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ОРГАНИЧЕСКАЯ И БИООРГАНИЧЕСКАЯ ХИМИЯ

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METHYLATION OF 1,2,4-TRIAZOLO[1,5-a]PYRIMIDINES AND METHODOLOGY FOR DETERMINING THE REGIOSELECTIVITY OF THE REACTION BY THE NOESY ^{1}H NMR SPECTROSCOPY TECHNIQUE

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The interaction of some 1,2,4-triazolo[1,5-a]pyrimidines with methyl iodide was investigated. It has been proven that methylation occurs at the nitrogen atom of the triazole ring resulting in the formation of quaternary salts of 3-methyl-1,2,4-triazolo[1,5-a]pyrimidinium. This differs from the previously noted direction of methylation of pyrazolo[1,5-a]pyrimidines which occured at the nitrogen atom of the pyrimidine ring. The basic deuterium exchange of protons of the synthesized systems has been studied. Regiospecifically proceeding deuterium substitution of protons of methyl groups located in the pyrimidine ring was noted. The efficiency of using the NOESY ^{1}H NMR spectroscopy technique in proving the structure of synthesized substances and determining the direction of the reactions is shown.

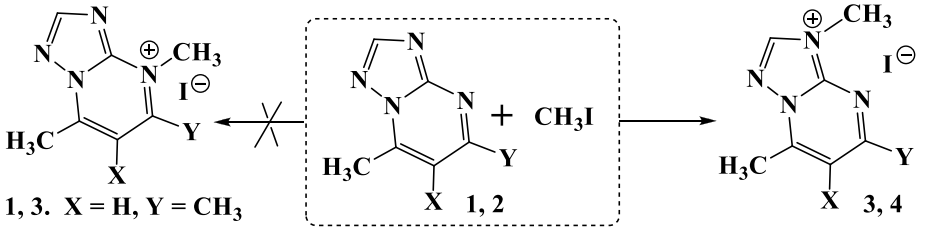
Figs. 3, references 11.

Annelated heteroarenes containing azine and azole rings in the molecule are compounds with an uneven (asymmetric) distribution of p-electron density. Five-membered heteroarenes, especially those containing nitrogen atoms exhibit pronounced π-redundancy, while six-membered azines are π-deficient systems. Such an uneven distribution of p-electron density should, as expected, be reflected in regional orientation of reactions both with electrophilic and nucleophilic reagents. Thus, the reactions of nucleophilic

substitution and nucleophilic recyclization are known to proceed with an attack on the electron-deficient azine ring [1-5].

Earlier, on a series of substituted pyrazolo[1,5-a]pyrimidines, it has been shown that methylation with methyl iodide occurs at the nitrogen atom of the pyrimidine ring, which leads to the formation of the corresponding N-4 methyl derivatives of pyrazolo[1,5-a]pyrimidinium salts [6, 7]. This direction of the electrophilic attack, however, is theoretically not uncontested, since the attack could proceed both at the nitrogen atom (N-4) of the pyrimidine ring (which was recorded in the noted works, and which is no less expected and more logical, taking into account the pronounced π-redundancy of the five-membered azole ring), and at the five-membered annelated ring (nitrogen atom N-1 of pyrazolo[1,5-a]pyrimidine). However, the study of ^{1}H NMR spectra recorded by the NOESY method, in which the interaction of the protons of the N-methyl group with the protons of the neighboring groups is observed, definitely indicates the alkylation of the N-4 nitrogen atom of the pyrimidine, rather than the pyrazole ring.

In continuation of these studies, in this work, the reactions of 5,7-dimethyl-1,2,4-triazolo [1,5-a]pyrimidine (**1**) and 7-methyl-6-ethoxycarbonyl-1,2,4-triazolo[1,5-a]pyrimidine (**2**) with methyl iodide were explored. The experiments, unexpectedly for us, showed that in both cases the reaction proceeded not at the pyrimidine ring, as was noted in the case of pyrazolo[1,5-a] pyrimidines, but at the N-3 nitrogen atom of the triazole ring.



This conclusion was made based on the study of the NMR spectra. The spectrum of both methylation products **3** and **4** showed signals of new methyl groups in the range of 4.0-4.2 *ppm* (which is typical for the quaternary nitrogen atom). The signals of aromatic protons were also displaced in a weak field, which is explained by the appearance of a positive charge in the molecule due to the quaternization of the nitrogen atom of the ring. However, on the basis of ^{1}H NMR spectra, it was not possible to unambiguously determine the position of N-methylation, i.e., the direction of the attack. This was proved by studying the NMR spectra obtained by the NOESY method. It turned out that the spectrum of compound **3** contained cross peaks between the protons of the N-methyl group and the proton of the triazole ring, and on the contrary, there was no interaction between the new

methyl group N-CH_3 and any of the methyl groups of the pyrimidine ring, which certainly indicates the occurrence of alkylation at one of the two triazole nitrogen atoms. We did not exclude the possibility of methylation at the triazole N-1 nitrogen atom. However, the absence of a cross-peak, indicating the interaction of protons of two methyl groups (pyrimidine ring and N-methyl triazole, which was expected during the formation of a methylated adduct at N-1), indicates that the reaction proceeds at the N-3 position of the studied molecule, i.e. obtaining iodide of 3,5,7-trimethyl-1,2,4-triazolo [1,5-a]pyrimidinium (**3**).

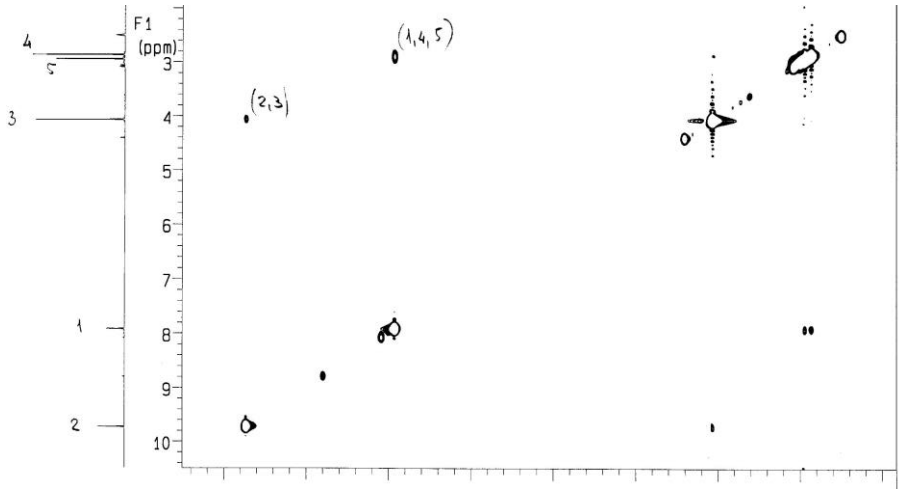


Fig. 1. NOESY ^{1}H NMR spectrum of compound **3.**

The fact that methylation at the triazole ring of the triazolo[1,5-a]pyrimidine derivative is not accidental was also confirmed by the example of the reaction of methyl iodide with 7-methyl-6-ethoxycarbonyl-1,2,4-triazolo[1,5-a]pyrimidine (**2**). And in this case, it was proved that the alkylation proceeded at the position N-3 of the bicyclic system. In particular, as in the above example, the NMR spectrum, recorded by the NOESY method, showed signals confirming the interaction between the protons H-2 of the triazole ring and N-CH_3. This is also evidenced by the absence of cross-peaks between the protons of the newly formed N-methyl group with any group or hydrogen atom in the pyrimidine ring.

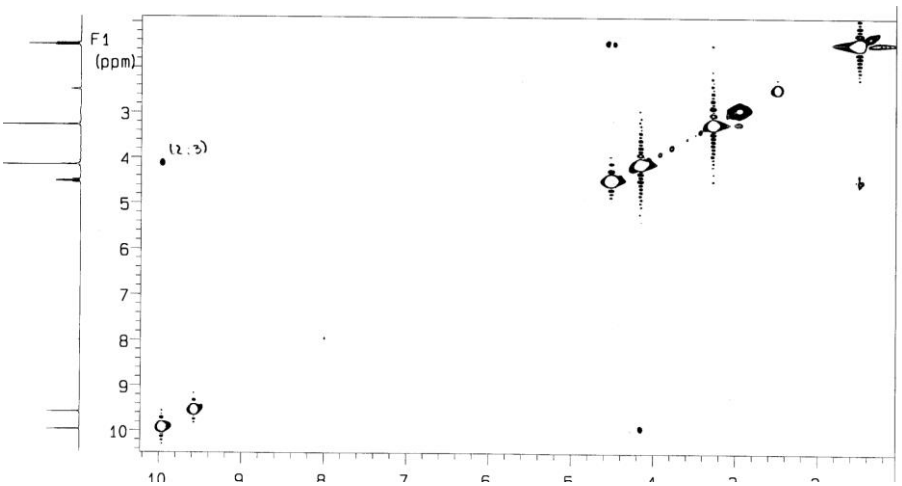
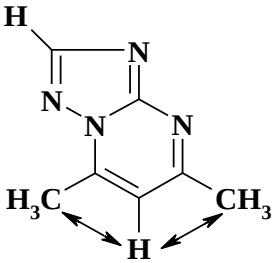


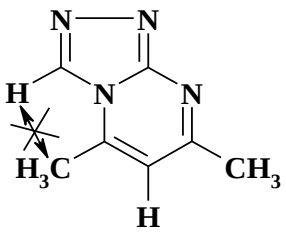
Fig. 2. NOESY ^{1}H NMR spectrum of compound **4.**

Thus, it can be concluded that the introduction of one more nitrogen atom into the azole ring (that is, the transition from pyrazolo[1,5-a]pyrimidines to triazolo[1,5-a]pyrimidines) leads to a significant shift of the electron density towards the five-membered ring, which becomes the reason for the alkylation of the triazole nitrogen atom rather than the pyrimidine fragment of the molecule.

Synthesis of the initial triazolopyrimidines **1** and **2** was carried out by the interaction of 3-amino-1,2,4-triazole, respectively, with acetylacetone and ethoxymethylidene acetoacetic ether (according to the methods published earlier [6, 8]), and their structure was also unambiguously confirmed using the NOESY technique. We considered it necessary and important to prove the structure of the initial substances, taking into account the possibility of the formation of isomers during the synthesis [2, 3, 6-8]. In the case of compound **1**, we excluded the possibility of the formation of the isomeric triazolo[4,3-a]pyrimidine derivative due to the absence of cross-peaks of the protons of the methyl groups of pyrimidine with the proton of the triazole ring. The spectrum shows only the interaction of the H-6 proton with the methyl groups of the pyrimidine ring.



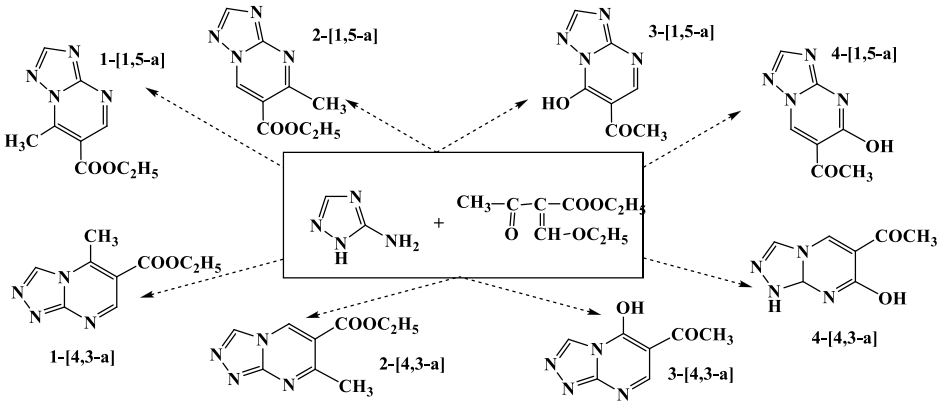
[1,5-a]



[4,3-a]

Spectral studies confirmed that compound **2** is also a derivative of 1,2,4-triazolo[1,5-a] pyrimidine, but not of an isomeric compound with a [4,3-a]-

junction. It is interesting that the reaction with ethyl ester of ethoxymethylidene acetoacetic acid, can theoretically result in the formation of 12 different isomers, and not only of two different isomeric systems – triazolo[1,5-a] pyrimidine and triazolo[4,3-a] pyrimidine. This is explained by the possibility of involving three different electrophilic groups of ethyl ester of ethoxymethylidene acetoacetic acid (ester ($COOC_2H_5$), acetyl (CH_3CO) and ethoxymethylidene (=CH-OC_2H_5), respectively) in the cyclocondensation process, as well as by two different directions of cyclization in the triazole ring, (with involvement of nitrogen atoms N-1 or N-4), as a result of which different reaction products should be obtained. Formulae for 8 of these molecules are given below. Isomeric triazolopyrimidines, in which condensation would have proceeded due to the acetyl and ester groups, and not due to the more active ethoxymethylidene group, are less probable. Therefore we did not show their formulae in the Scheme.



However, as our experiments have shown, the reaction is regiospecific and only one bicyclic product was isolated, the structure of which was determined on the basis of ^{1}H NMR spectra.

The spectrum of the obtained compound contains signals of the protons of the ethyl (triplet /1.43 *ppm*/ and quartet /4.45 *ppm*/) and methyl groups (singlet 3.27 *ppm*), as well as two single singlets of aromatic protons (8.48 and 9.32 *ppm*). On this basis, we concluded that the acetyl and ethoxymethylidene groups participated in the condensation of the pyrimidine ring, as a result of which the ester group remained in the synthesized substance. It can be seen from the above Scheme, that 4 of the compounds shown in the diagram – **1-[1,5-a], 2-[1,5-a], 1-[4,3-a]** and **2-[4,3-a]** can correspond to such a spectrum. Since in the spectrum obtained by the NOE method (nuclear Overhauser effect), apart from the long-range interaction between the protons of the methyl and ethyl groups, as well as the 7-H proton and the protons of the ethyl group, no other interactions were observed (for example, two aromatic protons or a proton of the triazole ring

and methyl group), the isolated compound was assigned the structure of the isomer **1-[1,5-a]** (compound **2**). The choice between **2-[1,5-a]** and **1-[1,5-a]** was made in favor of the latter model, since earlier [7] on the models of pyrazolo[1,5-a]pyrimidines it was proved that cyclization began from the attack of the amine group on the ethoxymethylidene group (=CH-OC_2H_5), which should lead to the production of compound **2**.

This methodology for determining the direction of attack turned out to be acceptable not only in the reaction with electrophilic, but also with nucleophilic reagents: in particular, in reactions with deuterated methylate ion, in the process of studying deuterium exchange of protons. Earlier, in a number of examples, it was noted that in a solution of deuterated sodium methoxide in deuterated methanol, isotopic exchange of protons of alkyl groups directly bound to the pyrimidine ring occurs [7, 9]. Such deuterium exchange can be carried out by attack of a nucleophilic particle at the alkyl group, and not at the pyrimidine carbon atoms due to the high CH-acidity of the alkyl groups. Similar transformations were noted in some heterocyclic systems capable of undergoing both basic [10] and acidic [11] deuterium exchange.

We have studied a similar interaction of the synthesized bicyclic pyrimidinium salts with solutions of deuterated sodium methoxide in deuterated methanol. In particular, the behavior of salts **3** and **4** with CD_3ONa in CD_3OD was studied, in which selective isotopic exchange (deuterium exchange) of C-alkyl groups was observed. ^1H NMR spectral studies of the products of this interaction were carried out, which confirmed such transformations.

Control experiments showed that in the ^1H NMR spectrum obtained in deuterated methanol (CD_3OD) without the addition of deuterated sodium methoxide, signals of all protons contained in the compound are observed.

However, in the NMR spectrum recorded after adding a small amount of CD_3ONa to the same ampoule, an easy, quantitative, and, most importantly, selectively proceeding basic deuterium exchange of protons of the C-methyl groups of the pyrimidinium salt was observed (within a few minutes, due to the replacement of hydrogen atoms with deuterium atoms). The signals of C-methyl groups disappeared completely at room temperature. With an increase in the duration of exposure to the deuterated reagent, the disappearance of the signal of one of the aromatic protons (apparently located in the triazole ring, in the position adjacent to the quaternized nitrogen atom) was noted.

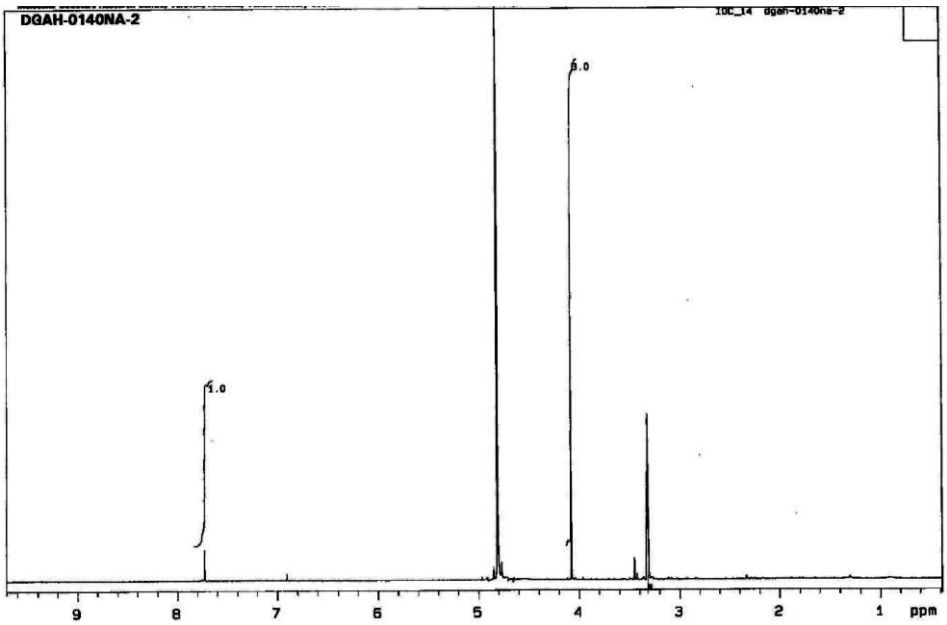
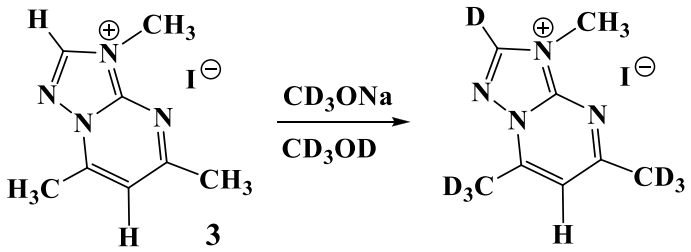
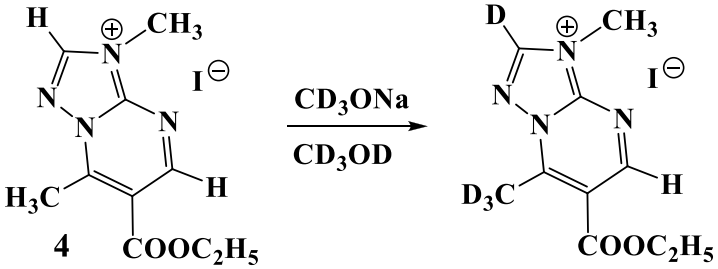


*Fig. 3. ^1H NMR spectrum of compound **3** after adding CD_3ONa.*



The scheme of the deuterium exchange reaction is apparently associated with the attack of the methylate ion at the most electrophilic position in the molecule, which leads to the elimination of a proton. The resulting carbanion is stabilized by the addition of a proton (or, when the reaction is carried out in a solution of deuterated methanol – of a deuterium atom).

It is important to note that in the spectrum of compound **4**, the signal of the protons of the 7th methyl group also rapidly disappeared completely, while the signals of other protons were retained. As in the example described above, with time (after 24 h), a deuterium exchange of one of the aromatic protons occurred.



The disappearance of the signals of the protons of the C-methyl groups of the pyrimidine ring in the ^{1}H NMR spectra unconditionally indicates the basic deuterium exchange of protons in the indicated groups.

The noted phenomenon of selective deuterium exchange, undoubtedly, can become a tool for studying the structure of various azines, as well as for the implementation of targeted isotopic exchange in heterocyclic systems, in particular, in the pyrimidine ring, and for the introduction of not only deuterium atoms into the molecule, but possibly tritium, which is especially important when studying drug metabolism. It is also shown that a convenient (and in some cases the only possible) method for determining the structure of substances is the methodology of using NOESY ^{1}H NMR spectroscopy.

Experimental part

NMR spectra were obtained at the Molecule Structure Research Center of the Scientific Technological Center of Organic and Pharmaceutical Chemistry of NAS RA on a Varian Mercury 300 device with a resonance frequency of 300.077 *MHz* for ^{1}H. TLC was performed on Silufol UV-254 plates, developed with iodine vapors and Ehrlich's reagent. Elemental analysis was performed on a Euro EA 3000 analyzer.

3,5,7-Trimethyl-1,2,4-triazolo[1,5-a]pyrimidinium iodide (3). A mixture of 1.5 *g* (0.01 *mol*) of 5,7dimethyl-1,2,4-triazolo[1,5-a]pyrimidine (**1**) [8] and 7.1 *g* (3 *ml*, 0.1 *mol*) of methyl iodide in a sealed ampoule placed in a boiling water bath is heated for 8-10 *h*. The precipitate formed is filtered off, washed with ether and dried. Yield 2.75 *g* (94.8%) of iodide **3**, mp 240-241°C. ^{1}H NMR spectrum δ, ppm, *Hz* (DMSO-d_6/CCl_4): 2.87 (3H, s, CH_3); 2.95 (3H, d, *J* = 0.9, CH_3); 4.07 (3H, s, N^+CH_3); 7.92 (1H, q, *J* = 0.9, 6-H), 9.73 (1H, s, 2-H). Found, %: C 33.41; H 3.75; N 19.24. $C_8H_{11}IN_4$. Calculated, %: C 33.12; H 3.82; N 19.31.

3,7-Dimethyl-6-ethoxycarbonyl-1,2,4-triazolo[1,5-a]pyrimidinium iodide (**4**). A mixture of 7.1 *g* (3 *ml*, 0.05 *mol*) of methyl iodide and 1.5 *g* (0.005 *mol*) of 7-methyl-6-ethoxycarbonyl-1,2,4-triazolo[1,5-a] pyrimidine (**2**) [6], placed in a sealed ampoule, is heated in a boiling water bath for 8-10 *hours*. The precipitate formed is filtered off, washed with ether and dried in air. Yield 1.6 *g* (91.4%) of 3,7-dimethyl-6-ethoxycarbonyl-1,2,4-triazolo[1,5-a]pyrimidinium iodide (**4**), mp 147-148°C. ^{1}H NMR spectrum δ, *ppm*, Hz): 1.50 (3H, t, *J* = 7.1, $OCH_2\underline{CH_3}$); 3.28 (3H, s, 7-CH_3); 4.17 (3H, s, N^+CH_3); 4.53 (2H, q, *J* = 7.1, $O\underline{CH_2}CH_3$); 9.58 (1H, s, = CH), 9.97 (1H, s, = CH). Found, %: C 33.89; H 4.04; N 17.28. $C_{10}H_{13}IN_4O_2$. Calculated, %: C 34.09; H 3.78; N 17.04.

Dynamics of the change in ^{1}H NMR spectra of 3,5,7-trimethyl-1,2,4-triazolo[1,5-a] pyrimidinium iodide (3) under the action of CD_3ONa in a CD_3OD solution. In an NMR ampoule, a solution of several mg of iodide **3**

in a CD_3OD solution is prepared and a control ^1H NMR spectrum is recorded. Next, 2-3 drops of a solution of CD_3ONa in CD_3OD prepared in advance by the interaction of sodium with CD_3OD are added to the ampoule and the spectrum is re-recorded. The registration of spectra is periodically repeated, observing the dynamics of change in the spectra, which occurs as a result of deuterium exchange, in time.

^1H NMR spectrum, δ, *ppm*, *Hz* of compound **3**: 2.87 (3H, s, CH_3); 2.95 (3H, d, *J* = 0.9, CH_3); 4.07 (3H, s, N^+CH_3); 7.92 (1H, q, *J* = 0.9, 6-H), 9.73 (1H, s, 2-H).

^1H NMR spectrum δ, ppm, *Hz* of compound **3** (*5 min* after adding CD_3ONa): 4.07 (3H, s, N^+CH_3); 7.82 (1H, q, *J* = 0.9, 6-H).

^1H NMR spectrum δ, ppm, *Hz* of compound **3** (*10 min* after adding CD_3ONa): 4.07 (3H, s, N^+CH_3); 7.75 (1H, q, *J* = 0.9, 6-H).

^1H NMR spectrum δ, ppm, *Hz* of compound **3** (*2 h* after adding more CD_3ONa): 3.25 (3H, s, N^+CH_3); 6.92 (1H, q, *J* = 0.9, 6-H).

Dynamics of the change in ^1H NMR spectra of 3,7-dimethyl-6-ethoxycarbonyl-1,2,4-triazolo [1,5-a]pyrimidinium iodide (4) under the action of CD_3ONa in a CD_3OD solution.

^1H NMR spectrum δ, ppm, *Hz* of compound **4**: 1.50 (3H, t, J = 7.1, $OCH_2\underline{CH_3}$); 3.28 (3H, s, 7-CH_3); 4.17 (3H, s, N^+CH3); 4.53 (2H, q, *J* = 7.1, $O\underline{CH_2}CH_3$); 9.58 (1H, s, = CH), 9.97 (1H, s, = CH).

^1H NMR spectrum δ, ppm, *Hz* of compound **4** *1 min* after adding CD_3ONa: 1.50 (3H, t, *J* = 7.1, $OCH_2\underline{CH_3}$); 3.28 (3H, s, 7-CH_3); 4.17 (3H, s, N^+CH_3); 4.53 (2H, q, *J* = 7.1, $O\underline{CH_2}CH_3$); 9.58 (1H, s, = CH), 9.97 (1H, s, = CH).

^1H NMR spectrum δ, ppm, *Hz* of compound **4** *10 min* after adding CD_3ONa: 1.50 (3H, t, *J* = 7.1, $OCH_2\underline{CH_3}$); 4.17 (3H, s, N^+CH_3); 4.53 (2H, q, *J* = 7.1, $O\underline{CH_2}CH_3$); 9.58 (1H, s, = CH), 9.97 (1H, s, = CH).

^1H NMR spectrum δ, ppm, *Hz* of compound **4** *24 h* after adding CD_3ONa: 1.50 (3H, t, *J* = 7.1, $OCH_2\underline{CH_3}$); 4.17 (3H, s, N^+CH_3); 4.53 (2H, q, *J* = 7.1, $O\underline{CH_2}CH_3$); 9.58 (0.5 H, s, = CH), 9.97 (1H, s, = CH).

^1H NMR spectrum δ, ppm, *Hz* of compound **4** *48 h* after adding a new amount of CD_3ONa: 1.50 (3H, t, *J* = 7.1, $OCH_2\underline{CH_3}$); 4.17 (3H, s, N^+CH_3); 4.53 (2H, q, *J* = 7.1, $O\underline{CH_2}CH_3$); 9.58 (0.2 H, s, = CH), 9.97 (1H, s, = CH).

1,2,4-ՏՐԻԱԶՈԼՈ[1,5-a]ՊԻՐԻՄԻԴԻՆՆԵՐԻ ՄԵԹԻԼԱՑՈՒՄ ԵՎ ՌԵԱԿՑԻԱՆԵՐԻ ՌԵԳԻՈՍԵԼԵԿՏԻՎՈՒԹՅԱՆ ՈՐՈՇՄԱՆ ՄԵԹՈԴՈԼՈԳԻԱՆ ՄՄՌ ^{1}Հ ՍՊԵԿՏՐՈՍԿՈՊԻԱՅԻ NOESY ՍՊԵԿՏՐՆԵՐԻ ՄԻՋՈՑՈՎ

Գ.Հ. ԴԱՆԱԳՈՒԼՅԱՆ, Ա.Փ. ԲՈՅԱԽՉՅԱՆ, Ա.Կ. ԹՈՒՄԱՆՅԱՆ. Ա.Գ. ԴԱՆԱԳՈՒԼՅԱՆ և Մ.Ռ. ԱՌԱՔԵԼՅԱՆ

Հետազոտվել է որոշ 1,2,4-տրիազոլո[1,5-a]պիրիմիդինների փոխազդեցությունը մեթիլյոդիդի հետ: Ապացուցվել է, որ մեթիլացումը ընթանում է տրիազոլային օղակի ազո-

ատ ատոմի վրայով, որի արդյունքում առաջանում են 3-մեթիլ-1,2,4-տրիազոլո[1,5-a]պիրիմիդինիումի չորրորդային աղեր: Դա տարբերվում է մինչ այդ պիրիզոլո[1,5-a]պիրիմիդինների շարքում նկատված ռեակցիայի ուղղությունից, որն ընթանում է պիրիմիդինային օղակի ազոտի ատոմով: Հետազոտվել է սինթեզված համակարգերում ընթացող պրոտոնների հիմնային դեյտերափոխանակությունը: Արձանագրվել է պիրիմիդինային օղակում գտնվող մեթիլ խմբերի պրոտոնների ռեգիոընտրողաբար ընթացող դեյտերափոխանակումը:

Հաստատվել է ՄՄՊ ^{1}H սպեկտրոսկոպիայի NOESY եղանակի կիրառման արդյունավետությունը սինթեզված միացությունների կառույցի ապացուցման և ռեակցիաների ուղղության որոշման համար:

МЕТИЛИРОВАНИЕ 1,2,4-ТРИАЗОЛО[1,5-a]ПИРИМИДИНОВ И МЕТОДОЛОГИЯ ОПРЕДЕЛЕНИЯ РЕГИОСЕЛЕКТИВНОСТИ РЕАКЦИИ ПО СПЕКТРАМ NOESY ЯМР ^{1}H-СПЕКТРОСКОПИИ

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Исследовано взаимодействие некоторых 1,2,4-триазоло[1,5-a]пиримидинов с метилйодидом. Доказано, что метилирование идет по атому азота триазольного кольца, приводя к получению четвертичных солей 3-метил-1,2,4-триазоло[1,5-a]пиримидиния. Это отличается от ранее отмеченного направления метилирования пиразоло[1,5-a]пиримидинов, протекающему по атому азота пиримидинового кольца. Изучен основный дейтерообмен протонов синтезированных систем. Отмечено региоспецифично протекающее дейтерозамещение протонов метильных групп, находящихся в пиримидиновом кольце. Показана эффективность использования методики NOESY ЯМР ^{1}H спектроскопии при доказательстве строения синтезированных веществ и определении направления протекания реакций.

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