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SYNTHESIS OF PROPERTIES N-METHYL-2-(PYRID-4-YL)-3,4-FULLEROPYRROLIDINE

Abstract. The article is devoted to the reactions of [2+3] cycloaddition of pyridine-4-aldehyde to fullerene C60, as well as to the preparation of its water-soluble from of the resulting reaction product N-methyl-2-(pyrid-4-yl)-3,4-fulleropyrrolidine. A literature review of organic compounds containing the pyrrolidine cycle was carried out. It is noted that such compounds have a wide spectrum of biological activity and are part of many drugs of both natural and synthetic origin. In this regard, an interesting "pharmacophore" group is the pyridine cycle, which is part of about 5% of all known drugs. The reaction of pyridin-4-aldehyde with fullerene C60 was carried out in the presence of sarcosine under the conditions of the Prato reaction.

The reaction mechanism of 1,2-dipolar cycloaddition, leading to fulleropyrrolidine, is described. The water-soluble complex fulleropyrrolidinas with poly-N-vinylpyrrolidone was obtained.

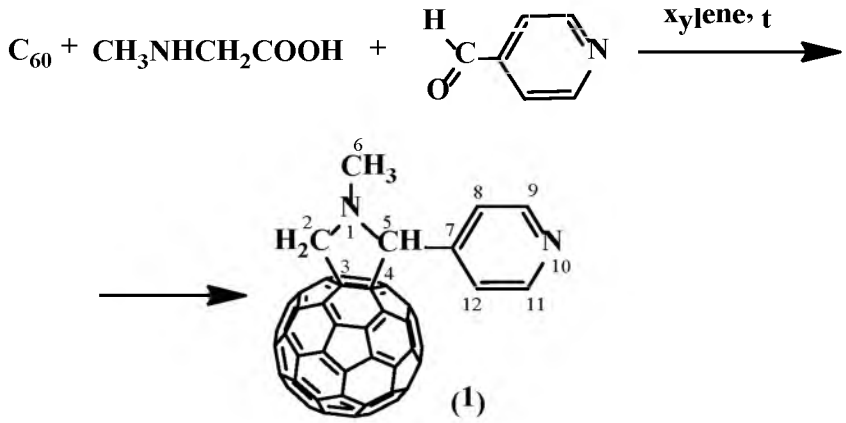
The structures of the synthesized compounds were studied by IR, UV, ^{1}H and ^{13}C NMR spectroscopy, as well as by the date of two-dimensional spectra of COSY (1H-1H) and HMQC (^{1}H-^{13}H). The values of chemical shifts, multiplicity and integrated intensity of ^{1}H and ^{13}C NMR signals in one-dimensional NMR spectra were determined. Using spectra in the formats COSY (1H-1H) and HMQC (1H-13C) homo- and heteronuclear interaction were established, confirming the structure of the studied compounds.

Key words: fullerene C60, sarcosine, pyridine-4-aldehyde, fulleropyrrolidines, Prato reaction, NMR spectra.

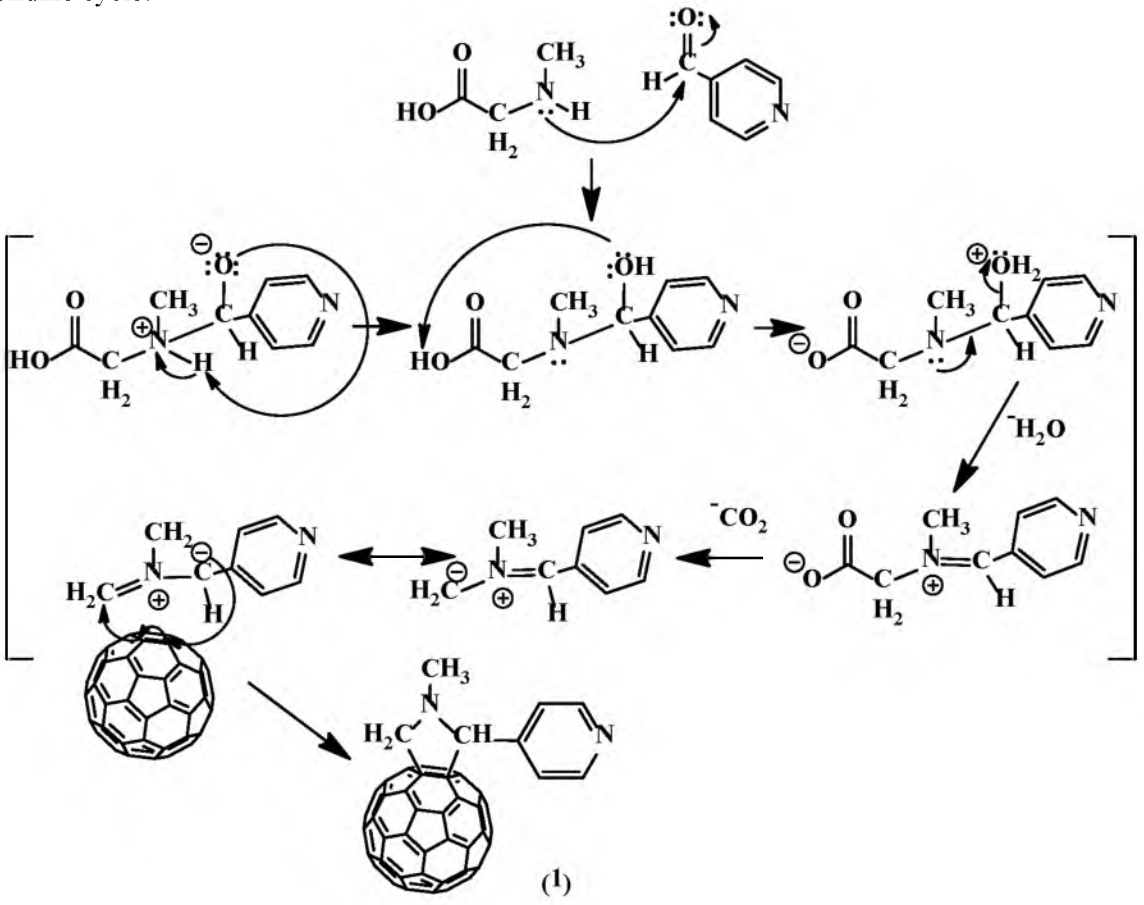
Currently, among a large number of functionalized C60 fullerene compounds, fulleropyrrolidine derivatives are one of the most intensively studied classes [1-3]. The 1,3-dipolar cycloaddition of azomethinilides to fullerene, known as the Prato reaction [4], is one of the most effective ways in obtaining fulleropyrrolidines. Compounds containing the pyrrolidine cycle in common organic compounds have a wide spectrum of biological activity and are part of many drugs of both natural and synthetic origin, for example, proline, atropine. It should be noted that some of the most important aspects of the biological activity of fullerens and its derivatives include the fight against HIV and antibacterial activity, inhibition of enzymes, antitumor therapy, controlled drug delivery, neuroprotective properties, and antioxidant activity. In fullerene synthesis, studies of the synthesis of C60 fullerene derivatives containing new "pharmacophore" groups are of great interest [4-12]. In this regard, an interesting "pharmacophore" group is the pyridine cycle, which is pert of about 5% of all known drugs. However, compounds containing both the pyrrolidine, pyridine rings and the fullerene sphere have so far been little studied.

Taking into account the scientific and applied prospects of the pyridine series and fullerene, we synthesized and conducted an NMR study of the structural features of the new fulleropyrrolidine 1 by the three-component condensation of fullerene C60, N-methylglycine (sarcosine) and pyridine-4-aldehyde under the conditions of the Prato reaction. One of the main factors affecting the yield of the final product in this reaction is the homogeneity of the medium, therefore the synthesis of fulleropyrrolidine 1 was carried out in xylene while the reaction medium was heated for 3 hours. The presence of an amino acid in

the reaction medium, which is a zwitterionic compound, probably negatively affects on the reaction rate (heterogeneity factor) [13-19].



The mechanism of formation of N-methyl-2-(pyrid-4-yl)-3,4-fulleropyrrolidine (**1**) involves the condensation of an α-amino acid (sarcosine) with an aldehyde (pyridin-4-aldehyde), leading to the formation of an ammonium salt, which undergoes decarboxylation process to obtain an *insitu* azomethine ylide. The latter reacts with a 6,6-double bond of fullerene by 1,3-dipolar cycloaddition, forming a pyrrolidine cycle.



The structure of the obtained new fulleropyrrolidine **1** was established by IR, UV, ^{1}H and ^{13}C NMR spectroscopy, as well as by the data of two-dimensional spectra of COSY (^{1}H-^{1}H) and HMQC (^{1}H-^{13}C).

In the spectrum of IR compound **1**, bands for C–N bonds of the pyridine ring are observed; vibrational frequencies of the fullerene skeleton, C–H, and N–H bonds are present (figure 1).

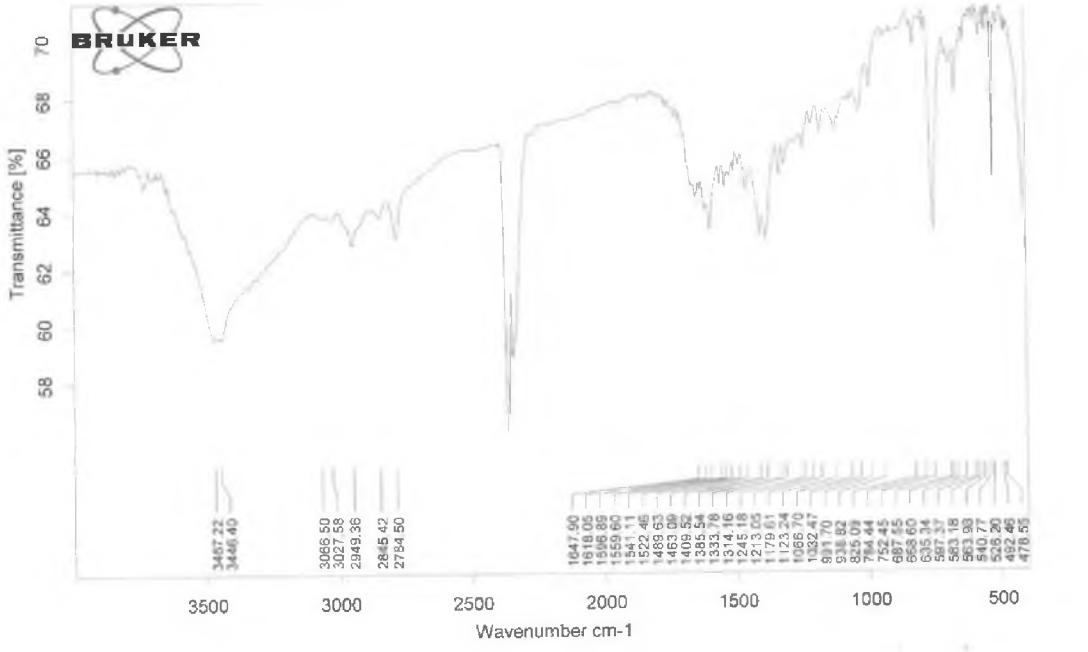


Figure 1 - IR spectrum of compound 1

The UV spectrum of compound **1** has 310, 319, and 430 nm (rigure 2). A peak with a low intensity at 430 nm is characteristic of all [6,6] - closed adducts of fullerene C60.

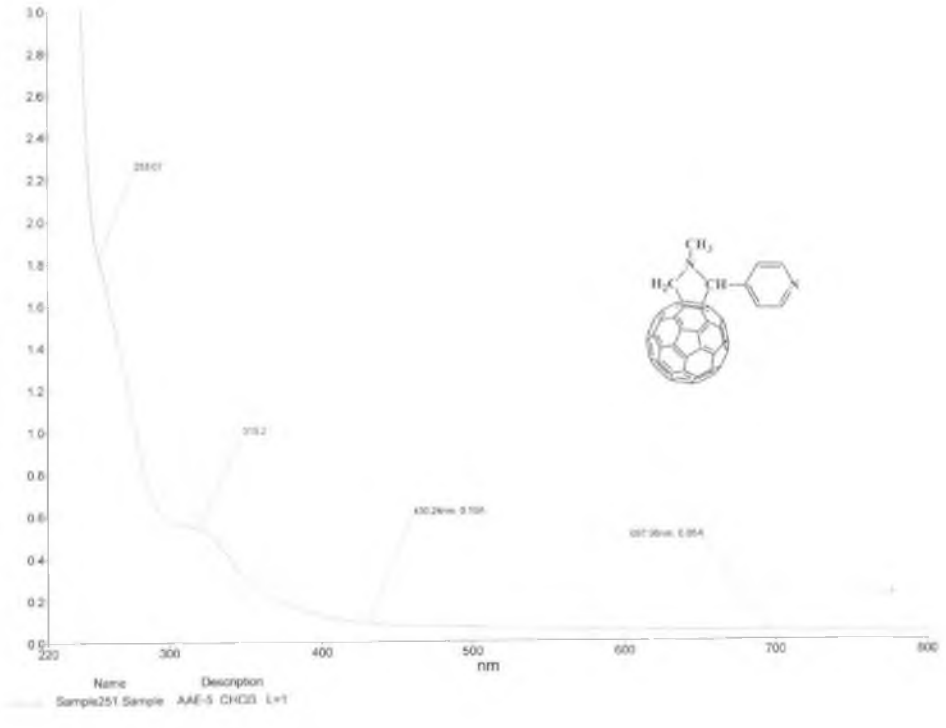


Figure 2 - UV spectrum of compound 1

The ^{1}H NMR spectrum of compound **1** is characterized by the presence of a three-proton singlet signal at 2.86 ppm. protons of the H-6,6,6N-methyl fragment of the pyrrolidine ring. Single-proton singlet signal at 4.97 ppm indicates the presence of the metin proton H-5 in the pyrrolidine cycle. The appearance of two single-proton doublet signals at 4.33 and 5.04 ppm with the same spin-spin coupling constant of ^{2}J 9.4 Hz confirms the presence of two axial and equatorial protons H-2ax and H-2eq of the pyrrolidine ring

bonded to the fullerene nucleus. The aromatic pyridine protons H-8, 12 and H-9, 11 were manifested by broadened two-proton siglets at 7.79 and 8.72 ppm respectively.

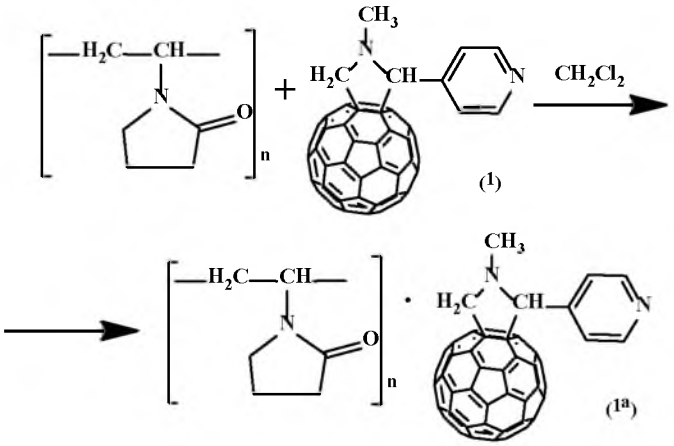
In the ^{13}C NMR spectrum of compound **1**, signals of the pyrrolidine ring with an N-methyl substituent are observed at 40.07 (C-6), 70.12 (C-2) and 82.42 (C-5) ppm. The carbon atoms of the pyridine fragment resonated at 124.24 (C-8.12), 150.13 (C-9.11) and 155.68 (C-7) ppm. Numerous signals in the range of 136-148 ppm belong to sp^2-hybridized carbon atoms of the fullerene nucleus.

The structure of compound **1** was also confirmed by two-dimensional NMR spectroscopy COSY (^1H-^1H) and HSQC (^1H-^{13}C), which allows one to establish spin-spin interactions of a homo- and heteronuclear nature. The observed correlations in the molecule are presented in the diagrams. In the spectra of the ^1H-^1H COSY compound, spin-spin correlations are observed through two bonds of methylene protons H^{2ax}-H^{2eq} (4.33, 5.04 and 5.04, 4.33) ppm and through three proton bonds of the neighboring methine groups $H^{8,12}$ –$H^{9,11}$ (7.79, 8.72 and 8.72, 7.79) ppm pyridine ring. Heteronuclear interactions of protons with carbon atoms through one bond were established using ^1H-^{13}C HSQC spectroscopy for the following pairs present in the compound: H^6-C^6 (2.86, 40.06), H^{2ax}-C^2 (4.33, 70.12), H^{2eq}-C^2 (5.04, 70.12) H^5-C^5 (4.97, 82.42), $H^{8.12}$-$C^{8.12}$ (7.79, 124.24), $H^{9,11}$-$C^{9,11}$ (8.72, 150.13) ppm (figure 3).

Figure 3 - Correlations in the spectra of COZY (^1H-^1H) (a) and HMQC (^1H-^{13}C) (b) of compounds **1**

The main problem that impedes the biological studies of fullerene derivatives and the creation of therapeutic agents based on them is the insolubility of fullerenes in water. One of the possible ways to overcome this problem is to obtain water-soluble complexes of fullerene derivatives with water-soluble polymers approved for use in medicine, for example, with poly-N-vinylpyrrolidone.

In this regard, a complex of compound **1** with poly-N-vinylpyrrolidone in methylene chloride was obtained:



The formation of complex **1a** occurs as a result of solubilization of fullerenepyrrolidine **1** by PVP chains and the physical interaction of the lactam group with the fullerene sphere. The resulting complex **1a** is soluble in water.

Thus, using the reaction [2+3] cycloaddition, the reaction of addition of pyridin-4-aldehyde to C60-fullerene in the presence of sarcosine under the conditions of Prato reactions was carried out. A new compound N-methyl-2-(pyrid-4-yl)-3,4- fulleropyrrolidine was obtained and its water-soluble derivative. The structure of the obtained substances was proved by ^1H and ^{13}C NMR spectroscopy, as well as by the data of two-dimensional spectra of COSY (^1H-^1H) and HMQC (^1H-^{13}C).

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Experimental part

The IR spectrum was recorded on a Vertex 70V spectrophotometer (Bruker) in KBr pellets. UV spectra were recorded on a Lambda 750 spectrophotometer (PerkinElmer). The ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d_6 on a JNM-ECA 400 spectrometer (399.78 and 100.53 MHz ^{1}H and ^{13}C nuclei, respectively) of the Jeol company from Japan. The survey was carried out at room temperature using a DMSO-d_6 solvent. Chemical shifts are measured relative to the signals of residual protons or carbon atoms of a deuterated solvent.

N-Methyl-2- (pyrid-4-yl) -3,4-fulleropyrrolidine (1). To a solution of 100 mg (0, 1388 mmol) of C60 in 20 ml of xylene were added 14, 78 mg (0, 138 mmol) of pyridin-4-aldehyde and 123,6 mg (1,388 mmol) of sarcosine (molar ratio of reactants 1: 1, respectively). The reaction mixture was boiled for 3 hours at 110-120^{0}C. After removal of the solvent, the residue was chromatographed on a silica gel column, eluting with toluene unreacted C60 and product1. Yield 28 mg (23%). ^{1}H NMR spectrum, δ, ppm (J, Hz): 2.86 s (3H, H-6.6.6), 4.33 d (1H, H-2ax, ^{2}J 9.4), 4.97 s (1H, H-5), 5.04 d (1H, H- 2eq, ^{2}J 9.4), 7.79 br. s (2H, H-8.12), 8.72 br. s (2H, H-9.11). ^{13}C NMR spectrum, δC, ppm: 40.07 (C-6), 70.12 (C-2), 82.42 (C-5), 124.24 (C-8,12), 150.13 (C-9,11), 155.68 (C-7). IR spectrum, ν, cm-1: 526, 825, 1409, 1596, 2784, 2949, 3446, 3467. UV spectrum ($CHCl_3$), λmax, nm: 310, 319, 430.

The method of obtaining complex (1a). To a solution of 2 mg of fulleropyrrolidine **1** in 2 ml of methylene chloride was added 200 mg of PVP in 3 ml of methylene chloride. The reaction mixture was stirred for 30 minutes at room temperature. After removal of solvent, the residue was dried by vacuum.

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N-МЕТИЛ-2-(ПИРИД-4-ИЛ)-3,4-ФУЛЛЕРОПИРРОЛИДИННІҢ СИНТЕЗІ ЖӘНЕ ҚАСИЕТТЕРІ

Аннотация. Мақала пиридин-4-альдегидтің C_{60} фуллеренге [2+3]-циклоқосылу реакциясын және реакция нәтижесінде алынған өнім N-метил-2-(пирид-4-ил)-3,4-фуллеропирролидиннің суда еритін туындысын алу әдістемелерін зерттеуғеарналған. Құрамында пирролидинді циклі бар орғаникалық заттардың алыну жолдары мен қасиеттері туралы әдебиеттік шолу жасалған. Ол заттардың биолоғиялық қасиеттерінің кең аумақтылығы және олардың көптеген дәрілік табиғи және синтетикалық заттардың құрамына кіретіні талқыланған. Фуллерендік синтезде фуллерен C_{60} құрамында жаңа «фармакопиялық» топтары бар заттарды синтездеуге арналған ғылыми жұмыстарына көп көңіл бөлінетіні айтылады. Орғаникалық заттардың құрамына фуллереңді фрагменттердің болуы осы заттардың биолоғиялық қасиеттерін жақсартуы немесе жаңа, бұрын болмаған механикалық, химиялық, физикалық және биолоғиялық қасиеттердің пайда болуына әкелетіні көсетіледі. Бұл жаңа ерекше қасиеттер нано масштабтағы факторлардың әсерлерімен байланысты болуы айтылады. Фуллеренніҥ көптеген жаңа туындылары адамның иммунды жетіспеушілік ауруларына және бактерияларға қарсы, сондай-ақ ферменттерді тежеушілік, қатерлі ісікке қарсы, нейропротекторлық терапияда, сонымен бірге антиоксидантты қасиеттерді көптеп көрсететіне назар аударады. Жұмыста пиридин-4-альдегидтің C_{60} фуллеренмен қосылу реакциясы үшінші реағент амин қышқылы ғлициннің (саркозиннің) қатысуында Прато реакциясы жағдайында жүргізіледі. Реакциялық жағдайдың тиімді жолдарын табу үшін еріткіштердің (толуол, ксилол) табиғатының, реакцияның жүру уақыты ұзақтығының, әрекеттесуші заттардың мөлшерлік қатынасының, сондай-ақ реакциялық ортаның температуралық режимінің әсерлері зерттелген. Осы зерттеулердің нәтижесінде алынатын өнім реакциялық ортадан 28% бөлінін алынады. Алынған ғылыми нәтижелерді талдау мәліметтері бойынша 1,3-диполярлы циклді қосылу реакциясының іке асырылғаны туралы тұжырым жасалады. Аланған жаңа N-метил-2-(пирид-4-ил)-3,4-фуллеропирролидиннің биолоғиялық қасиеттерін зерттеу үшін оның суда еритін қосылысы поли-N-винилпирролидонмен коваленттi байланыссыз жағдайда алынады. Жұмыста синтезделініп алынған заттардың химиялық-физикалық қасиеттерінқазіргі заманғы ИК-, УФ-, ЯМР ^{1}H және ^{13}C спектроскопия, сондай-ақ қосөлшемді COSY (^{1}H-^{1}H) и HMQC (^{1}H-^{13}C) спектрлерімен зерттеу нәтижелері келтірілген. Алынған заттардың құрылысындағы ^{1}H мен ^{13}C атомдарының ЯМР-спектрлеріндегі химиялық жылжулары

мен интегралды сызықтары талқыланған. Қосөлшемді COSY (^{1}H-^{1}H) и HMQC (^{1}H-^{13}C) спектрлері бойынша алынған заттардағы гомо- мен гетероядролы әрекеттесушілерді талқылау нәтижесінде алынған жаңа заттардың құрылысы дәлелденеді.

Түйін сөздер: фуллерен С60, саркозин, пиридин-4-альдегид, фуллеропирролидиндер, Прато реакциясы, ЯМР-спектрлер

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СИНТЕЗ И СВОЙСТВА N-МЕТИЛ-2-(ПИРИД-4-ИЛ)-3,4-ФУЛЛЕРОПИРРОЛИДИНА

Аннотация. Статья посвящена изучению реакции [2+3] циклоприсоединения пиридин-4-альдегида к фуллерену C_{60}, а также получению водорастворимой формы полученного продукта реакции N-метил-2-(пирид-4-ил)-3,4-фуллеропирролидина. Проведен литературный обзор по органическим соединениям, содержащим пирролидиновый цикл. Отмечено, что такие соединения обладают широким спектром биологической активности и входят в состав многих лекарственных препаратов как природного, так и синтетического происхождения. В этом плане интересной «фармакофорной» группой является пиридиновый цикл, который входит в состав около 5 % от всех известных лекарственных препаратов. Однако соединения, содержащие одновременно пирролидиновый, пиридиновый циклы и фуллереновую сферу исследованы пока мало. В фуллереновом синтезе большой интерес представляют исследования синтеза производных фуллерена C_{60}, содержащие в своем составе новые «фармакофорные» группы. Показано, что наличие фуллеренового фрагмента в структуре соединения может привести к существенному улучшению или появлению качественно новых механических, химических, физических, биологических и других свойств соединений. Эти свойства связаны с проявлением наномасштабных факторов. Отмечено, что некоторые из наиболее важных аспектов биологической активности фуллеренов и его производных включают борьбу с ВИЧ и антибактериальную активность, ингибирование ферментов, противоопухолевую терапию, контролируемую доставку лекартственных средств, нейропротекторные свойства, а также антиоксидантную активность. Реакция взаимодействия пиридин-4-альдегида и фуллерена C_{60} проводилась в присутствии аминокислоты глицина (саркозина) в условиях реакций Прато. С целью нахождения оптимальных условий реакции проведено изучение влияния природы растворителей, соотношение реагирующих веществ, продолжительность реакции, а также температурный режим реакционной среды. На основании анализа полученных данных описан механизм реакции 1,3-диполярного циклоприсоединения, приводящее к фуллеропирролидину. Для изучения биологических свойств получен водорастворимый комплекс нового фуллеропирролидина с поли-N-винилпирролидоном. Исследованы строения синтезированных соединений методами ИК-, УФ-, ЯМР ^{1}H и ^{13}C спектроскопии, а также данными двумерных спектров COSY (^{1}H-^{1}H) и HMQC (^{1}H-^{13}C). Определены значения химических сдвигов, мультиплетность и интегральная интенсивность сигналов ^{1}H и ^{13}C в одномерных спектрах ЯМР. С помощью спектров в форматах COSY (^{1}H-^{1}H) и HMQC (^{1}H-^{13}C) установлены гомо- и гетероядерные взаимодействия, подтверждающие структуру исследуемых соединений.

Ключевые слова: фуллерен C_{60}, саркозин, пиридин-4-альдегид, фуллеропирролидины, реакция Прато, ЯМР-спектры.

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