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ALKYLATION AND ACYLATION REACTIONS OF 3-(MORPHOLINOMETHYL)-4-PHENYL-1*H*-1,2,4-TRIAZOLE-5(4*H*)-THIONE

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Key words: morpholine, thiosemicarbazide, triazole, cyclization, S-alkylation, N-acylation.

Abstract. Derivatives of 1,2,4-triazole-5-thiones are heterocyclic compounds with thiol-thione grouping. This assumes tautomeric transformations of 1,2,4-triazoline-5-thione to 1,2,4-triazole-5-thiol. 3-(Morpholinomethyl)-4-phenyl-1*H*-1,2,4-triazole-5(4*H*)-thione (II) exists in two tautomeric forms (IIa and IIb). This conducts the reaction of (II) by two reaction centers (by NH or SH groups). The presence of substituents in the 1,2,4-triazole ring promotes the reaction of substitution in the core of 1,2,4-triazole. During the alkylation or acylation of substituted 1,2,4-triazol-5(4H)-thione (II) the acceding group may be attached to either nitrogen atom or a sulfur atom. Thus alkylation with ethyl bromoacetate, methyl iodide and/or butyl bromide in alkaline media gave the corresponding S-alkylated compounds (III), (IV) and (V) respectively. While acylation of triazole (II) with benzoyl chloride in the presence of triethylamine yielded the N-acylated derivative (VI). The structures of the synthesized compounds were confirmed by elemental analyses, IR and H^1 NMR spectra.

Introduction. Search and development of highly biologically active compounds and other practically useful substances and materials is one of the priorities of organic chemistry. In this regard, a promising is the use of a systematic approach, including a targeted synthesis of potentially biologically active substances, the determination of its structure, chemical modification and bioscreening. A decisive role in the chain plays electronic and spatial structure of the synthesized compounds, which determine its reactivity, tendency to tautomeric transformations and biological activity [1].

Among the variety of classes of organic compounds that exhibit a wide range of biological activity leading place saturated heterocycles. Among the heterocyclic derivatives found many hundreds of highly drugs, pesticides, plant growth regulators, and many other substances and materials with application properties. The combination of hydrocarbon fragments and single hetero cyclic or polycyclic system gives those compounds of a number of properties that reflect the particular carbocyclic moiety and a heteroatom functions. Hetero significantly affect the reactivity of neighboring atoms can be included in the π-electron system are structural elements of σ-skeleton. In constructing heterocyclic system often use nitrogen, oxygen, sulfur, phosphorus [2].

Currently, there is an increased interest in the nitrogen-containing heterocyclic compounds having piperidine ring and heterocyclic systems combining different loop nature heteroatoms (morpholine, triazole, thiadiazole, triazoltion, oxadiazole, etc.) or different carbo- and heterocycles. This attention is due to the fact that among them found effective painkillers, antispasmodics, antidepressants, anticholinergics, blockers and other biologically active compounds. As a result of research in a number of heterocyclic derivatives, a whole cluster of painkillers, having as a framework the piperidine ring (lidol, morferidin, prodin, promedol prosidol, kazkain, Rihlokain). Among structurally related compounds found drugs with anti-inflammatory action (flazolon) psychotropic properties (haloperidol Benperidol). A

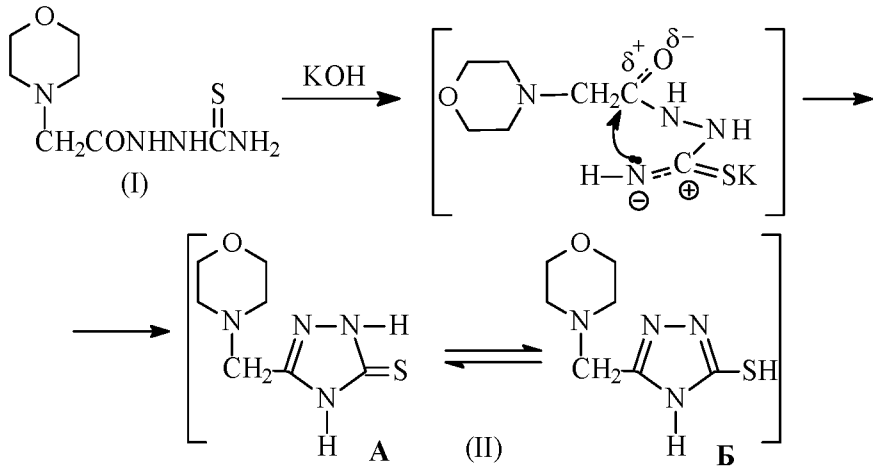
compound fused to various cycles, continue the structural number of physiologically active substances - teforin anticholinergic medication, analgesic morphine agonists (oksilarfon) and antagonists (nalorphine, naloxone) [3-6].

In recent years, we had the idea of the piperidine ring as an important component of the fragment of immunomodulation drugs. This, in particular, in the example of the preparation Rihlokain which test data in oncological practice exerts a synergistic effect with respect to cytostatics and acts as an immuno-modulator and antitumor drugs prolongator [7].

Among the derivatives of 1,2,4-triazole compounds are also found with antitumor properties, antifungal and sedatives, moreover, a number of compounds known as tranquilizers and substances with analgesic and anti-hypoxic action [1, 8].

Combining piperidine, morpholine fragments with other heterocycles (triazole, oxadiazole) may lead to new reaction centers and changing dietary properties. In the course of our research efforts towards the preparation of new compounds containing the morpholine ring, since several biological activities have reported in morpholine derivatives, have been described here on the synthesis and reactions of new compounds containing the 1, 2, 4-triazole ring as well as morpholine ring.

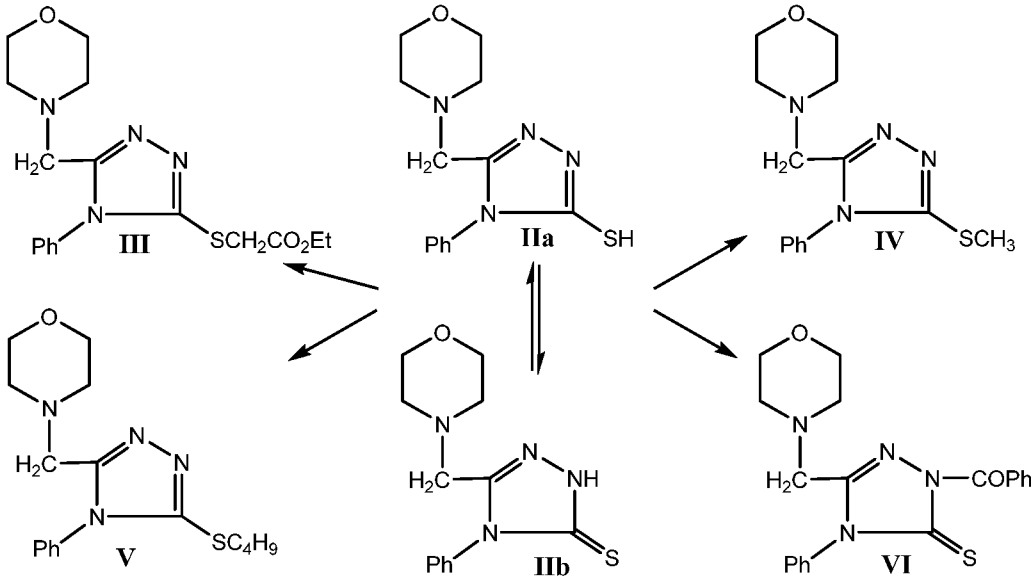
The starting compound, 3-(morpholinomethyl)-4-phenyl-1*H*-1,2,4-triazole-5(4*H*)-thione (II), was synthesized by the reaction of (morpholil-1-yl)-acetic acid thiosemicarbazide (I) with potassium hydroxide solution [9].



According to IR spectroscopic data of the original compound (II) which has triazoline-5-thione specture, the observation of C=S stretching band of 1240 cm^{-1} and the absence of an absorption about in 2600-2550 cm^{-1} region cited for SH group have proved that this compound was in the thionic form (IIb) in the solid state. The IR spectrum of triazole (II) showed attributable bands for NH group at 3100 cm^{-1}, for C=N group at 1650 cm^{-1} and for aromatic group at 1455-1500 cm^{-1}.

It is well known that alkylation of 1,2,4-triazole-5-thione derivatives with alkyl/arylalkyl halides or alkyl haloester gave the corresponding thioether derivatives. Therefore alkylation of 3-(morpholino-methyl)-4-phenyl-1*H*-1,2,4-triazole-5(4*H*)-thione (II) with ethyl bromo acetate in the presence of potassium carbonate gave ethyl 2-(5-(morpholinomethyl)-4-phenyl-4*H*-1,2,4-triazol-3-ylthio)acetate (III).

The IR spectrum of compound (III) showed attributable bands for C=O ester group at 1730 cm^{-1} and for C=N group at 1630 cm^{-1}. In the IR spectrum of compound (II), the absorption band of C=S group was absent which elucidate that the alkylation reaction was occurred at the sulfur atom.



The H^1 NMR spectrum of compound (III) showed signal at δ 4.0 ppm characteristic for S-CH_2. The ethyl protons resonate at δ 4.1 and 1.3 ppm characteristic for CH_2 protons (quarter).

The absence of signals in the region 4.5 -5.5 ppm elucidate that the alkylation reaction was occurred at the sulfur atom.

Similarly alkylation of (II) with methyl iodide and / or butyl bromide in the presence of triethylamine gave 4-((5-(alkylthio)-4-phenyl-4*H*-1.2.4-triazole-3-yl)methyl)morpholine (IV) and (V).

Table 1 – The H-NMR spectra of some synthesized compounds in $CDCl_3$

Compound (II)		Compound (III)		Compound (VI)	
Group	δ value	Group	δ value	Group	δ value
1H, NH	11.25	5H, Ar	7.1-7.5	10H, Ar-H	7.3-7.6
8H, Ar-H	7.4-7.5	2H, N-CH_2	4.09	2H, N-CH_2	4.3
2H, N-CH_2	3.3	2H, S-CH_2	4.04	4H, 2-CH_2	2.1
4H, 2-CH_2	2.3	4H, 2-CH_2	2.2	6H, 3-CH_2	1.7
6H, 3-CH_2	1.4	6H, 3-CH_2	1.5		

The IR spectra of compounds (IV) and (VI) showed attributable bands for C=N groups at 1605-1615 cm^{-1} and for phenyl groups at 1520-1540 cm^{-1}.

In the IR spectra for the alkylated compounds the absorption bands characteristic for C=S group were absent, this means that the alkylation reaction occurred at the sulfur atom and not at the nitrogen atom.

Acylation reaction of (II) with benzoyl chloride in dry benzene in the presence of triethylamine produced the N-acyl derivative (VI).

The IR spectrum of (3-(morpholinomethyl)-4-phenyl-5-thioxo-4,5-dihydro-1*H*-1,2,4-thiazol-1-yl)(phenyl)methanone (VI) showed attributable bands for C=O acyl group at 1730 cm^{-1}, for C=N group at 1620 cm^{-1}, for phenyl group at 1575-1600 cm^{-1} and for C=S group at 1235 cm^{-1}.

Table 2 – Physical data of the new compounds

Comp. №	m.p. ^0C	Formula (M. wt)	Calculated/found				
			C	H	N	O	S
II	183-184	$C_{13}H_{16}N_4OS$ (276.10)	56.50/56.25	5.84/5.66	20.27/20.02	5.79	11.60
III	254-255	$C_{17}H_{22}N_4O_3S$ (362.14)	56.33/56.01	6.12/5.96	15.46/15.76	13.24	8.85
IV	109-110	$C_{14}H_{18}N_4OS$ (290.12)	57.91/58.04	6.25/6.42	19.29/19.04	5.51	11.04
V	238-240	$C_{17}H_{24}N_4OS$ (330.43)	61.41/60.96	7.28/7.01	16.85/16.55	4.81	9.64
VI	240-241	$C_{20}H_{20}N_4O_2S$ (381.43)	63.14/63.56	5.30/5.04	14.73/14.21	8.41	8.43

Experimental

Synthesis ethyl 2-(5-(morpholinomethyl)-4-phenyl-4*H*-1,2,4-triazol-3-ylthio)acetate (III). To a solution of triazole (II) (0.01 mole) and anhydrous K_2CO_3 (0.01 mole) in 30 ml acetone was added ethyl bromo acetate (0.011 mole). The reaction mixture was heated at 55-60 ^{0}C with stirring for 6 hrs., after filtration the solvent was removed under vacuum and the solid product was filtered off and crystallized from ethanol to give white crystals of ethyl 2-(5-(morpholinomethyl)-4-phenyl-4*H*-1,2,4-triazol-3-ylthio)acetate (III).

Synthesis 4-((5-(alkylthio)-4-phenyl-4*H*-1.2.4-triazole-3-yl)methyl)-morpholine (IV) and (V). To a stirred solution of triazole (II) (0.01 mole) and triethylamine (0.01 mole) in absolute ethanol 20 ml, alkyl halide (0.01 mole) namely methyl iodide and / or butyl bromide was added. The reaction mixture was heated under reflux for 6 hrs. the solvent was removed under vacuum and the solid product was filtered off and crystallized from proper solvent to give white crystals of (IV) and (V) respectively.

Synthesis (3-(morpholinomethyl)-4-phenyl-5-thioxo-4,5-dihydro-1*H*-1,2,4-thiazol-1-yl)(phenyl)-methanone (VI). To a suspension of triazole (II) (0.01 mole) and triethylamine (0.01 mole) in dry benzene 20 ml, benzoyl chloride (0.01 mole) was added. The reaction mixture was heated under reflux for 6 hrs. The solid product obtained after cooling was filtered off and crystallized from chloroform to give white crystals of (3-(morpholinomethyl)-4-phenyl-5-thioxo-4,5-dihydro-1*H*-1,2,4-thiazol-1-yl)(phenyl)-methanone (VI).

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3-(МОРФОЛИНОМЕТИЛ)-4-ФЕНИЛ-1*H*-1,2,4-ТРИАЗОЛ-5(4*H*)-ТИОННЫҢ АЛКИЛДЕНУ РЕАКЦИЯЛАРЫ

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Тірек сөздер: морфолин, тиосемикарбазид, триазол, циклдену.

Аннотация. 1,2,4-Триазол-5-тиондардың туындылары тион-тиолды топтасуы бар гетероциклді қосылыстарға жатады. Бұл 3-(морфолинометил)-4-фенил-1*H*-1,2,4-триазол-5(4*H*)-тионның (II) екі таутомерлі формада (IIa и IIb) кездесетіндігін білдіреді және осы қасиеті реакцияларды екі реакциялық орталықтар арқылы жүргізуге мүмкіндік береді (NH немесе SH топтар арқылы). 1,2,4-Триазол сақинасында орынбасарлардың болуы 1,2,4-триазол ядросында орынбасу реакцияларының жүруіне алып келеді. Орынбасқан 1,2,4-триазол-5(4*H*)-тионды (II) алкилдеген немесе ацилдеген кезде енуші топ азот атомына немесе күкірт атомына қосыла алады. Осылайша бромсірке қышқылының этил эфирімен, метилиодид және бромды бутилмен сілтілік ортада алкилдегенде, сәйкесінше S-алкилденген туындылар (III), (IV) және (V) синтезделді. Ал 1,2,4-триазол-5(4*H*)-тионды (II) хлорлы бензоилмен триэтиламин қатысында ацилдеу, нәтижесінде N-ацилденген туындыны (VI) берді. Алынған қосылыстардың құрылыстары элементтік талдау, ИК және H-ЯМР спектрлермен дәлелденді.

РЕАКЦИИ АЛКИЛИРОВАНИЯ 3-(МОРФОЛИНОМЕТИЛ)-4-ФЕНИЛ-1*H*-1,2,4-ТРИАЗОЛ-5(4*H*)-ТИОНА

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Ключевые слова: морфолин, тиосемикарбазид, триазол, циклизация, S-алкилирование, N-ацилирование.

Аннотация. Производные 1,2,4-триазол-5-тионов относятся к гетероциклическим соединениям с тион-тиольной группировкой. Это предполагает таутомерные превращения 1,2,4-триазолин-5-тиона в 1,2,4-триазол-5-тиол. 3-(Морфолинометил)-4-фенил-1*H*-1,2,4-триазол-5(4*H*)-тион (II) существует в двух таутомерных формах (IIa и IIb). И это позволяет проводить реакции по двум реакционным центрам (по NH или SH группам). Наличие заместителей в кольце 1,2,4-триазола способствует неоднозначному протеканию реакции замещения в ядре 1,2,4-триазола. При алкилировании или ацилировании замещенного 1,2,4-триазол-5(4*H*)-тиона (II) вступающая группа может присоединиться либо к атому азота, либо к атому серы. Таким образом, при алкилировании этиловым эфиром бромуксусной кислоты, метилиодидом и бромистым бутилом в щелочной среде синтезированы S-алкилированные производные (III), (IV) и (V) соответственно. В то время как ацилирование 1,2,4-триазол-5(4*H*)-тиона (II) хлористым бензоилом в присутствии триэтиламина привело к N-ацилированному производному (VI). Структуры полученных соединений были подтверждены данными элементного анализа, ИК и спектров H-ЯМР.

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