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Д.В. Сокольский атындағы «Жанармай,
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Х А Б А Р Л А Р Ы

ИЗВЕСТИЯ

НАЦИОНАЛЬНОЙ АКАДЕМИИ НАУК
РЕСПУБЛИКИ КАЗАХСТАН
АО «Институт топлива, катализа и
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Қазақстан Республикасы Ұлттық ғылым академиясы "ҚР ҰҒА Хабарлары. Химия және технология сериясы" ғылыми журналының Web of Science-тің жаңаланған нұсқасы Emerging Sources Citation Index-те индекстелуге қабылданғанын хабарлайды. Бұл индекстелу барысында Clarivate Analytics компаниясы журналды одан әрі the Science Citation Index Expanded, the Social Sciences Citation Index және the Arts & Humanities Citation Index-ке қабылдау мәселесін қарастыруда. Webof Science зерттеушілер, авторлар, баспашылар мен мекемелерге контент тереңдігі мен сапасын ұсынады. ҚР ҰҒА Хабарлары. Химия және технология сериясы Emerging Sources Citation Index-ке енуі біздің қоғамдастық үшін ең өзекті және беделді химиялық ғылымдар бойынша контентке адалдығымызды білдіреді.

НАН РК сообщает, что научный журнал «Известия НАН РК. Серия химии и технологий» был принят для индексирования в Emerging Sources Citation Index, обновленной версии Web of Science. Содержание в этом индексировании находится в стадии рассмотрения компанией Clarivate Analytics для дальнейшего принятия журнала в the Science Citation Index Expanded, the Social Sciences Citation Index и the Arts & Humanities Citation Index. Web of Science предлагает качество и глубину контента для исследователей, авторов, издателей и учреждений. Включение Известия НАН РК в Emerging Sources Citation Index демонстрирует нашу приверженность к наиболее актуальному и влиятельному контенту по химическим наукам для нашего сообщества.

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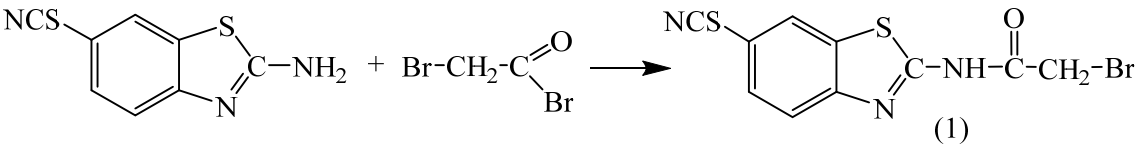
SOME DIRECTIONS IN THE MODIFICATION OF AZOLES

Abstract. This article presents studies on the targeted search for new derivatives of azoles, such as benzthiazole, 3,5-dimethylpyrazole, 1,3,4-oxadiazole-2-thione, 1,3,4-thiadiazole. The possibility of combining in one molecule of the azole ring with other cyclic compounds: the alkaloid cytisine, morpholine, furan and some arenes has been studied. To obtain new compounds, the reactions of bromination, acylation, and interaction with isothiocyanates were studied. Optimal synthesis conditions were studied for all reactions. It was found that the reaction of 4-bromo-3,5-dimethylpyrazole with isothiocyanates, in contrast to the previously written derivatives of anilines, takes a longer time and requires heating the reaction mixture. The combination of a pirasol fragment with halide substituents often results in an enhanced therapeutic effect. The synthesized 2-bromine-N-(6-rodanbenzo[d]thiazole-2-yl)acetamide, due to the alkylbromide group, is an important synth in the synthesis of new benzthiazole derivatives. Its derivatives combine in one molecule the rest of rhodanbenzthiazole with alkaloid cytisine and biogenic amine morpholine and are potentially biologically active compounds, since the molecule structure contains several pharmacophoric fragments: benzthiazole and alkaloid (amine) heterocycles, rhodane and urea groups. The mechanism of formation of 1,3,4-oxadiazole-2-tyons from hydrazides under action on them by carbon disulfide was studied and assumed. It was shown that dithiocarbamates in acidic medium decompose with the release of hydrogen sulfide and the formation of highly reactive isothiocyanate group. Then, intra-molecular cyclization occurs, with the formation of end products - 1,3,4-oxadiazole-2-thions. The structures of the synthesized compounds were studied by ^{1}H and ^{13}C NMR spectroscopy. All synthesized substances are potentially biologically active compounds, since they contain several pharmacophore fragments in their structure.

Key words: azoles, benzothiazole, 3,5-dimethylpyrazole, 1,3,4-oxadiazole-2-thione, heterocyclization.

Condensed nitrogen-containing heterocycles with various heteroatoms are widely used in medical practice as drugs with various therapeutic effects [1-5]. However, practically available benzothiazoles are of limited use due to their incomplete and comprehensive research, including through further chemical modification.

Thus, 2-amino-6-rhodanebenzothiazole is a by-product in the preparation of 4-rhodananiline. In order to use it as a starting reagent for the synthesis of various derivatives, we carried out its acylation with bromoacetic acid bromide. Due to its poor solubility in common organic solvents, acylation was performed in anhydrous DMF.

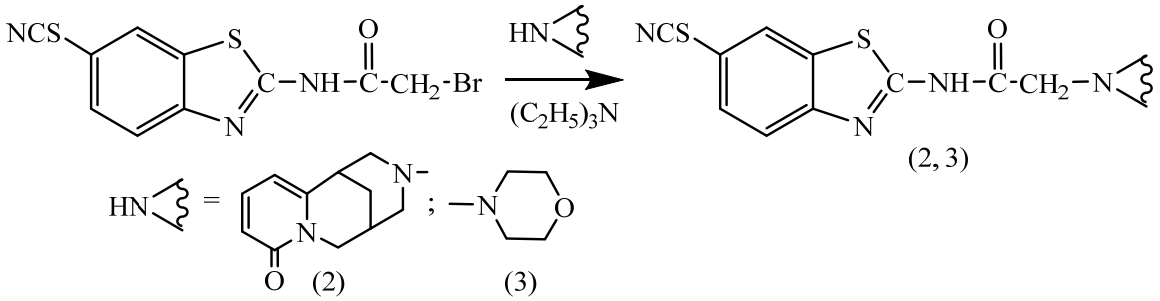


(1)

The resulting 2-bromo-N- (6-rhodanebenzo [d] thiazol-2-yl) acetamide (1) was further used in nucleophilic substitution reactions with the alkaloid cytisine and morpholine [4-8].

The synthesis was carried out by boiling the desired reagents in toluene, in the presence of an acceptor of hydrogen bromide – triethylamine. The obtained compounds (2, 3) are yellowish powdery substances soluble in hot polar solvents.

The composition, structure, and individuality of the synthesized compounds (2, 3) were confirmed using elemental analysis and IR spectroscopy. Physicochemical constants and elemental analysis data are presented in table 1.



In the IR spectra of the synthesized compounds (2, 3) there is an intense absorption band of the amide carbonyl C(O)NH in the region of 1703-1646 cm^{-1}, the NH group in the region of 3400-3200 cm^{-1}, in the region of 2150-2160 cm^{-1} the absorption band of the rhodane group –S–C≡N.

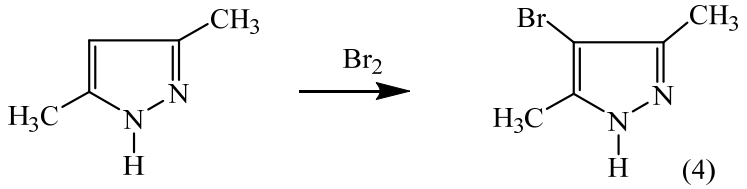
Table 1 – Physicochemical constants and data of elemental analysis of compounds (1-3)

№ of compounds	Yield, %	M.p., °C	Found, %			Molecular formula	Calculated, %		
			C	H	N		C	H	N
1	37.2	204-205	32.36	1.92	11.03	$C_{20}H_{13}Br_3N_6O_2S_4$	32.58	1.78	11.40
2	93.2	193-195	57.42	4.51	15.91	$C_{21}H_{19}N_5O_2S_2$	57.65	4.38	16.03
3	83.8	120-122	50.42	4.01	16.51	$C_{14}H_{14}N_4O_2S_2$	50.28	4.22	16.75

Compound (1), due to the presence of an alkyl bromide group, is an important synthon in the synthesis of new benzothiazole derivatives. Compounds (2, 3) combine in one molecule the rodanebenzthiazole residue with the alkaloid cytisine (2) and with the biogenic amine morpholine (3). Substances (2, 3) are potentially biologically active compounds, since they contain several pharmacophore fragments in the structure of the molecule: benzthiazole and alkaloid (amine) heterocycles, rodane and urea groups [6-9].

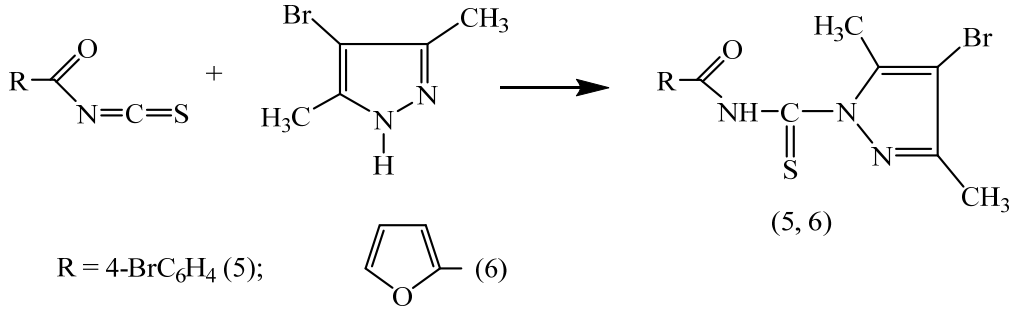
Another representative of azoles is pyrazole, whose derivatives have established themselves as the oldest drugs with antipyretic and analgesic properties [10-13]. At the same time, practically no data are available in the literature on the basis of the basic pyrazole moiety of compounds containing thiourea or thioamide groups. The combination of the pyrazole moiety with halogen substituents can lead to an increase in the therapeutic effect.

It should also be noted that pyrazole derivatives are practically available compounds. In this regard, we have carried out the synthesis of 4-bromo-3,5-dimethylpyrazole (4) by bromination of the corresponding derivative.



Further, on the basis of 4-bromo-3,5-dimethylpyrazole (4), we carried out the interaction with 4-bromobenzoyl isothiocyanate and 2-furancarbisothiocyanate.

The synthesis of the starting isothiocyanates was carried out in situ (without isolation) by heating the corresponding acid chlorides (4-bromobenzoyl chloride and 2-furancarboxylic acid chloride) with potassium thiocyanate in acetone for 2 hours. Next, the obtained solutions of isothiocyanates were added to acetone solutions of 4-bromo-3,5-dimethylpyrazole.



R = 4-BrC$_6$H$_4$ (5); (6)

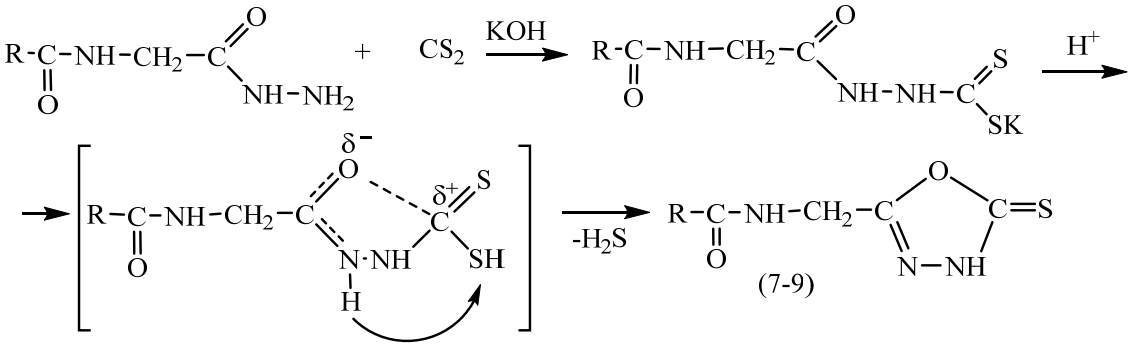
It was found that the reaction of 4-bromo-3,5-dimethylpyrazole with isothiocyanates, in contrast to the above-described aniline derivatives, takes longer and requires heating the reaction mixture to 50°C. In this case, almost all the reaction products are released from the reaction acetone medium in the form of yellow or slightly yellowish acicular crystalline substances.

The composition, structure, and individuality of the synthesized compounds (5, 6) were confirmed by the data of elemental analysis, IR, and PMR spectroscopy. Physicochemical constants and elemental analysis data for thiourea derivatives (5, 6) are presented in Table 2.

Table 1 – Physicochemical constants and data of elemental analysis of compounds (5, 6)

№ of compounds	Yield, %	M.p., °C	Found, %			Molecular formula	Calculated, %		
			C	H	N		C	H	N
5	30	147-150	37,86	3,04	10,55	$C_{13}H_{11}Br_2N_3OS$	37,43	2,66	10,07
6	50	120-122	40,65	3,32	13,21	$C_{11}H_{10}BrN_3O_2S$	40,26	3,07	12,80

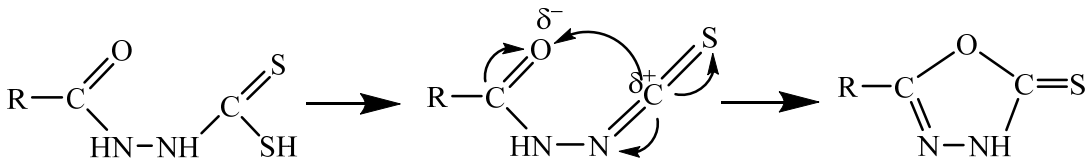
Derivatives of oxadiazole-2-tines are of undoubted interest in the search for new antibacterial drugs, since they contain a number of pharmacophore groups [14-16]. In this regard, in order to search for new anti-tuberculosis drugs and study the structure-activity relationship [17-21], we studied the interaction of acylglycine hydrazides with carbon disulfide in the presence of potassium hydroxide. Further acidification of the resulting potassium salt of dithiocarbamic acid with 0.1 N HCl solution leads to the formation of cyclic products - 1,3,4-oxadiazole-2-thiones. Product yields (7-9) were 70-80%.



R= C$_6$H$_5$ (7), *м*-CH$_3$C$_6$H$_4$ (8), *о*-BrC$_6$H$_4$ (9).

As can be seen from the equation, the cyclization reaction is promoted by the formation of dithiocarbamic acid, which is an unstable compound.

Based on this, we can assume the following mechanism for the formation of 1,3,4-oxadiazole-2-thiones from hydrazides when exposed to carbon disulfide. Dithiocarbamates in an acidic medium decompose with the release of hydrogen sulfide and the formation of a highly reactive isothiocyanate group. Further, intramolecular cyclization occurs due to the attack by the electron-deficient carbon atom of the isothiocyanate group of the nucleophilic center - the carbonyl oxygen atom with a further redistribution of the electron density, with the formation of the final products - 1,3,4-oxadiazole-2-thiones



The synthesized compounds (7-9) are white crystalline substances, readily soluble in polar organic solvents. The resulting 1,3,4-oxadiazole-2-thiones are heterocyclic compounds containing a thion-thiol group capable of tautomeric transformations. IR spectral data indicate that compounds (7-9) in the crystalline state have the structure of thions (thioamides).

In the IR spectra of compounds (7-9), vibrations of the SH-group are absent and characteristic bands appear for stretching vibrations of the thioamide group at 1510-1460 cm^{-1}, there is also a peak of average intensity at 1230-1210 cm^{-1}, referred to C=S - group.

When analyzing the PMR spectrum of compound (7), recorded in D2O, a group of lines at 7.31 ppm. and 7.59 ppm. represents the signals of the protons of the aromatic ring in the form of complex multiplets. Singlet at 4.44 ppm. assigned to the methylene proton CH_2–NH. The physicochemical constants of the synthesized compounds (7-9) are shown in Table 3.

Table 3 – Physicochemical constants and data of elemental analysis of compounds (7-9)

№ of compounds	Yield, %	M.p., °C	R_f*	Found, %			Molecular formula	Calculated, %		
				C	H	N		C	H	N
7	82	175 (decomp.)	0,47	51,17	3,79	17,96	$C_{10}H_9N_3O_2S$	51,06	3,82	17,87
8	78	149-150	0,72	53,11	4,31	16,92	$C_{11}H_{11}N_3O_2S$	53,01	4,41	16,86
9	69	148-149	0,68	51,33	3,33	18,01	$C_{10}H_8N_3O_2SBr$	51,28	3,41	17,94
* Note: eluent – propanol-2 : ammonia : water (7:2:1)										

Thus, based on the review of the literature and experimental data, it can be concluded that azole derivatives have high chemical and physiological activity, their derivatives are low-toxic and are promising in the creation of new drugs with antibacterial, insecticidal, antitumor and other effects.

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 ^1H and ^{13}C NMR spectra were recorded in DMSO-d6 on a JNM-ECA 400 spectrometer of the Jeol company from Japan. The survey was carried out at room temperature using a DMSO-d6 solvent. Chemical shifts are measured relative to the signals of residual protons or carbon atoms of a deuterated solvent.

N-(6-rhodanobenzothiazol-2-yl)-2-(cytisine-1-yl)acetamide (2) To a solution of 1 g (0.003 mol) 2-bromo-N- (6-rhodanebenzo[d]thiazol-2-yl)acetamide in 10 ml of dioxane was poured into 1.12 g of triethylamine and 0.57 g (0.012 mol) of cytisine was added. Heated under reflux for 5 hours. Was filtered hot from the precipitate of triethylamine hydrobromide. The solvent was distilled off. The oily product was triturated and crystallized with hexane. It was recrystallized from a benzene-hexane mixture. Yield 1.24 g (93.2%), mp. 193-195°C.

N-(6-rhodanebenzothiazol-2-yl)-2-morpholinoacetamide (3) Synthesized similarly to compound (2) from 2-bromo-N- (6-rhodanebenzo[d]thiazol-2-yl)acetamide and morpholine. Yield 0.42 g (83.8%), mp. 120-122°C.

N-(4-bromo-3,5-dimethyl-1H-pyrazole-1-carbamothioyl)-4-bromobenzamide (5). To a solution of 1.55 g (0.007 M) of p-bromobenzene chloride in 5 ml of acetone with stirring on a magnetic stirrer was added 0.69 g (0.007 M) of potassium thiocyanate. Stirred at reflux for two hours, then filtered through a paper filter to a solution of 1.23 g (0.007 M) of 4-bromo-3,5-dimethylpyrazole in 10 ml of acetone. Then the mixture was stirred at a temperature of 45-50°C for 2-3 hours. The precipitated crystalline product was filtered off, washed with 2-propanol. The product was recrystallized with a mixture of organic solvents isopropyl alcohol and hexane. Received 0.45 g (30%) of a crystalline substance with mp. 147-150°C.

N-(4-bromo-3,5-dimethyl-1H-pyrazole-1-carbamothioyl) furan-2-carboxyamide (6) was synthesized similarly to compound (2.20), from 1.37 g (0.01 M) acid chloride 2-furancarboxylic acid, 1.10 g (0.011 M) potassium thiocyanate and 1.75 g (0.01 M) 4-bromo-3,5-dimethylpyrazole. Received 1.54 g (50%) of crystalline substance with mp 120-122°C.

5-(Benzoylaminomethylene)-3,4-dihydro-1,3,4-oxadiazole-2-thione (7). To a solution of 1.90 g (0.01 mol) of N-benzoylglycine hydrazide in 20 ml of ethanol was added with constant stirring 0.56 g (0.01 mol) of potassium hydroxide. Then 0.76 g (0.01 mol) of carbon disulfide dissolved in 10 ml of alcohol was added slowly. Stirred at 35-40°C for 1.5 hours. The reaction mixture was cooled to room temperature, acidified with 0.1 N hydrochloric acid solution to pH = 5-6. The precipitate that formed was filtered off. 1.92 g (82%) of a powdery substance was obtained, mp 175-176°C.

5-(*m*-Methylbenzoylaminomethylene)-3,4-dihydro-1,3,4-oxadiazole-2-thione (8) was synthesized similarly to compound (119) from 2.07 g (0.01 mol) of hydrazide N-m- methylbenzoylglycine, 0.56 g (0.01 mol) of potassium hydroxide and 0.76 g (0.01 mol) of carbon disulfide. 1.94 g (78%) of a powdery substance with a melting point of 149-150°C was obtained.

5-(*o*-Bromobenzoylaminomethylene)-3,4-dihydro-1,3,4-oxadiazole-2-thione (9) was synthesized similarly to compound (119) from 2.86 g (0.01 mol) of hydrazide N-o- bromobenzoylglycine, 0.56 g (0.01 mol) potassium hydroxide and 0.76 g (0.01 mol) carbon disulfide. Received 1.27 g (69%) of a powdery substance with a melting point of 140-141°C.

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АЗОЛ МОДИФИКАЦИЯСЫНДАҒЫ КЕЙБІР БАҒЫТТАР

Аннотация. Мақалада бензтиазол, 3,5-диметилпиразол, 1,3,4-оксадиазол-2-тион, 1,3,4-тиадиазол сияқты азолдардың жаңа туындыларын мақсатты іздеу бойынша эксперименттік зерттеу нәтижелері келтірілген. Азолды сақина молекуласының басқа циклдік қосылыстармен, мысалы, цитизин алкалоидымен, морфолин, фуран және де кейбір арендермен араласу мүмкіндігі зерттелген. Жұмыста қолданылған түрлендіруші заттар биологиялық белсенділіктің әртүрінің тасымалдаушысы болып саналады. Бір зат құрылымындағы бірнеше химиялық қосылыстар әрекеті олардың әрқайсысының биологиялық әсерін өзгерте алады. Бұл жұмыста азолдардың жаңа туындыларын алу үшін түрлі бромдау, ацилдеу, 4-бромбензойл изотиоцианатпен және 2-фуранкарбизотиоцианатпен әрекеттесу реакциялары зерттелді. Олардың оңтайлы реакциядағы жүру шарттары анықталды. Бұл жағдайда реакция өнімдерінің барлығы дерлік реакциялық ацетонды еріткіштік ортадан сары немесе сәл сарғыш сары түсті кристалды заттар түрінде бөлініп алынады. 4-Бромо-3,5-диметилпиразолдың изотиоцианаттармен реакциясы, анилиндердің бұрыннан белгілі туындыларынан айырмашылығы, көп уақытты алатындығы және реакция қоспасын қыздыруды қажет ететіндігі анықталды. Пиразол бөлігінің галогенді алмастырғышпен үйлесуі көбінесе олардың бактерияға қарсы терапиялық әсерін жоғарылатады. 4-Бромо-3,5-диметилпиразолдың изотиоцианаттармен реакциясы, жоғарыда сипатталған анилин туындыларынан айырмашылығы, көп уақытты алатындығы және реакция қоспасын ұзақ уақыт қыздыруды қажет ететіндігі анықталды. 2-Амин-6-роданебензотиазолды бром-сірке қышқылы бромидімен ацилдеу әртүрлі ортада жүргізілді. Өнімділік пен тазалық бойынша ең жақсы нәтижелер диметилформамид (ДМФА) еріткіші ортасында алынды. Синтезделген 2-бром-N-(6-роданебензо[д]тиазол-2-ил) ацетамид, алкил бромид тобына байланысты жаңа бензотиазол туындыларын синтездеуде маңызды синтон болып саналады. Оның туындылары бір молекулада роданебензтиазол қалдықтарын өсімдіктен алынатын цитизин алкалоиды мен биогенді амин морфолинмен біріктіреді. Синтезделген жаңа қосылыстар потенциалды биологиялық белсенді заттар болып саналады, өйткені олардың құрамында молекула құрылымында бірнеше маңызды фармакофорлы фрагменттер: бензотиазолды және алкалоидты (амин) гетероциклдер, родан және мочевина топтары бар. Көміртекті дисульфидтің әсерінен гидразидтерден 1,3,4-оксадиазол-2-тиондардың түзілу реакциялары зерттелген және ұсынылған. Алынған эксперименттік мәліметтер негізінде 1,3,4-оксадиазол-2-тиондардың түзілу механизмі ұсынылды. Дитиокарбаматтар қышқылды ортада күкіртсутек бөліп, нәтижесінде жоғары реакциялық қабілеті бар изотиоцианат тобы түзіліп ыдырайтыны көрсетілген. Арықарай

молекулааралық циклизация реакциясы жүреді де, соңғы өнімдер пайда болады. Алынған 1,3,4-оксадиазол-2-тиондар таутомерлі түрлендіруге қабілетті маңызды гетероциклді қосылыстар болып саналады. Барлық зерттелген реакцияларға оңтайлы синтез шарттары жасалды. Бұл жұмыста алынған түрлі биофрагментті қосарландырылған азотты гетероциклдарды түрлі терапиялық әсері бар жаңа биологиялық белсенді заттарды іздеуде маңызды синтондар ретінде пайдалануға болады. Синтезделген қосылыстардың құрылымы қазіргі заманғы физикалық-химиялық ИК, ^{1}H ЯМР және ^{13}C спектроскопия әдістерін қолдана отырып зерттелді. Барлық синтезделген заттар потенциалды биологиялық белсенді қосылыстар болып саналады, өйткені олардың құрылысында бірнеше фармакофорлық фрагменттер бар.

Түйін сөздер: азол, бензтиазол, 3,5-диметилпиразол, 1,3,4-оксадиазол-2-тион, гетероциклизация

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НЕКОТОРЫЕ НАПРАВЛЕНИЯ В МОДИФИКАЦИИ АЗОЛОВ

Аннотация. В данной статье представлены результаты экспериментальных исследований по направленному поиску новых производных азолов, таких как бензтиазол, 3,5-диметилпиразол, 1,3,4-оксадиазол-2-тион, 1,3,4-тиадиазол. Изучена возможность совмещения в одной молекуле азолового цикла с другими циклическими соединениями, такими как алкалоид цитизин, морфолин, фуран и некоторыми аренами. Использованные в работе модифицирующие вещества являются носителями различных видов биологической активности. Одновременное действие нескольких химических соединений может изменить биологическое действие каждого из них. Для получения новых производных азолов исследованы разнообразные реакции бромирования, ацилирования, взаимодействие с 4-бромбензоилизотиоцианатом и 2-фуранкарбизотиоцианатом в различных средах. Определены оптимальные условия проведения реакции. При этом практически все продукты реакции выделяются из реакционной ацетоновой среды в виде желтых или слегка желтоватых игольчатых кристаллических веществ. Установлено, что реакция 4-бром-3,5-диметилпиразола с изотиоцианатами, в отличие от ранее писанных производных анилинов, протекает продолжительнее и требует нагрева реакционной смеси. Комбинация пиразольного фрагмента с галоидными заместителями зачастую приводит к усилению их антибактериального терапевтического эффекта. Установлено, что реакция 4-бром-3,5-диметилпиразола с изотиоцианатами, в отличие от вышеописанных производных анилинов, протекает продолжительнее и требует продолжительного нагрева реакционной смеси. Осуществлено ацилирование 2-амино-6-роданбензотиазол бромангидридом бромуксусной кислоты в различных средах. Показано, что наилучшие результаты по выходу и чистоте продуктов получаются в среде ДМФА. Синтезированный 2-бром-N-(6-роданбензо[d]тиазол-2-ил)ацетамид, благодаря наличию алкилбромидной группы, является важным синтоном в синтезе новых производных бензтиазола. Его производные совмещают в одной молекуле остаток роданбензтиазола с растительным алкалоидом цитизин и с биогенным амином морфолином. Синтезированные новые соединения являются потенциально биологически активными веществами, так как содержат в структуре молекулы несколько фармакофорных фрагментов: бензтиазоловый и алкалоидный (аминный) гетероциклы, родано- и карбамидную группы. Изучен и предположен механизм образования 1,3,4-оксадиазол-2-тионов из гидразидов при действии на них сероуглеродом. На основании полученных экспериментальных данных предложен механизм образования 1,3,4-оксадиазол-2-тионов. Показано, что дитиокарбаматы в кислой среде распадаются с выделением сероводорода и образованием высокореакционной изотиоцианатной группы в их составе. Далее в реакционной среде происходит внутримолекулярная циклизация, с образованием конечных продуктов. Полученные 1,3,4-оксадиазол-2-тионы относятся к важным гетероциклическим соединениям, способным к таутомерным превращениям. Для всех изученных реакций установлены оптимальные условия синтеза. Все полученные в работе конденсированные азотсодержащие гетероциклы с различными биофрагментами могут быть использованы в качестве исходных синтонов в поиске новых биологически активных веществ с разнообразным терапевтическим эффектом. Структуры синтезированных соединений изучены с применением современных физико-химических методов ИК, ЯМР ^{1}H и ^{13}C-спектроскопии. Все синтезированные вещества являются потенциально биологически активными соединениями, так как содержат в своей структуре по несколько фармакофорных фрагментов.

Ключевые слова: азолы, бензтиазол, 3,5-диметилпиразол, 1,3,4-оксадиазол-2-тион, гетероциклизация.

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