CH_2); 24.6 (CH_2); 28.2 (CH_2); 30.3 (C*); 30.6 (C*); 38.9 (CH_2); 39.2 (CH_2); 40.05 (CH_2); 45.7 (CH_2); 46.6 (CH_2); 57.3 (CH_2); 57.9 (CH_2); 72.3 (CH_2); 95.5 (CH_2); 95.6 (CH_2); 174.1 (COOH); 208.8 (C*). Found, %: C 73.60; H 7.22; N 7.02. $C_{20}H_{34}N_2O_3$. Calculated, %: C 73.47; H 7.14; N 7.14.

5,7-Diisopropyl-2-carboxy-2-methyl-6-oxo-1,3-diazaadamantane (22). Yield 1.2 *g* (82%), R_f 0.31, mp > 300°C (DMF). IR-spectrum, ν, *cm*$^{-1}$: 1670, 1714 (C = O); 2600 (OH). ^{1}H NMR spectrum, δ, ppm, *Hz*: 0.84 d (6H, J = 7.0, 2×CH3-isopropyl); 0.91 d (6H, J = 7.0, 2×CH_3-isopropyl); 1.63 cc (3H, CH_3); 1.85 s (1H, J = 7.0, CH-isopropyl); 1.90 s (1H, J = 7.0, CH-isopropyl); 2.84 br.s (2H, J = 13.8, NCH_2); 2.90 br.d (2H, J = 13.6, NCH_2); 3.51-3.70 m (4H, 2×NCH_2); 4.25 br.s (1H, COOH). Found, %: C 65.50; H 9.00; N 9.36. $C_{16}H_{26}N_2O_3$. Calculated, %: C 65.35; H 8.86; N 9.52.

2-Carboxyethyl-6-hydroxy-2,5,7-trimethyl-1,3-diazaadamantane (23). Yield 1.7 *g* (75%), R_f 0.31, mp 286-287°C (isopropanol:methanol 1:1). IR-spectrum, ν, *cm*$^{-1}$: 2600 (OH); 3246 (COOH). ^{1}H NMR spectrum, δ, ppm, *Hz*: 0.64 s (6H, 2×CH_3); 1.31 s (3H, CH_3); 1.98-2.18 m (4H, 2×CH_2); 2.51 s (2H, NCH_2); 2.82-3.02 m (6H, 3×NCH_2); 3.33 t (2H, J = 12.8, CHOH); 8.76 br.s (1H, COOH). ^{13}C NMR spectrum, ppm: 19.87 (2×CH_3); 21.57 (CH_3); 29.08 (C*); 29.45 (CH_2); 30.4 (C*); 31.04 (CH_2); 51.09 (CH_2); 51.12 (CH_2); 57.06 (CH_2); 57.67 (CH_2); 79.3 (C*); 78.63 (CH); 175.20 (C*). Found, %: C 62.58; H 8.83; N 10.34. $C_{14}H_{24}N_2O_3$. Calculated, %: C 62.69; H 8.95; N 10.44.

2-Carboxy-2-methyl-5,7-diethyl-6-hydroxy-1,3-diazaadamantane (24). Yield 1.8 *g* (67.4%), R_f 0.31, mp 280-282°C (isopropanol:methanol 1:1). IR-spectrum, ν, *cm*$^{-1}$: 2600 (OH); 3246 (COOH). ^{1}H NMR spectrum, δ, ppm, *Hz*: 0.77-0.88 m (6H, 2×CH_3); 1.08-1.22 m (4H, 2×CH_2); 1.32 s (3H, CH_3); 1.96 dd (2H, J = 13.3, 2.4, NCH_2); 2.21 dd (2H, J = 13.3, 2.4, NCH_2); 2.78-3.02 m (4H, 2×NCH_2); 3.22-3.36 m (2H, CHOH); 4.46 br.s (1H, COOH). Found, %: C 72.08; H 7.78; N 11.33. $C_{14}H_{24}N_2O_3$. Calculated, %: C 71.96; H 7.91; N 11.44.

2-Carboxyethyl-2-methyl-5,7-diethyl-6-hydroxy-1,3-diazaadamantane (25). Yield 2.1 *g* (71.4%), R_f 0.41, mp 269-270°C (ethyl acetate:methanol 1:1). IR-spectrum, ν, *cm*$^{-1}$: 2600 (OH); 3245 (COOH). ^{1}H NMR spectrum, δ, ppm, *Hz*: 0.66-0.78 m (6H, 2×CH_3); 0.91-1.10 m (3H, CH_3); 1.13-1.28 m (4H,

2×CH_2); 2.01-2.38 m (6H, 3×CH_2); 2.8-3.06 m (5H, 2×CH_2, CH); 3.18-3.22 m (2H, NCH_2); 3.32 s (1H, OH); 4.8 br.s (1H, COOH). ^{13}C NMR spectrum, ppm: 5.93 (CH_3) and 5.96 (CH_3); 21.71 (CH_3); 25.2 (C*); 25.3, 29.26 (CH_2); 30.37 (C*); 31.08 (CH_2); 50.50 (CH_2); 51.13 (CH_2); 51.16 (CH_2); 53.93 (CH_2); 53.97 (CH_2); 54.59 (CH2); 72.79 (C*); 73.19 (CH); 95.4 (C*); 174.98 (COOH). Found, %: C 64.98; H 9.59; N 10.32. $C_{16}H_{28}N_2O_3$. Calculated, %: C 64.85; H 9.48; N 10.43.

2-Carboxyethyl-2-methyl-5,7-dipropyl-6-hydroxy-1,3-diazaadamantane (26). Yield 1.2 *g* (74%), R_f 0.3, mp 240-241°C (ethyl acetate:methanol 1:1). IR-spectrum, ν, cm^{-1}: 2600 (OH); 3240 (COOH). 1H NMR spectrum, δ, ppm, *Hz*: 0.81-0.98 m (6H, 2×CH_3); 1.18 d (4H, J = 12.8, 2×CH_2); 1.22-1.36 m (3H, CH_3); 1.88-2.14 m (2H, CH_2); 2.21 dd (2H, J = 12.8, 1.4, CH_2); 2.80-2.96 m (4H, 2×CH_2); 3.31 ss (8H, J = 13.9, 4×NCH_2); 3.38 s (2H, CHOH); 4.42 br.s (1H, COOH). Found, %: C 66.80; H 10.00; N 8.52. $C_{18}H_{32}N_2O_3$. Calculated, %: C 66.67; H 9.87; N 8.64.

2-Carboxyethyl-2-methyl-5,7-diphenyl-6-hydroxy-1,3-diazaadamantane (27). Yield 2.7 *g* (68.9%), R_f 0.31, mp 239-240°C (ethyl acetate:methanol 1:1). IR-spectrum, ν, cm^{-1}: 1603 (arom); 2600 (OH); 3245 (COOH). ^{1}H NMR spectrum, δ, ppm, *Hz*: 1.42 s (3H, CH_3); 2.1-2.54 m (6H, 2×CH_2, NCH_2); 2.62 dd (1H, J = 5.8, 5.9, OH); 3.45-3.65 m (6H, 3×NCH_2); 4.05 dd (1H, CH); 4.46 br.s (COOH); 7.12-7.38 m (10H, H-arom). Found, %: C 73.60; H 7.22; N 7.02. $C_{24}H_{28}N_2O_3$. Calculated, %: C 73.47; H 7.14; N 7.14.

ԿԱՐԲՈՆԱԹԹՈՒՆԵՐԻ ՖՐԱԳՄԵՆՏ ՊԱՐՈՒՆԱԿՈՂ 5,7-ԴԻԱԼԿԻԼԴԻԱԶԱԱԴԱՄԱՆՏԱՆՆԵՐԻ ՍԻՆԹԵԶԸ ԵՎ ՆՐԱՆՑ ՀԱԿԱՕՔՍԻԴԱՆՏԱՅԻՆ ՀԱՏԿՈՒԹՅՈՒՆՆԵՐԻ ՈՒՍՈՒՄՆԱՍԻՐՈՒԹՅՈՒՆԸ

Ա. Դ. ՀԱՐՈՒԹՅՈՒՆՅԱՆ, Ք. Ա. ԳԵՎՈՐԳՅԱՆ, Մ. Վ. ԳԱԼՍՏՅԱՆ, Ժ. Մ. ԲՈՒՆԻԱԹՅԱՆ և Հ. Ա. ՓԱՆՈՍՅԱՆ

Առաջին անգամ սինթեզվել են 3,7-դիազաբիցիկլո/3.3.1/նոնաններ, որոնք 1- և 5-դիրքերում ունեն տարբեր ալկիլ տեղակալիչներ՝ 1-մեթիլ-(5-էթիլ-, 5-պրոպիլ-, 5-բուտիլ): Սինթեզված դիազաբիցիկլոնոնանները կոնդենսվել են կետոթթուների՝ պիրոխաղողաթթվի կամ լևուլինաթթվի հետ: Արդյունքում ստացվել է դիազաադամանտանների նոր շարք, որտեղ 5- և 7-դիրքերում ալկիլ տեղակալիչներ են, 6-ում կետո, հիդրօքսիլ, իսկ 2-րդ դիրքում կարբոնաթթվային ֆրագմենտ:

Սինթեզված միացությունների կենսաբանական ուսումնասիրությունը ցույց է տվել, որ այս շարքի որոշ միացություններ ցուցաբերում են թույլ արտահայտված հակաօքսիդանտային ակտիվություն:

СИНТЕЗ И ИЗУЧЕНИЕ АНТИОКСИДАНТНОЙ АКТИВНОСТИ 5,7-ДИАЛКИЛДИАЗААДАМАНТАНОВ, СОДЕРЖАЩИХ ФРАГМЕНТЫ КАРБОНОВЫХ КИСЛОТ

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Реакцией Манниха впервые синтезированы смешанные 9-оксо-1-метил-(5-этил-, 5-пропил, 5-бутил-)-3,7-диазабицикло/3.3.1/нонаны. Конденсацией последних и 9-гидрокси--1,5-(диметил-, диэтил-, дипропил-, дибутил-)-3,7-диазабицикло/3.3.1/нонанов с пировиноградной или левулиновой кислотой синтезированы 16 новых 2-замещенных диазаадамантанов, содержащих фрагмент карбоновой кислоты.

Согласно результатам биологических испытаний, некоторые соединения этого ряда проявляют слабую антиоксидантную активность. Активны те соединения, в структуре которых находится гидроксильная группа в 6-ом положении адамантанового кольца.

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ՀԱՅԱՍՏԱՆԻ ՀԱՆՐԱՊԵՏՈՒԹՅԱՆ ԳԻՏՈՒԹՅՈՒՆՆԵՐԻ
ԱԶԳԱՅԻՆ ԱԿԱԴԵՄԻԱ
НАЦИОНАЛЬНАЯ АКАДЕМИЯ НАУК РЕСПУБЛИКИ АРМЕНИЯ
NATIONAL ACADEMY OF SCIENCES OF THE REPUBLIC OF ARMENIA

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ALKYLATION OF IMIDAZOLE WITH DICHLOROETHANE AND DEHYDROCHLORINATION OF THE IN-SITU OBTAINED 1-(2'-CHLOROETHYL)IMIDAZOLE TO 1-VINYLIMIDAZOLE IN AN AQUEOUS ALKALINE MEDIUM IN THE N-METHYLMORPHOLINE N-OXIDE SYSTEM USING PHASE TRANSFER CATALYST

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In this article, the possibility of applying phase transfer catalysis (PTC) in the N-methylmorpholine-N-oxide-water system for the alkylation of imidazole with dichloroethane was considered. It has been shown that the alkylation of imidazole with dichloroethane in the aforementioned system is accompanied by dehydrochlorination of the in situ obtained 1-(2'-chloroethyl)imidazole, which allows the synthesis of 1-vinylimidazole without the use of explosive acetylene.

References 21.

N-vinylazoles are an important class of azole derivatives that can form radical polymerization and copolymerization products [1-7]. Many vinylazole-based polymeric compounds exhibit biological activity and serve as effective drugs [8-10].

In [11-12] articles, we showed that the alkylation reaction of azoles in the NMO/H_2O system in comparison to various phase transfer catalysts was not inferior in reaction yields during phase transfer catalysis (PTC).

In this communication, the possibility of using phase transfer catalysis (PTC) in the N-methylmorpholine-N-oxide-water (NMO) system was considered.

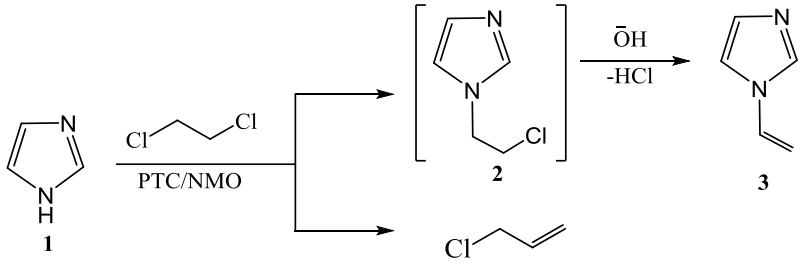
Further, our studies on the alkylation of imidazole (**1**) with dichloroethane using phase transfer catalysts (quaternary ammonium salts) in an aqueous solution of N-methylmorpholine-N-oxide (NMO/H_2O) were carried out.

According to published data, there are many examples of N-alkylation of imidazole (**1**) under PTC conditions [13-17], but there is no alkylation of imidazole with dichloroethane.

The need for development was dictated by the fact that 1-(2-chloroethyl)imidazole (**2**) is simultaneously an intermediate product in the synthesis of an important class of 1-vinylimidazole, on the other hand, 1-vinylimidazole and its derivatives are still obtained under acetylene pressure at a temperature of 130 °C and higher [18].

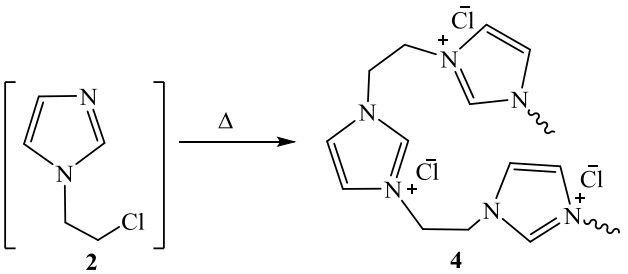
During the alkylation reaction of imidazole (**1**) with dichloroethane (^{1}H NMR spectroscopic control) in the PTC/NMO system, it has been found that in the absence of a base the alkylation reaction does not proceed, and in the presence of sodium hydroxide, alkylation is also accompanied by elimination of dichloroethane according to Scheme 1.

Scheme 1



It has been found that the basicity is the determining factor for the isolation of 1-(2'-chloroethyl)imidazole (**2**) from the reaction medium. The basicity of imidazole (**1**) upon proton addition is $_pk^a$=6.95, while the basicity value of pyrazole or 1,2,4-triazole is $_pk^a$=2.2-2.5 [19]. Therefore, the monoalkylation product of imidazole (**1**), in comparison with pyrazole or 1,2,4-triazole [20-21], undergoes intermolecular quaternization upon distillation with the formation of polysalt **4** according to Scheme 2.

Scheme 2



The presence of 1-(2'-chloroethyl)imidazole (**2**) in the reaction medium was proved by ^{1}H NMR spectroscopy. With an equimolar ratio of imidazole: sodium hydroxide and a five-fold excess of dichloroethane (DCE), the yield of compound **2** after three hours is 1.2 *g* (9.2%). The low yield of 1-(2'-chloroethyl)imidazole (**2**) is due to the fact that the relatively high basicity of

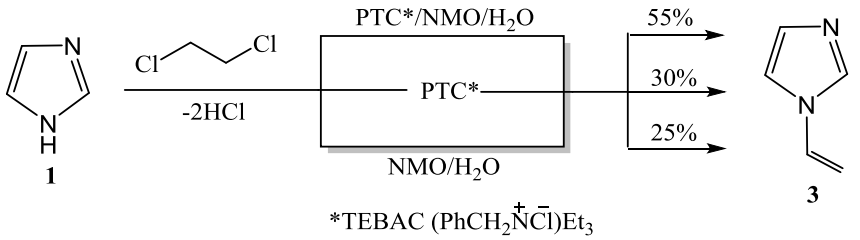
imidazole ($_pk^a$ 6.95) makes it difficult to deprotonate it under the influence of sodium hydroxide and the base is used to eliminate dichloroethane.

When a second portion of sodium hydroxide is added, the alkylation continues, at the same time the alkylated product is in-situ dehydrochlorinated to 1-vinylpyrazole (**3**), the elimination of dichloroethane continues parallel, therefore, both dichloroethane and sodium hydroxide must be taken in excess.

It has been experimentally found that the molar ratio of reagents – imidazole:NaOH:DCE is equal to 0.1:1.2:1.5, which within 7-8 hours provides 50-55% yield of 1-vinylimidazole (**3**) in the PTC/NMO/H_2O system.

Alkylation of imidazole (**1**) with dichloroethane and the dehydrochlorination of the in-situ obtained 1-(2'-chloroethyl)imidazole in an aqueous alkaline medium in the presence of NMO and PTC has also been studied (Scheme 3).

Scheme 3



Thus, it has been shown that PTC can be successfully used compatible with an aqueous solution of NMO during alkylation reactions.

The study was carried out at the Russian-Armenian University at the expense of the funds allocated under the subsidy of the Ministry of Education and Science of Russia to finance research activities of the RAU. The research was carried out with the financial support of the State Committee for Science of the Ministry of Education and Science of the Republic of Armenia within the framework of the scientific project №18T-2E151.

Experimental Section

IR spectra are recorded on a "Termo Nicoletion Nexus" spectrometer in vaseline oil. NMR spectra of ^1H and ^{13}C of the synthesized compounds were recorded on a Varian "Mercury-300 VX" spectrometer (300 and 75 MHz, respectively) at a temperature of 300 K in a solution of DMSO-d6-CCl_4 1:3 (internal standard-TMS). Elemental analysis is performed on a "Eurovector EA-3000" device.

1-(2'-Chlorethyl)imidazole (2). A mixture of 6.8 *g* (0.1 *mol*) of imidazole (**1**), 50 *g* (0.5 *mol*) of dichloroethane, 4 *g* (0.1 *mol*) of sodium hydroxide, 1 *g* (TEBAC) in 50 *ml* of 50% aqueous NMO solution at 70-80°C was stirred vigorously for 3 hours. After cooling, it was extracted with chloroform. After removal of chloroform, 1.2 *g* (9.2%) of 1-(2'-chloroethyl)imidazole (**2**) was

obtained, which was proved by ^{1}H NMR spectroscopy. NMR ^{1}H δ, ppm, *J* (Hz): 3.85 t (2H, CH_2, *J* = 6.2), 4.39 t (2H, CH_2, *J* = 6.2), 7.12 br. s (1H, 4-H), 7.39 t (1H, 5-H, *J* = 1.5), 7.78 br. s (1H, 2-H). Upon distillation, compound (**2**) was quaternized to polysalt (**4**) with a m.p. 144-149 °C, [ή]=0.02 dl/g. IR spectrum, ν, cm^{-1}: 1510 (ring), 2000 (salt effect).

1-Vinylimidazole (3). A mixture of 6.8 *g* (0.1 *mol*) of imidazole (**1**), 156 *g* (1.6 *mol*) of dichloroethane, 8 *g* (0.2 *mol*) of sodium hydroxide, 1 *g* (TEBAC) in 50 *ml* of 50% aqueous NMO solution at 70-80°C was stirred vigorously for 3 hours. Then, a solution of 40 *g* (1.0 *mol*) of sodium hydroxide in 100 *ml* of water is added dropwise over 2 *hours* and stirring is continued for 5 hours. After cooling, 100 *ml* of water was added to the mixture and extracted with chloroform, the organic layer was dried over calcium chloride. After removal of chloroform, the residue was distilled off under reduced pressure. The yield of 1-vinylimidazole (**3**) 5.2 *g* (55%), b.p. 71°C / 2 mm Hg, n_D^{20} 1.5300, d_4^{20} 1.039. IR spectrum, ν, cm^{-1}: 1510 (ring), 1650 (C=C). NMR ^{1}H δ, ppm, *J* (Hz): 5.06 dd (1H, $=CH_2$, *J* = 8.9 и 1.7), 5.50 dd (1H, $=CH_2$, *J* =15.8), 7.12 dd (1H, =CH, *J* = 15.8 и 8.9), 7.12 br. s (1H), 7.48 br. s (1H) и 7.91 br. s (1H, protons of the cycle). ^{13}C: 101.8 ($=CH_2$), 116.1 (C=H), 127.8 (N-CH), 128.7 (N=CH), 136.3 (NCHN). Found, %: C 63.78; H 6.04; N 30.13. $C_5H_6N_2$. Calculated, %: C, 51.79; H, 6.47; N, 30.21.

Synthesis of 1-vinylimidazole (3) under PTC conditions. A mixture of 6.8 *g* (0.1 *mol*) of imidazole (**1**), 156 *g* (1.6 *mol*) of dichloroethane, 8 *g* (0.2 *mol*) of sodium hydroxide, 1 *g* (TEBAC) at 70-80°C was stirred vigorously for 2 hours. Then, a solution of 40 *g* (1.0 *mo*l) of sodium hydroxide in 100 *ml* of water was added dropwise over 2 hours and stirring is continued for 5 hours. After cooling, 100 *ml* of water was added to the mixture and extracted with chloroform. After removal of chloroform, the residue was distilled off under reduced pressure. Yield of 1-vinylimidazole (**3**) 2.8 *g* (30%), b.p. 68 °C / 1 mm Hg, n_D^{20} 1.5300.

Synthesis of 1-vinylimidazole (3) in the NMO/H_2O system. A mixture of 6.8 *g* (0.1 *mol*) of imidazole (**1**), 156 *g* (1.6 *mol*) of dichloroethane, 8 *g* (0.2 *mol*) of sodium hydroxide in 50 *ml* of 50% aqueous NMO solution at 70-80°C was stirred vigorously for 2 *hours*. Then, a solution of 40 *g* (1.0 *mol*) of sodium hydroxide in 100 *ml* of water is added dropwise over 2 *hours* and stirring is continued for 5 *hours*. After cooling, 100 *ml* of water was added to the mixture and extracted with chloroform. After removal of chloroform, the residue was distilled off under reduced pressure. The yield of 1-vinylimidazole (**3**) 2.3 *g* (25%), b.p. 71°C / 3 *mm* Hg, n_D^{20} 1.5300.

ԻՄԻԴԱԶՈԼԻ ԱԼԿԻԼԱՑՈՒՄԸ ԴԻՔԼՈՐԷԹԱՆՈՎ ՋՐԱԽԻՄՆԱՅԻՆ ՄԻՋԱՎԱՅՐՈՒՄ N-ՄԵԹԻԼՄՈՐՖՈԼԻՆ N-ՕՔԻԴԻ ՀԱՄԱԿԱՐԳՈՒՄ ՄԻՋՓԱԶ ԿԱՏԱԼԻԶԱՏՈՐԻ ՕԳՏԱԳՈՐԾՄԱՄԲ ԵՎ IN-SITU ՊԱՅՄԱՆՆԵՐՈՒՄ ԱՌԱՋԱՑԱԾ 1-(2'-ՔԼՈՐԷԹԻԼ)ԻՄԻԴԱԶՈԼԻ ԴԵՀԻԴՐՈՔԼՈՐԱՑՈՒՄԸ 1-ՎԻՆԻԼԻՄԻԴԱԶՈԼԻ

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Գ. Գ. ԴԱՆԱԳՈՒԼՅԱՆ[1] և Հ. Ս. ԱԹԹԱՐՅԱՆ[1]

Ներկայացված աշխատանքում իրականացվել է իմիդազոլը ալկիլացումը դիքլորէթանով ջրահիմնային միջավայրում միջֆազ կատալիզի օգտագործմամբ N-մեթիլմորֆոլին N-օքիդ-ջուր համակարգում: Ցույց է տրվել, որ նշված համակարգում իմիդազոլի ալկիլացումը դիքլորէթանով ուղեկցվում է in situ պայմաններում ստացված 1-(2'-քլորէթիլ)իմիդազոլի դեհիդրոքլորացման՝ 1-վինիլիմիդազոլի առաջացմամբ, ինչը թույլ է տալիս վերջինիս սինթեզը առանց պայթունավտանգ ացետիլենի օգտագործման:

АЛКИЛИРОВАНИЕ ИМИДАЗОЛА ДИХЛОРЭТАНОМ И ДЕГИДРОХЛОРИРОВАНИЕ IN-SITU ПОЛУЧЕННОГО 1-(2'-ХЛОРЭТИЛ)ИМИДАЗОЛА ДО 1-ВИНИЛИМИДАЗОЛА В ВОДНО-ЩЕЛОЧНОЙ СРЕДЕ В СИСТЕМЕ N-МЕТИЛМОРФОЛИН N-ОКСИДА С ИСПОЛЬЗОВАНИЕМ КАТАЛИЗАТОРА МЕЖФАЗНОГО ПЕРЕНОСА

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В настоящей работе рассматривается возможность применения межфазного катализа в системе N-метилморфолин-N-оксид-вода при алкилировании имидазола дихлорэтаном. Показано, что алкилирование имидазола дихлорэтаном в вышеуказанной системе сопровождается дегидрохлорированием in situ полученного 1-(2'-хлорэтил)имидазола, что позволяет провести синтез 1-винилимидазола без использования взрывоопасного ацетилена.

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ՀԱՅԱՍՏԱՆԻ ՀԱՆՐԱՊԵՏՈՒԹՅԱՆ ԳԻՏՈՒԹՅՈՒՆՆԵՐԻ
ԱԶԳԱՅԻՆ ԱԿԱԴԵՄԻԱ
НАЦИОНАЛЬНАЯ АКАДЕМИЯ НАУК РЕСПУБЛИКИ АРМЕНИЯ
NATIONAL ACADEMY OF SCIENCES OF THE REPUBLIC OF ARMENIA

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SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF 4-AMINO-1,3,5-TRIARYL-1H-PYRROL-2(5H)-ONES

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By acylation of α-aminonitriles with phenylacetyl chloride and subsequent intramolecular cyclization in the presence of caustic potassium, the synthesis of 4-amino-1,3,5-triaryl-1H-pyrrol-2(5H)-ones was carried out. The antibacterial activity of synthesized compounds was studied, among which 4-amino-5-(4-isopropoxyphenyl)-3-phenyl-1-o-tolyl-1H-pyrrol-2(5H)-one is the most active, inhibiting the growth of gram-positive microorganisms in the zone with diameter d = 17-18 mm. Other derivatives are inactive or completely devoid of antibacterial activity.

Table 1, references 13.

Pyrrolones are well known compounds due to their presence in natural products. They have various biological properties and are potential compounds in the development of new drugs [1].

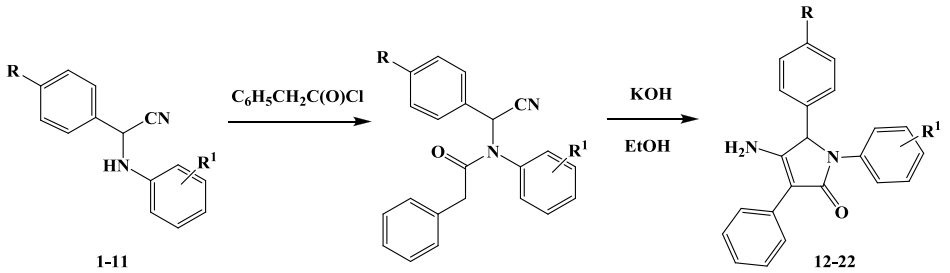
Several approaches to the synthesis of pyrrolones are known in the literature, particularly, the reaction of *α,β*-diketones with various acetamides possessing a strong electron-withdrawing group in the *α*-position, the cycloisomerization reaction of alkylidenecarbene derivative of amides, the condensation reaction of benzoylformanilide with acetophenones to yield aldol-type products and the subsequent treatment with HCl, the ruthenium-catalyzed reaction of *α,β*-unsaturated imines with carbon monoxide and ethylene [2-5].

4-Aminosubstituted pyrrolones are little known compounds, and there are few reports about their synthesis in the literature. These include reactions of pyrrolidine-2,4-diones with primary amines and reactions of secondary amines with phenylacetyl chloride and further cyclization of amides in the presence of caustic potassium [1,6].

We have previously developed an effective method for the synthesis of substituted *β*- and *γ*-lactams based on acylation reactions of corresponding *α*-aminonitriles (obtained by the Strecker reaction) with monochloroacetyl or 3-

chloropropionyl chlorides and subsequent intramolecular cyclization under phase transfer catalysis condition.

In continuation of research in this direction, by acylation of *α*-aminonitriles **1-11** with phenylacetyl chloride and subsequent intramolecular cyclization in the presence of caustic potassium, 4-amino-1,3,5-triaryl-1*H*-pyrrol-2(5*H*)-ones **12-22** were synthesized.



R = R^1 = H (**1**,**12**); R = H, R^1 = 4-CH_3 (**2**,**13**); R = H, R^1 = 2-CH_3 (**3**,**14**); R = H, R^1 = 3,5-$(CH_3)_2$ (**4**,**15**); R = H, R^1 = 4-CH_3O (**5**,**16**); R = H, R^1 = 2-CH_3O (**6**,**17**); R = 4-*iso*-C_3H_7O, R^1 = H (**7**,**18**); R = 4-*iso*-C_3H_7O, R^1 = 4-CH_3 (**8**,**19**); R = 4-*iso*-C_3H_7O, R^1 = 2-CH_3 (**9**,**20**); R = 4-*iso*-C_3H_7O, R^1 = 3,5-$(CH_3)_2$ (**10**,**21**); R = 4-*iso*-C_3H_7O, R^1 = 2-CH_3O (**11**,**22**).

The structure of the synthesized compounds was confirmed by elemental analysis, IR, ^1H and ^{13}C NMR spectra.

The antibacterial activity of synthesized compounds **12-22** was studied using the "diffusion in agar" method [7], with a bacterial load of 20 *mln* microbial cells per 1 *ml* of medium. Gram-positive staphylococci (*St. aureus 209p, Bac. subtilis*) and gram-negative rods (*Sh. flexneri* 6858, *E. coli* 055) were used in experiments. Solutions of tested compounds and the control preparation were prepared in DMSO at a dilution of 1:20. On Petri dishes with crops of the above strains, solutions of compounds were applied in a volume of 0.1 *ml*. The results were recorded by the diameter (d, *mm*) of the zone of no microbial growth at the site of application of the compounds after daily growth of the test cultures in a thermostat at 37°C. Furazolidone was used as a positive control [8].

Among synthesized compounds, 4-amino-5-(4-isopropoxyphenyl)-3-phenyl-1-*o*-tolyl-1*H*-pyrrol-2(5*H*)-one **(20)** was found to be the most active, inhibiting the growth of gram-positive microorganisms in the zone with diameter d = 17-18 *mm*, the remaining derivatives were inactive or completely devoid of antibacterial activity (Table).

Table

Antibacterial activity of 4-amino-1,3,5-triaryl-1H-pyrrol-2(5H)-ones

Comp. №	The diameter of the zone of absence of microbial growth (d, *mm*)			
	St. aureus 209p	*Bac. subtilis*	*Sh. flexneri 6858*	*E. coli 055*
12	0	0	0	0
13	0	0	0	0
14	0	0	0	0
15	13	12	12	12
16	12	11	15	15
17	13	13	12	10
18	10	10	12	10
19	0	0	0	0
20	17	17	13	13
21	0	0	0	0
22	0	0	0	0
Furazolidone	25	24	24	24

Experimental part

IR spectra were recorded on a "Nicolet Avatar 330" spectrometer from samples dispersed in mineral oil. The ^{1}H and ^{13}C NMR spectra were recorded on a Varian "Mercury-300VX" instrument at 303 *K* with a frequency of 300.078 and 75.46 *MHz*, respectively. In the assignment of signals, the methods of double resonance, DEPT and HMQC were used. Chemical shifts are given in ppm relative to the internal TMS for DMSO-d_6/CCl_4 1/3 solutions. The course of the reactions and the purity of the substances were controlled using thin-layer chromatography on Silufol UV-254 plates, in eluent systems: acetone–nonane, 2:1 (a), acetone–nonane, 3:2 (b) and acetone–nonane, 1:1 (c), spots were visualized by treatment with iodine vapor.

Syntheses of α-aminonitriles 1-3**,** 5-11 **are described in [9-13].**

2-(3,5-Dimethylphenylamino)-2-phenylacetonitrile (4). To a solution of 1.06 *g* (10 *mmol*) of benzaldehyde in 20 *ml* of EtOH with stirring at room temperature, a solution of 0.5 *g* (10 *mmol*) of NaCN in 10 *ml* of water is added, stirred for 10 *min*, then 0.6 *g* (10 *mmol*) of AcOH is added, stirred for another 10 *min* and a solution of 1.2 *g* (10 *mmol*) of 3,5-dimethylaniline in 10 *ml* of EtOH is added. Stirring is continued for 2 *h*, 10 *ml* of cold water is added and left overnight. The precipitate formed is filtered, washed with water, dried and recrystallized from EtOH. Yield 2.0 *g* (85%) of compound 4, mp 103-104°C, R_f 0.60 (a). ^{1}H NMR spectrum, δ, ppm, *Hz*: 2.24 (s, 6H, 2×CH_3); 5.65 (d, 1H, *J* = 9.4, CH); 6.18 (d, 1H, *J* = 9.4, NH); 6.36 (br., 1H, 4-H C_6H_3); 6.39 (br., 2H, 2,2'-H C_6H_3); 7.34-7.46 (m, 3H, *m*,*p*-C_6H_5); 7.57-7.62 (m, 2H, *o*- C_6H_5). ^{13}C

NMR spectrum δ_c, ppm: 21.0 (2×CH_3); 48.4 (CH); 111.6 (2,2'-CH C_6H_3); 118.4 (CN); 120.1 (4-H C_6H_3); 126.8 (2×CH C_6H_5); 128.0 (*p*- C_6H_5); 128.2 (2×CH C_6H_5); 135.0; 137.4 (3,3'-CH C_6H_3); 145.4 (1-C C_6H_3). Found, %: C 81.17; H 6.91; N 12.03. $C_{16}H_{16}N_2$. Calculated, %: C 81.32; H 6.82; N 11.85.

General procedure for the preparation of 4-amino-1,3,5-triaryl-1H-pyrrol-2(5H)-ones (12-22). To a mixture of 10 *mmol* of the corresponding 2-arylacetonitrile **1-11** in 20 *ml* of 1,2-dichloroethane and 1.4 *g* (10 *mmol*) of dry K_2CO_3, 1.6 *g* (10 *mmol*) of phenylacetyl chloride is added dropwise at 10-15°C, the reaction mixture is stirred at room temperature for 30 *min* and then 2 *h* at 40-45°C. Upon completion, the whole is cooled, 20 *ml* of 1,2-dichloroethane is added, washed several times with water and dried with $CaCl_2$. The solvent is removed, the residue is dissolved in 30 *ml* of EtOH, 2.8 *g* (50 *mmol*) of KOH in 10 *ml* of water is added, and stirred at 60–65 °C for 1 *h*. After cooling, 20 *ml* of water is added, the precipitate formed is filtered and recrystallized from EtOH.

4-Amino-1,3,5-triphenyl-1*H*-pyrrol-2(5*H*)-one (12). Yield 78%, mp 246-248°C, R_f 0.60 (b). IR spectrum, ν, cm^{-1}: 1632 (C=O), 3306 (NH_2). ^{1}H NMR spectrum, δ, ppm: 5.58 (s, 1H, CH); 6.08 (br., 2H, NH_2); 6.80-6.83 (m, 1H, *p*-C_6H_5); 7.11-7.19 (m, 3H, Ar); 7.21-7.38 (m, 5H, Ar); 7.42-7.46 (m, 2H, *o*-C_6H_5); 7.51-7.56 (m, 2H, *o*- C_6H_5); 7.58-7.63 (m, 2H, *o*-C_6H_5). ^{13}C NMR spectrum δ_c, ppm: 62.4 (CH); 98.5; 119.3 (2×CH); 121.5 (CH); 124.8 (CH); 126.9 (2×CH); 127.4 (2×CH); 127.5 (CH); 127.66 (2×CH); 127.71 (2×CH); 128.2 (2×CH); 132.5; 137.5; 138.5; 159.0; 169.0. Found, %: C 80.78; H 5.45; N 8.64. $C_{22}H_{18}N_2O$. Calculated, %: C 80.96; H 5.56; N 8.58.

4-Amino-3,5-diphenyl-1-*p*-tolyl-1*H*-pyrrol-2(5*H*)-one (13) is described in [1].

4-Amino-3,5-diphenyl-1-*o*-tolyl-1*H*-pyrrol-2(5*H*)-one (14). Yield 65%, mp 213-215°C, R_f 0.57 (c). IR spectrum, ν, cm^{-1}: 1638 (C=O), 3297 (NH_2). ^{1}H NMR spectrum, δ, ppm: 2.11 (s, 3H, CH_3); 5.36 (s, 1H, CH); 5.95 (br., 2H, NH_2); 6.97-7.12 (m, 4H, Ar); 7.13-7.19 (m, 1H, *p*- C_6H_5); 7.25-7.32 (m, 5H, Ar); 7.33-7.39 (m, 2H, *m*-C_6H_5); 7.65-7.69 (m, 2H, *o*-C_6H_5). ^{13}C NMR spectrum δ_c, ppm: 18.2 (CH_3); 64.8 (CH); 98.9; 124.6 (CH); 125.3 (CH); 125.9 (CH); 127.4 (2×CH); 127.4 (CH); 127.5 (2×CH); 127.7 (CH); 127.8 (2×CH); 128.0 (2×CH); 130.0 (CH). Found, %: C 81.30; H 5.78; N 8.32. $C_{23}H_{20}N_2O$. Calculated, %: C 81.15; H 5.92; N 8.23.

4-Amino-1-(3,5-dimethylphenyl)-3,5-diphenyl-1*H*-pyrrol-2(5*H*)-one (15). Yield 82%, mp 205-206 °C, R_f 0.46 (a). IR spectrum, ν, cm^{-1}: 1638 (C=O), 3333 (NH_2). ^{1}H NMR spectrum, δ, ppm: 2.21 (s, 6H, 2×CH_3); 5.53 (s, 1H, CH); 6.03 (br., 2H, NH_2); 6.51 (m, 1H, 4H C_6H_3); 7.12 (br., 2H, 2,2'-H C_6H_3); 7.13-7.18 (m, 1H, 4-CH C_6H_5); 7.21-7.27 (m, 1H, 4-CH C_6H_5); 7.28-7.37 (m, 4H, 2 *m*- C_6H_5); 7.39-7.43 (m, 2H, *o*-C_6H_5); 7.58-7.62 (m, 2H, *o*-C_6H_5). ^{13}C NMR spectrum δ_c, ppm: 21.0 (2×CH_3); 62.6 (CH); 98.5; 117.7 (2×CH); 123.6 (CH); 124.7 (CH); 127.0 (2×CH); 127.4 (2×CH); 127.5 (CH); 127.6 (2×CH); 128.1

(2×CH); 132.6; 136.5 (2 C CH_3); 137.6; 138.2; 158.8. Found, %: C 81.30; H 5.78; N 8.32. $C_{24}H_{22}N_2O$. Calculated, %: C 81.33; H 6.26; N 7.90.

4-Amino-1-(4-methoxyphenyl)-3,5-diphenyl-1*H*-pyrrol-2(5*H*)-one (16). Yield 73%, mp 225-226°C, R_f 0.40 (a). IR spectrum, ν, cm^{-1}: 1634 (C=O), 3302 (NH_2). ^{1}H NMR spectrum, δ, ppm: 3.70 (s, 3H, OCH_3); 5.52 (s, 1H, CH); 6.00 (br., 2H, NH_2); 6.68-6.73 (m, 2H, C_6H_4); 7.13-7.19 (m, 1H, *p*-C_6H_5); 7.21-7.43 (m, 9H, Ar); 7.60-7.64 (m, 2H, Ar). ^{13}C NMR spectrum δ_c, ppm: 54.4 (OCH_3); 63.0 (CH); 98.6; 113.1 (2×CH C_6H_4); 121.8 (2×CH C_6H_4); 124.7 (CH); 127.2 (CH Ph); 127.5 (2×CH Ph); 127.5 (CH Ph); 127.6 (2×CH Ph); 128.1 (2×CH Ph); 131.5; 132.7; 137.5; 154.6; 158.6; 169.6. Found, %: C 77.63; H 5.41; N 7.60. $C_{23}H_{20}N_2O_2$. Calculated, %: C 77.51; H 5.66; N 7.86.

4-Amino-1-(2-methoxyphenyl)-3,5-diphenyl-1*H*-pyrrol-2(5*H*)-one (17). Yield 71%, mp 154-156°C, R_f 0.42 (a). IR spectrum, ν, cm^{-1}: 1627 (C=O), 3297 (NH_2). ^{1}H NMR spectrum, δ, ppm, *Hz*: 3.86 (s, 3H, OCH_3); 5.60 (s, 1H, CH); 5.95 (br., 2H, NH_2); 6.78 (td, 1H, J = 7.6, J = 1.4, C_6H_4); 6.89 (dd, 1H, J = 8.2, J = 1.3, C_6H_4); 7.05-7.12 (m, 2H, Ar); 7.13-7.19 (m, 1H, Ar); 7.21-7.31 (m, 5H, Ar); 7.33-7.39 (m, 2H, Ar); 7.64-7.68 (m, 2H, Ar). ^{13}C NMR spectrum δ_c, ppm: 55.0 (OCH_3); 63.7 (CH); 99.6; 111.3 (CH); 119.6 (CH); 124.5 (CH); 126.0; 126.3 (CH); 127.4 (2×CH); 127.4 (CH); 127.5 (2×CH); 127.7 (2×CH); 127.8 (2×CH); 129.6 (CH); 133.0; 137.2; 154.4; 159.0; 170.0. Found, %: C 77.33; H 5.52; N 7.71. $C_{23}H_{20}N_2O_2$. Calculated, %: C 77.51; H 5.66; N 7.86.

4-Amino-5-(4-isopropoxyphenyl)-1,3-diphenyl-1*H*-pyrrol-2(5*H*)-one (18). Yield 68%, mp 207-209°C, R_f 0.46 (a). IR spectrum, ν, cm^{-1}: 1610 (C=O), 3307 (NH_2). ^{1}H NMR spectrum, δ, ppm, *Hz*: 1.30 (d, 6H, J = 6.0, 2×CH_3); 4.52 (sp, 1H, J = 6.0, OCH); 5.51 (s, 1H, CH); 6.03 (br., 2H, NH_2); 6.76-6.81 (m, 2H, C_6H_4); 6.85-6.90 (m, 1H, *p*- C_6H_5); 7.13-7.20 (m, 3H, *m*-C_6H_5); 7.29-7.38 (m, 4H, Ar); 7.52-7.56 (m, 2H, *o*-C_6H_5); 7.53-7.63 (m, 2H, *o*-C_6H_5). ^{13}C NMR spectrum δ_c, ppm: 21.61 (CH_3); 21.65 (CH_3); 61.9 (NCH); 68.7 (OCH); 98.4; 115.2 (2×CH C_6H_4); 119.5 (2×CH C_6H_4); 121.5 (CH); 124.7 (CH); 127.5 (2×CH Ph); 127.65 (2×CH Ph); 127.7 (2×CH Ph); 128.1 (2×CH Ph); 128.7; 132.6; 138.5; 157.1; 159.2; 169.7. Found, %: C 78.22; H 6.41; N 7.04. $C_{25}H_{24}N_2O_2$. Calculated, %: C 78.10; H 6.29; N 7.29.

4-Amino-5-(4-isopropoxyphenyl)-3-phenyl-1-*p*-tolyl-1*H*-pyrrol-2(5*H*)-one (19). Yield 72%, mp 194-196°C, R_f 0.46 (a). IR spectrum, ν, cm^{-1}: 1627 (C=O), 3321 (NH_2). ^{1}H NMR spectrum, δ, ppm, *Hz*: 1.29 (d, 6H, J = 6.0, 2×CH_3); 2.23 (s, 3H, CH_3-Ar); 4.51 (sp, 1H, J = 6.0, OCH); 5.46 (s, 1H, CH); 5.96 (br., 2H, NH_2); 6.74-6.79 (m, 2H, $C_6H_4OC_3H_7$); 6.93-6.98 (m, 2H, *p*-C_6H_5); 7.11-7.17 (m, 1H, *p*-C_6H_5); 7.25-7.30 (m, 2H, $C_6H_4OC_3H_7$); 7.31-7.40 (m, 4H, $C_6H_4CH_3$ и *m*-C_6H_5); 7.58-7.62 (m, 2H, *o*-C_6H_5). ^{13C} NMR spectrum δ_c, ppm: 20.2 (CH_3); 21.6 and 21.6 (2×CH_3); 62.0 (NCH); 68.6 (OCH); 98.4; 115.1 (2×CH); 119.8 (2×CH); 124.6 (CH); 127.4 (2×CH); 127.6 (2×CH); 128.1 (2×CH); 128.3 (2×CH). Found, %: C 78.51; H 6.39; N 7.19. $C_{26}H_{26}N_2O_2$. Calculated, %: C 78.36; H 6.58; N 7.03.

4-Amino-5-(4-isopropoxyphenyl)-3-phenyl-1-*o*-tolyl-1*H*-pyrrol-2(5*H*)-one (20). Yield 68%, mp 198-200°C, R_f 0.45 (a). IR spectrum, ν, cm^{-1}: 1632 (C=O), 3297 (NH_2). ^{1}H NMR spectrum, δ, ppm, *Hz*: 1.30 (d, 6H, *J* = 6.0, 2×CH_3); 2.13 (s, 3H, CH_3-Ar); 4.53 (sp, 1H, *J* = 6.0, OCH); 5.29 (s, 1H, CH); 5.90 (br., 2H, NH_2); 6.73-6.78 (m, 2H, $C_6H_4OC_3H_7$); 6.97-7.20 (m, 7H, Ar); 7.33-7.39 (m, 2H, Ar); 7.65-7.70 (m, 2H, Ar). ^{13}C NMR spectrum δ_c, ppm: 18.2 (CH_3); 21.6 (2×CH_3); 64.4 (NCH); 68.7 (OCH); 98.9; 114.9 (2×CH); 124.6 (CH); 125.3 (CH); 125.9 (CH); 127.4 (2×CH); 127.5 (2×CH); 128.3; 129.2 (2×CH); 130.0 (CH); 133.0; 136.6; 136.7; 157.3; 158.8; 169.4. Found, %: C 78.18; H 6.46; N 6.82. $C_{26}H_{26}N_2O_2$. Calculated, %: C 78.36; H 6.58; N 7.03.

4-Amino-1-(3,5-dimethylphenyl)-5-(4-isopropoxyphenyl)-3-phenyl-1*H*-pyrrol-2(5*H*)--one (21). Yield 87%, mp 198-200°C, R_f 0.64 (a). IR spectrum, ν, cm^{-1}: 1639 (C=O), 3302 (NH_2). ^{1}H NMR spectrum, δ, ppm, *Hz*: 1.29 (d, 6H, *J* = 6.0, 2×CH_3); 2.21 (t, 6H, *J* = 0.5, CH_3-Ar); 4.51 (sp, 1H, *J* = 6.0, OCH); 5.45 (s, 1H, CH); 5.96 (br., 2H, NH_2); 6.51 (m, 1H, 4-H $C_6H_3(CH_3)_2$); 6.75-6.80 (m, 2H, C_6H_4); 7.11 (br., 2H, 2,2′-H $C_6H_3(CH_3)_2$); 7.12-7.17 (m, 1H, 4-H C_6H_4); 7.25-7.30 (m, 2H, C_6H_4); 7.30-7.37 (m, 2H, *m*- C_6H_5); 7.57-7.62 (m, 2H, *o*- C_6H_5). ^{13}C NMR spectrum δ_c, ppm: 21.1 (2×CH_3); 21.66 (CH_3); 21.71 (CH_3); 62.1 (NCH); 68.7 (OCH); 98.5; 115.2 (2×CH); 117.9 (2×CH); 123.6; 124.7; 127.5 (2×CH); 127.7 (2×CH); 128.2 (2×CH); 128.8; 132.8; 136.6; 138.2; 157.2; 159.1; 169.7. Found, %: C 78.44; H 6.93; N 6.70. $C_{27}H_{28}N_2O_2$. Calculated, %: C 78.61; H 6.84; N 6.79.

4-amino-5-(4-isopropoxyphenyl)-1-(2-methoxyphenyl)-3-phenyl-1*H*-pyrrol-2(5*H*)- -one (22). Yield 64%, mp 210-212°C, R_f 0.64 (b). IR spectrum, ν, cm^{-1}: 1640 (C=O), 3268 (NH_2). ^{1}H NMR spectrum, δ, ppm, *Hz*: 1.28 (d, 3H, *J* = 6.0, CH_3); 1.29 (d, 3H, *J* = 6.0, CH_3); 3.86 (s, 3H, OCH_3); 4.50 (sp, 1H, *J* = 6.0, OCH); 5.52 (s, 1H, CH); 5.87 (br., 2H, NH_2); 6.71-6.76 (m, 2H, $C_6H_4OC_3H_7$); 6.80 (ddd, 1H, *J* = 7.9, *J* = 7.2, *J* = 1.3, $C_6H_4OCH_3$); 6.88-6.92 (m, 1H, $C_6H_4OCH_3$); 7.06-7.18 (m, 5H, Ar); 7.32-7.38 (m, 2H, *m*- C_6H_5); 7.63-7.67 (m, 2H, *o*-C_6H_5). ^{13}C NMR spectrum δ_c, ppm: 21.59 (CH_3); 21.62 (2×CH_3); 55.0 (OCH_3); 63.2 (NCH); 68.6 (OCH); 98.5; 111.3; 114.8 (2×CH); 119.6; 124.5; 126.1; 126.3; 127.4 (2×CH); 128.5; 128.8; 129.6; 133.1; 154.5; 157.1; 159.1; 169.9. Found, %: C 75.21; H 6.13; N 6.58. $C_{26}H_{26}N_2O_3$. Calculated, %: C 75.34; H 6.32; N 6.76.

4-ԱՄԻՆՈ-1,3,5-ՏՐԻԱՐԻԼ-1Հ-ՊԻՐՐՈԼ-2(5Հ)-ՈՆՆԵՐԻ ՍԻՆԹԵԶԸ ԵՎ ՆՐԱՆՑ ՀԱԿԱՄԱՆՐԷԱՅԻՆ ԱԿՏԻՎՈՒԹՅՈՒՆԸ

Մ. Վ. ԱԼԵՔՍԱՆՅԱՆ, Գ. Կ. ՀԱՐՈՒԹՅՈՒՆՅԱՆ, Ս. Պ. ԳԱՍՊԱՐՅԱՆ, Ն. Մ. ՍՏԵՓԱՆՅԱՆ և Ռ. Ե. ՄՈՒՐԱԴՅԱՆ

Ֆենիլքացախաթթվի քլորանհիդրիդով α-ամինոնիտրիլների ացիլմամբ և կալիումի հիդրօքսիդի առկայությամբ հետագա ներմոլեկուլային ցիկլման արդյունքում իրակա-նացվել է 4-ամինո-1,3,5-տրիարիլ-1Հ-պիրրոլ-2(5Հ)-ոննների սինթեզ և հետազոտվել են

սինթեզված միացությունների հակամանրէային հատկությունները: Ըստ կենսաբանական արդյունքների, ամենաբարձր ակտիվություն ցուցաբերել է 4-ամինո-5-(4-իզոպրոպօքսիֆենիլ)-3-ֆենիլ-1-օ-տոլիլ-1H-պիրրոլ-2(5H)-ոնը, ճնշելով գրամդրական միկրոօրգանիզմների աճը d = 17-18 մմ տրամագծով գոտում, մնացած ածանցյալներն օժտված են թույլ հակամանրէային ակտիվությամբ կամ ընդհանրապես զուրկ են ակտիվությունից:

СИНТЕЗ И АНТИБАКТЕРИАЛЬНАЯ АКТИВНОСТЬ 4-АМИНО-1,3,5-ТРИАРИЛ-1Н-ПИРРОЛ-2(5Н)-ОНОВ

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Ацилированием α-аминонитрилов хлорангидридом фенилуксусной кислоты и последующей внутримолекулярной циклизацией в присутствии едкого калия осуществлен синтез 4-амино-1,3,5-триарил-1*H*-пиррол-2(5*H*)-онов. Изучена антибактериальная активность синтезированных соединений, среди которых наиболее активным является 4-амино--5-(4-изопропоксифенил)-3-фенил-1-*о*-толил-1*H*-пиррол-2(5*H*)-он, подавляющий рост грамположительных микроорганизмов в зоне диаметром d = 17-18 *мм*. Остальные производные малоактивны или вовсе лишены антибактериальной активности.

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ՀԱՅԱՍՏԱՆԻ ՀԱՆՐԱՊԵՏՈՒԹՅԱՆ ԳԻՏՈՒԹՅՈՒՆՆԵՐԻ
ԱԶԳԱՅԻՆ ԱԿԱԴԵՄԻԱ
НАЦИОНАЛЬНАЯ АКАДЕМИЯ НАУК РЕСПУБЛИКИ АРМЕНИЯ
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Հայաստանի քիմիական հանդես
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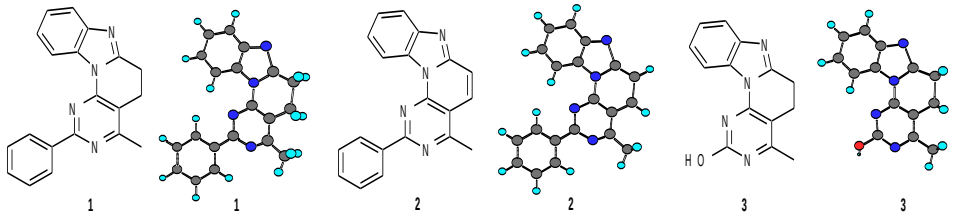
LETTER TO EDITORS

UDC 547.854, 577.32

PRELIMINARY EVALUATION OF THE BIOLOGICAL ACTIVITY OF BENZO[4′,5′]IMIDAZO[2′, 1′: 6,1]PYRIDO[2,3-d]PYRIMIDINE DERIVATIVES BY THE METHODS OF MOLECULAR MODELING

It is known that the molecular modeling method is one of the modern methods for identifying and preliminary assessing the bioactivity of chemical compounds, which allows for the rational search for new drugs. In this study, we, based on the above method, summarized preliminary results on the assessment of the possible pharmacological activity of three tetracyclic fused pyrimidines.

During *in silico* studies, pharmacokinetic parameters were obtained, biophysical and conformational interaction parameters were calculated for the following compounds: 4-methyl-2-phenyl-5,6-dihydrobenzo[4',5']imidazo [1',2':1,6]pyrido[2,3-d]pyrimidine **(1)**, 4-methyl-2-phenyl-benzo[4',5']imidazo [1',2':1,6]pyrido[2,3-d]pyrimidine **(2)** and 4-methyl-5,6-dihydrobenzo-[4',5']-imidazo[1',2':1,6]pyrido[2,3-d]pyrimidine-2-ol **(3)** [1] (Fig. 1).



Experimental part

The pharmacokinetic properties and target screening for the studied compounds were determined using ExPASy online portal [2]; molecular models of compounds for docking analysis were obtained using Cambridge Soft Corporation Chem software package 3D 5.0. The studied targets were taken from the UniProt database [3]. Docking and conformational analyses were carried out using AutoDock Vina, AutoDock Tools [4].

The statistical reliability of the research results was achieved through the integrated application of standard statistical methods, including the calculation of standard deviations, average values, and standard average errors.

Pharmacokinetic property (ADME) obtained *in silico* indicates that all test compounds have acceptable ADME compliance values; wherein the 2-hydroxy derivative **3** meets the criteria of a lead compound [5]. *In silico* screening was performed on 3000 initial targets, based on 2D and 3D similarities. The top 15 targets with high affinity for the compounds under study were selected. A docking analysis of the top targets with the studied compounds revealed that for compound **1** interactions were observed with 10 targets, for compound **2** - with 11 and for compound **3** - with 10 (results not shown). The obtained spatial-energy parameters of interaction revealed targets with high binding energies during complex formation. Binding constants (K_b) were also calculated for all the studied interactions (Table).

Table

The calculated parameters of ADME, *in silico* screening and docking analysis for the studied compounds

Compound	Pharmacokinetics			Drug-likeness		Medical chemistry		*In silico* screening (quantities)			Docking-analysis		
	Gastrointestinal absorption	Transition through BBB	Log K_p	Lipinski	Bioavailability (0-1)	Leadlikeness	Synthetic availability (1-10)	Primary targets	Primary screening	Secondary screening	Targets (UniProt ID)	Binding energy (kkal/mol)	Binding constant (K_b)
1.	High	Yes	-5.29	Yes	0.55	No	3.14	3000	15	10	Q9P1W9	-11,33±0,56	$1,8X10^8$
2.	High	Yes	-5.08	Yes	0.55	No	2.40	3000	15	11	P24941	-9.85±0.49	$1.50X10^7$
3.	High	Yes	-6.12	Yes	0.55	Yes	2.84	3000	15	10	P08913	-9.06±0.45	$4.00X10^6$

The results of complexation have shown that compound **1** has the highest K_b with serine-threonine protein kinase 2 (PIM 2) (UniProt ID: Q9P1W9) with a value of 1.8×10^8, and in compound **2** with cyclin-dependent kinase 2 (CDK2) (UniProt ID: P24941) with a value of 1.50×10^7 and for compound **3**, the highest K_b is found at α_2-A adrenergic receptor (ADRA2A) (UniProt ID: P08913) with a value of 4.00×10^6 (Table).

As a result of conformational analysis, amino acid residues involved in the complexation process were identified and types of interactions were determined.

The complexation of compound **1** with PIM-2 occurs due to hydrophobic interactions in the ATP pocket of the N-terminal of the protein kinase domain

with the amino acid residues Ala122, Val46, Leu116, Leu170, Ile181, which play an important role in ATP phosphorylation. A similar type of interaction is inherent in compounds – PIM 2 kinase inhibitors, and therefore, compound **1** may exhibit an antitumor activity against hematological forms of malignant neoplasms and prostate cancer [6]. The interaction of compound **2** with CDK2 is also hydrophobic in the ATP binding pocket of the active center of the protein with the involvement of Leu83, Asp86, Phe80, Lys89, Asp145 amino acid residues; however, the interaction with the amino acid Phe80, which regulates the entry of ATP into the active center of the protein, can lead to blocking the passage of the native ligand. Since in the cell cycle CDK2 is involved in the growth of tumors in different types of cancer, selective inhibition of CDK2 can be used in anti-cancer therapy strategies for specific tumors [7].

Our results indicate that compound **3** interacts with ADRA2A due to hydrogen bonds with the amino acid residue Leu26 with a binding length of 2.82 Å and Lys27, the binding length of which does not exceed 2.98 Å, and also due to hydrophobic interactions with amino acid residues Arg28, Glu23, Tyr24 and Asn25, which may suggest that compound **3** has a sedative effect [8].

Thus, according to the results of *in silico* studies in a series of poorly studied class of tetracyclic condensed pyrimidines, several types of biological activity can be expected.

ՄՈԼԵԿՈՒԼՅԱՐ ՄՈԴԵԼԱՎՈՐՄԱՆ ԵՂԱՆԱԿՈՎ ԲԵՆԶՕ[4′,5′]ԲԵՆԶՕԻՄԻԱԶԱԶՕ [2′,1′:6,1]ՊԻՐԻԴՈ[2,3-d]ՊԻՐԻՄԻԴԻՆԻ ԱԾԱՆՑՅԱԼՆԵՐԻ ԿԵՆՍԱԲԱՆԱԿԱՆ ԱԿՏԻՎՈՒԹՅԱՆ ՆԱԽՆԱԿԱՆ ԳՆԱՀԱՏՈՒՄԸ

Լ. Ս. ՀՈՒՆԱՆՅԱՆ, Ա. Տ. ՄԱԿԻՉՅԱՆ, Վ. Ս. ՔԱՄԱՐՅԱՆ, Ա. Ա. ՀԱՐՈՒԹՅՈՒՆՅԱՆ և Ղ. Ղ. ԴԱՆԱԳՈՒԼՅԱՆ

*Կենսաբանական ակտիվության սպեկտրի կանխատեսման նպատակով թիրախի հետադարձ սկրինինգի եղանակով իրականացվել է եռակոնդենսացված պիրիմիդինային թիթախների insilico հետազոտությունը և վալիդացիան: Դրանք են՝ 4-մեթիլ-2-ֆենիլ-5,6-դիհիդրոբենզո-[4′,5′]իմիդազո-[1′,2′:1,6]պիրիդո[2,3-d]պիրիմիդինը, 4-մեթիլ-2-ֆենիլ-բենզո[4′,5′]իմիդազո[1′,2′:1,6]պիրիդո[2,3-d]պիրիմիդինը և 4-մեթիլ-5,6-դիհիդրոբենզո-[4′,5′]իմիդազո[1′,2′:1,6]պիրիդո[2,3-d]պիրիմիդին-2-ոլը: Ցույց է տրվել, որ վերը նշված միացությունները ցուցաբերում են կապման բարձր հաստատուններ տարբեր ֆերմենտների հետ, համապատասխանաբար սերինտրոնին-պրոտեինկինազայի, ցիկլին կախվածությամբ կինազայի և ալֆա 2*a-ադրեներգիկ ռեցեպտորի հետ:

ПРЕДВАРИТЕЛЬНАЯ ОЦЕНКА БИОЛОГИЧЕСКОЙ АКТИВНОСТИ ПРОИЗВОДНЫХ БЕНЗО[4′,5′]ИМИДАЗО[2′,1′:6,1]ПИРИДО [2,3-d]ПИРИМИДИНА МЕТОДАМИ МОЛЕКУЛЯРНОГО МОДЕЛИРОВАНИЯ

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С целью прогнозирования спектра биологической активности на основе методологии обратного скрининга мишени проведено предварительное исследование *in silico* и валида-ция мишеней трех конденсированных пиримидинов: 4-метил-2-фенил-5,6-дигидробензо-[4',5']имидазо-[1',2':1,6]пиридо[2,3-d]пиримидина, 4-метил-2-фенилбензо[4',5']имидазо-[1',2':1,6]-пиридо[2,3-d]пиримидина и 4-метил-5,6-дигидробензо[4',5']имидазо[1',2':1,6]-пиридо[2,3-d]пиримидин-2-ола .

Установлено, что вышеуказанные соединения показали высокие константы связыва-ния с различными ферментами, соответственно с серинтреонин-протеин-киназой, циклинзависимой киназой и с альфа 2а-адренергическим рецептором.

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ՀԱՅԱՍՏԱՆԻ ՀԱՆՐԱՊԵՏՈՒԹՅԱՆ ԳԻՏՈՒԹՅՈՒՆՆԵՐԻ
ԱԶԳԱՅԻՆ ԱԿԱԴԵՄԻԱ
НАЦИОНАЛЬНАЯ АКАДЕМИЯ НАУК РЕСПУБЛИКИ АРМЕНИЯ
NATIONAL ACADEMY OF SCIENCES OF THE REPUBLIC OF ARMENIA

Հայաստանի քիմիական հանդես
Химический журнал Армении **72, №4, 2019** Chemical Journal of Armenia

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CORRIGENDUM TO "VOLUMETRIC PROPERTIES OF BINARY MIXTURES OF ACRYLONITRILE WITH DIMETHYLSULFOXIDE (OR DIETHYLSULFOXIDE) AT TEMPERATURES FROM 298.15 TO 323.15K" [CHEMICAL JOURNAL OF ARMENIA 70 (2017) 462-476]

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This is corrigendum to our paper [1] in which the study of volumetric properties of binary mixtures of acrylonitrile (AN) with dimethylsulfoxide (DMSO) (or diethylsulfoxide (DESO)) over the full range of compositions at several temperatures was carried out. In our paper [1] errors in thermodynamic parameters calculation are noted especially for calculation of partial excess molar volumes, $\overline{V}_i^E$, for the individual mixture components. Although, we mentioned in the text that the partial molar volumes are mainly smaller than molar volumes of pure components for both AN-DMSO and AN-DESO systems at each temperature which thermodynamically consistent, however, there was technical error. Instead of as usually procedure [2, 3], to obtain the partial excess molar volumes by subtracting the pure component molar volumes from the partial molar volumes of components ($\overline{V}_i^E = \overline{V}_i - V_i^*$) we did opposite. The authors would like to apologize for any inconvenience caused. Now, the corrections are incorporated and final versions of calculated values of partial excess molar volumes are presented in Tables 1 and 2.

Table 1

Partial excess molar volumes, $\overline{V}_i^E \times 10^6 \left(m^3 mol^{-1}\right)$, for AN and DMSO in binary AN(1)-DMSO(2) solutions at T= (298.15 to 323.15)K

X_2	$\overline{V}_1^E$	$\overline{V}_2^E$	$\overline{V}_1^E$	$\overline{V}_2^E$	$\overline{V}_1^E$	$\overline{V}_2^E$
	T=298.15K		T=303.15K		T=308.15K	
0.1056	-0.120	-1.283	-0.057	-1.354	-0.012	-1.442
0.2079	-0.166	-0.587	-0.086	-0.639	-0.024	-0.676
0.2988	-0.261	-0.400	-0.171	-0.386	-0.110	-0.395
0.3968	-0.295	-0.120	-0.223	-0.090	-0.166	-0.060
0.5016	-0.353	0.058	-0.291	0.129	-0.257	0.175
0.5999	-0.391	0.196	-0.351	0.287	-0.336	0.352
0.6986	-0.453	0.279	-0.466	0.370	-0.491	0.439
0.7976	-0.625	0.280	-0.712	0.360	-0.802	0.422
0.8979	-0.955	0.195	-1.030	0.262	-1.087	0.318
	T=313.15K		T=318.15K		T=323.15K	
0.1056	-0.012	-1.552	0.008	-1.657	0.002	-1.781
0.2079	-0.024	-0.748	0.003	-0.812	-0.003	-0.899
0.2988	-0.114	-0.451	-0.093	-0.495	-0.103	-0.574
0.3968	-0.159	-0.073	-0.136	-0.076	-0.146	-0.135
0.5016	-0.274	0.152	-0.274	0.155	-0.284	0.111
0.5999	-0.361	0.340	-0.374	0.361	-0.396	0.318
0.6986	-0.562	0.419	-0.615	0.440	-0.618	0.414
0.7976	-0.820	0.429	-0.893	0.457	-0.903	0.433
0.8979	-1.141	0.320	-1.219	0.345	-1.309	0.319

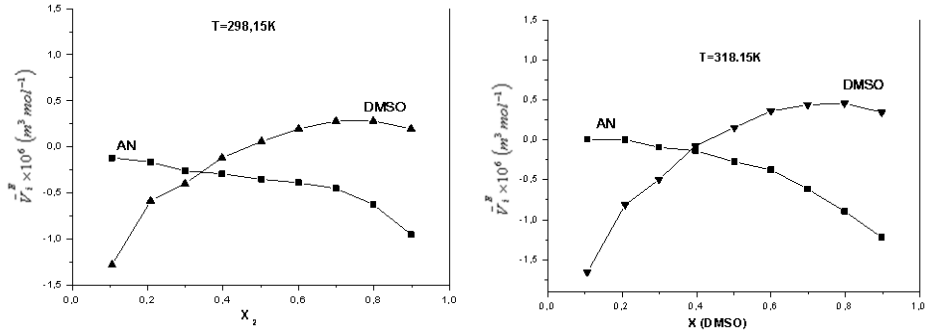
Table 2

Partial excess molar volumes, $\overline{V}_i^E \times 10^6 \left(m^3 mol^{-1}\right)$, for AN and DESO in binary AN(1)-DESO(2) solutions at T= (298.15 to 323.15)K

X_2	$\overline{V}_1^E$	$\overline{V}_2^E$	$\overline{V}_1^E$	$\overline{V}_2^E$	$\overline{V}_1^E$	$\overline{V}_2^E$
	T=298.15K		T=303.15K		T=308.15K	
0.1014	-0.554	-2.205	-0.543	-2.279	-0.554	-2.387
0.1992	-0.852	-1.896	-0.844	-1.967	-0.860	-2.044
0.3033	-0.967	-1.475	-0.957	-1.506	-0.976	-1.557
0.4002	-1.127	-1.393	-1.106	-1.384	-1.127	-1.419
0.4927	-1.247	-1.266	-1.243	-1.264	-1.268	-1.290
0.6003	-1.383	-1.119	-1.369	-1.095	-1.396	-1.110
0.6914	-1.265	-0.885	-1.249	-0.854	-1.280	-0.864
0.7963	-1.318	-0.718	-1.309	-0.690	-1.348	-0.696
0.9003	-1.617	-0.481	-1.702	-0.472	-1.757	-0.476
	T=313.15K		T=318.15K		T=323.15K	
0.1014	-0.564	-2.489	-0.573	-2.608	-0.578	-2.733
0.1992	-0.877	-2.123	-0.892	-2.207	-0.899	-2.292
0.3033	-0.994	-1.605	-1.011	-1.660	-1.019	-1.708
0.4002	-1.148	-1.455	-1.168	-1.491	-1.180	-1.522
0.4927	-1.292	-1.315	-1.316	-1.340	-1.332	-1.357
0.6003	-1.419	-1.123	-1.445	-1.136	-1.464	-1.140
0.6914	-1.307	-0.873	-1.337	-0.880	-1.363	-0.879
0.7963	-1.382	-0.703	-1.425	-0.707	-1.461	-0.703
0.9003	-1.814	-0.481	-1.875	-0.484	-1.927	-0.480

The figures (Fig. 4 in [1]) in which presented partial excess molar volumes versus molar fractions of DMSO (or DESO) at T=(298.15 and 318.15)K are corrected in this corrigendum as well (Fig.).

a)



b)

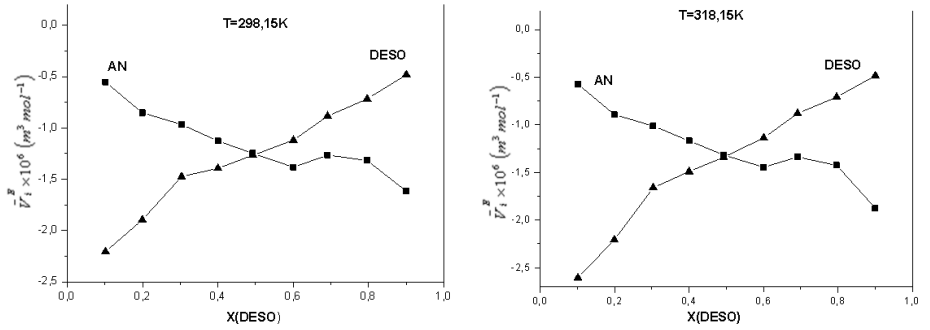


Fig. Excess partial molar volumes, $\overline{V}_i^E \times 10^6 \left(m^3 mol^{-1}\right)$, of components in binary solutions of AN at T = (298.15 and 318.15) K: (a) AN-DMSO; (b) AN-DESO.

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ГОДОВОЙ УКАЗАТЕЛЬ АВТОРОВ И СТАТЕЙ

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К публикации **в «*Химическом журнале Армении*»** принимаются материалы, содержащие результаты оригинальных исследований, оформленные в виде **полных статей, кратких сообщений и писем в редакцию.**

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Статьи, предлагаемые к публикации в разделе биоорганической химии, должны быть посвящены получению новых потенциально биологически активных соединений, в том числе и выделенных из природных объектов. **При описании новых веществ, обладающих значительной (в сравнении с применяемыми в медицине лекарствами) биологической активностью,** статья может содержать результаты биологических исследований, включающие ссылки на использованные методы изучения биологической активности, информацию о типе использованных биообъектов, активности и токсичности синтезированных препаратов в сопоставлении с соответствующими показателями применяемых в медицине лекарств.

В заключении следует привести краткий аргументированный вывод о связи между структурой и биологической активностью исследованных соединений. Опубликованные материалы, а также материалы, представленные для публикации в других журналах, к рассмотрению не принимаются.

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2) экспертное заключение (для граждан РА) (в 1 экз.);

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Публикация **обзоров, полных статей и кратких сообщений** начинается с индекса УДК, затем следуют заглавие статьи, инициалы и фамилии авторов, развернутые названия научных учреждений, полные почтовые адреса с индексами почтовых отделений, номера факсов и адреса электронной почты. Далее приводится краткая аннотация (не более 20 строк) с указанием конкретных результатов работы и вытекающих из них выводов.

В статьях **теоретического и физико-химического характера** приводятся сжатое введение в проблему и постановка задачи исследования, экспериментальная или методическая часть, обсуждение полученных результатов с **заключением**, а в статьях, **посвященных синтезу**, — общая часть (введение и задача исследования), обсуждение полученных результатов с **заключением** и экспериментальная часть. Рисунки с подрисуночными подписями и таблицы могут быть введены в текст. В **письмах в редакцию** аннотация на русском языке не приводится и разбивка на разделы не требуется; даются индекс УДК, название статьи, инициалы и фамилии авторов, название научных учреждений и их адреса, резюме на армянском и английском языках.

Графический реферат прилагается на отдельной странице (120×55 мм) и представляет собой **информативную иллюстрацию** (ключевую схему, структуру соединения, уравнение реакции, график и т.п.), отражающую суть статьи в **графическом** виде. Текст в графическом реферате допускается только в случае крайней необходимости, при этом следует избегать дублирования названия статьи и текста аннотации.

При несоблюдении указанных выше правил статья не принимается к публикации.

Пример оформления заглавия статьи, списка авторов, адресов учреждений, аннотации.

УДК.....

АСИММЕТРИЧЕСКИЙ СИНТЕЗ β-ГЕТЕРОЦИКЛИЧЕСКИ ЗАМЕЩЕННЫХ L-α-АМИНОКИСЛОТ

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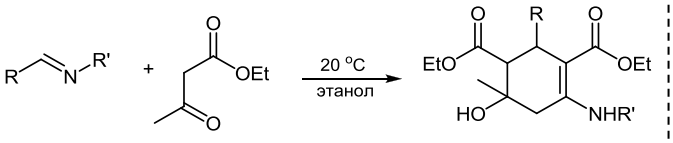
Разработан новый эффективный метод асимметрического синтеза β-гетероциклически замещенных L-α-аминокислот посредством присоединения 3-амино-1,2,4-тиадиазола и 5-меркапто-1,2,4-триазолов, содержащих различные заместители в положениях 3 и 4, к C=C связи Ni(II) комплекса с основанием Шиффа дегидроаланина и (S)-2-N-(N'-бензилпролил)аминобензофенона.

Примеры оформления графических рефератов

О взаимодействии N-алкилиминов с ацетоуксусным эфиром

М. С. Саргсян
С. С. Айоцян
А. Х. Хачатрян
А. Э. Бадасян
С. Г. Конькова

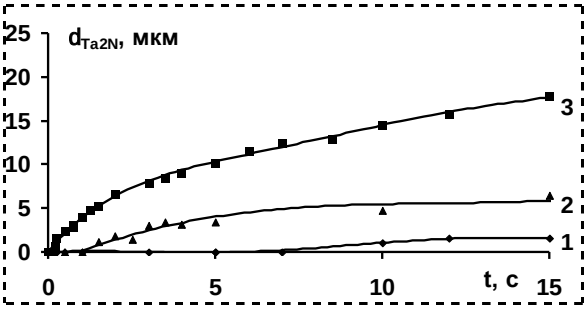


Хим. ж. Армении, 2011, т. 64, №4, с. 511

Кинетика высокотемпературного азотирования тантала в изотермических условиях

Ц. А. Адамян
Е. Н. Степанян
А. А. Чатилян
С. Л. Харатян

Хим. ж. Армении, 2011, т. 64, №3, с. 316



Оформление статей в «Химическом журнале Армении»

Текст статьи печатается **через 1.5 интервала** (без помарок и вставок) на белой бумаге стандартного размера (формат А4) с полями 3 см с левой стороны, 1.5 см с правой стороны, 2.5 см сверху, 2.5 см снизу, **размер шрифта — 12.**

Все страницы рукописи, включая список литературы и графический реферат, нумеруются.

Уравнения, схемы, таблицы, рисунки и ссылки на литературу нумеруются **в порядке их упоминания в тексте.**

Список цитируемой литературы должен включать ссылки на наиболее существенные работы по теме статьи. В тексте статьи должны быть упомянуты **все ссылки**, приведенные в списке литературы. В тексте **ссылки** на литературу даются в квадратных скобках и нумеруются **строго в порядке их упоминания**. Список литературы печатается на отдельной странице с указанием инициалов и фамилий **всех авторов.**

Список литературы должен быть оформлен следующим образом:

Книги: *Бучаченко А.Л., Вассерман А.М.* Стабильные радикалы. М., Химия, 1973, 58 с.

Статьи в сборниках: Ола *Дж., Фарук О., Пракаш Дж. К.С.* в кн: Активация и каталитические реакции алканов / под ред. К.М.Хилла. М., Наука, 1992, с. 39.

При цитировании переводных изданий после выходных данных русскоязычной версии в квадратных скобках необходимо указать выходные данные оригинального издания. Например: *Внутреннее вращение молекул.*/ под ред. В.Д.Орвилл-Томаса. М., Мир, 1974, 374 с. [*Internal Rotation in Molecules*, Ed. W. J. Orville-Thomas, Wiley, New York, 1974, 329 pp.].

Журналы: *Gal´pern E.G., Stankevich I.V., Chistyakov A.L., Chernozatonskii L.A.* // Chem. Phys. Lett., 1997, v.269, p.85.

При цитировании русскоязычного журнала, переводимого за рубежом, необходимо приводить ссылку и на англоязычную версию. Например: Лайков Д. Н., Устынюк Ю. А.// *Изв. АН, Сер. хим.,* 2005, с.804 [*Russ. Chem. Bull., Int. Ed.*, 2005, 54, 820].

Патенты: А.с. 9854 СССР // *Б.И.*, 1978, 61. или: US Pat. 55973 // *Chem. Abstrs*., 1982, **97**, 150732.

Диссертации: Ковалев Б.Г. Автореф. дисс. «....» доктора хим. наук. Город, институт, год, стр.

Программы: Sheldrick G. M., *SHELXL93, Program for the Refinement of Crystal Structure*, Göttingen University, Göttingen (Germany), 1993.

Банки данных: *Cambridge Structural Database System, Version 5.17*, 1999.

Ссылки на неопубликованные результаты и частные сообщения даются исключительно в виде сносок, а в списке литературы не приводятся и не нумеруются. При цитировании неопубликованных работ и частных сообщений необходимо представить разрешение от лица, на чьи данные приводится ссылка.

Памятка для авторов

Для максимального **сокращения сроков публикации** редакция просит авторов обратить особое внимание на **оформление статьи**.

Общие положения

Материалы, представляемые в редакцию:

- фамилия, имя, отчество и координаты лица, с которым редакция должна вести переписку (почтовый адрес, номер телефона, номер факса, адрес электронной почты). Фамилия автора, ответственного за переписку, должна быть отмечена звездочкой.
- направление от организации
- экспертное заключение (для граждан РА)
- текст статьи, аннотации на русском, английском и армянском языках на отдельных страницах (либо в тексте), рисунки и таблицы (все в 2 экз.)
- графический реферат
- **последовательность расположения частей статьи** (кроме писем в редакцию):
- индекс УДК
- название статьи
- автор(ы)
- развернутое название научной организации
- почтовый адрес с индексом
- факс
- адрес электронной почты
- аннотация
- **собственно текст статьи**
- введение
- постановка задачи

для статей физико-химической тематики:

- экспериментальная часть
- обсуждение полученных результатов с заключением

для статей, посвященных синтезу:

- обсуждение полученных результатов с заключением
- экспериментальная часть
- благодарности
- список литературы

В экспериментальной части должны быть представлены **доказательства строения и чистоты** всех новых соединений, источники использованных **нетривиальных реагентов** или **методики их получения**, а также условия **дополнительной** подготовки реагентов и растворителей.

Для всех синтезированных соединений следует дать **названия по номенклатуре** IUPAC. Металлоорганические комплексы могут быть названы по системе *Chemical Abstracts*.

Все **таблицы**, **схемы**, **рисунки**, **соединения и ссылки на литературу** должны нумероваться строго в порядке упоминания в тексте.

На осях графиков должны быть указаны **наименования** и **единицы измерения** соответствующих величин.

Рисунки спектров не должны быть выполнены от руки.

Все используемые **аббревиатуры** и **сокращения** должны соответствовать приведенному в Правилах для авторов списку или расшифровываться при первом упоминании.

Данные рентгеноструктурного исследования следует представлять в виде рисунка(ков) молекулы (с пронумерованными атомами) или кристаллической упаковки и таблиц, содержащих **необходимые** геометрические характеристики молекул (**основные** длины связей, валентные и торсионные углы).

Для основного текста статьи обязательно использование шрифта Unicode, желательно Times New Roman, для греческих букв — шрифт Symbol.

Символы переменных физических величин (например, температура — *T*), единицы их измерения (K), стереохимические дескрипторы (*цис*, *Z*, *R*), локанты (*N*-метил), буквенные (но не цифровые) символы при обозначении групп симметрии должны быть напечатаны *курсивом* (*C2v*, но не *C2v*).

В списке литературы должны использоваться только стандартные сокращения названий журналов.

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