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Synthesis and research on properties of 2-(4-ethyl-5-((3'-methylxantine-7'-yl)methyl)-4*H*-1,2,4-triazole-3-ylthio) acetic acid's salts

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Key words:
Xanthines, 1,2,4-triazole, Physical and Chemical Properties.

1,2,4-Triazole derivatives are successfully used in medicine as antibacterial and antifungal agents.

Aim of our research is the study of synthesis of 7'-((3-thio-4-ethyl-4*H*-1,2,4-triazole-5-yl)methyl)-3'-methylxanthine.

Methods and results. Sodium salt of 3-methylxanthine has been used as the initial substance to obtain a new series of these compounds. It has been shown that the reaction of the corresponding hydrazide interaction with ethylisothiocyanate finds its continuation in the intramolecular cyclization. The synthesis of 2-(4-ethyl-5-((3'-methylxantine-7'-yl) methyl)-4*H*-1,2,4-triazol-3-ylthio)acetic acid's salts has been performed. Physical-chemical properties of compounds have been researched and their structure and individuality has been confirmed by elemental analysis, IR-spectroscopy, ^{1}H NMR-spectroscopy, chromato-mass and mass-spectrometry.

Conclusion. 12 New compounds have been obtained and their structure has been confirmed.

Синтез і дослідження властивостей солей 2-(4-етил-5-((3'-метилксантин-7'-іл)метил)-4*H*-1,2,4-тріазол-3-ілтіо) ацетатної кислоти

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Похідні 1,2,4-тріазолу успішно використовуються в медичній практиці як протимікробні та протигрибкові засоби. Метою нашого дослідження був синтез 7'-((3-тіо-4-етил-4*H*-1,2,4-тріазол-5-іл)метил)-3'-метилксантину. Як вихідну сполуку для отримання цільового ряду сполук використали натрієву сіль 3-метилксантину. Показано, що реакція взаємодії відповідного гідразиду з етилізотіоціанатом знаходить своє продовження у внутрішньомолекулярній циклізації. Здійснили синтез солей 2-(4-етил-5-((3'-метилксантин-7'-іл)метил)-4*H*-1,2,4-тріазол-3-ілтіо)ацетатної кислоти. Досліджені фізико-хімічні властивості сполук, що одержали, та підтверджена їхня будова за допомогою елементного аналізу, ^{1}Н ЯМР-спектрометрії, ІЧ-спектрофотометрії, хромато-мас- і мас-спектрометрії. Отримали 12 сполук, підтверджена їхня структура.

Ключові слова: *3-метилксантин, 1,2,4-тріазол, фізико-хімічні властивості.*

Актуальні питання фармацевтичної і медичної науки та практики. – 2016. – № 1 (20). – С. 4–7

Синтез и исследование свойств солей 2-(4-этил-5-((3'-метил-ксантин-7'-ил)метил)-4*H*-1,2,4-триазол-3-илтио) ацетатной кислоты

А. С. Гоцуля

Производные 1,2,4-триазола успешно используются в медицинской практике в качестве антимикробных и противогрибковых средств. Осуществлён синтез 7'-((3-тио-4-этил-4*H*-1,2,4-триазол-5-ил)метил)-3'-метилксантина. В качестве исходного вещества для получения целевого ряда соединений была использована натриевая соль 3-метилксантина. Показано, что реакция взаимодействия соответствующего гидразида с этилизотиоцианатом находит своё продолжение во внутримолекулярной циклизации. Проведён синтез солей 2-(4-этил-5-((3'-метилксантин-7'-ил)-метил)-4*H*-1,2,4-триазол-3-илтио)ацетатной кислоты. Исследованы физико-химические свойства полученных соединений и подтверждено их строение с помощью элементного анализа, ^{1}Н ЯМР-спектрометрии, ИК-спектрофотометрии, хромато-масс- и масс-спектрометрии. Получены 12 соединений и подтверждена их структура.

Ключевые слова: *3-метилксантин, 1,2,4-триазол, физико-химические свойства.*

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Chemistry of heterocyclic compounds attracts the attention of scientists for its practical significance and theoretical interest. Among the rich diversity of this group of compounds, 1,2,4-triazoles-3-thiole derivatives attract great attention. These compounds are able to show wide range of physiological activity and have already recommended themselves as medicines. The presence of two nucleophilic centers in the structure of 1,2,4-triazoles 3-thiols creates general opportunities for the synthesis of great number of new derivatives. Therefore, the work, related with the research of compounds, containing a sinton of 1,2,4-triazole is actual and perspective.

The aim of work was the synthesis of new derivatives of 1,2,4-triazole-3-thiole, which contain a sinton of 3-methylxanthine in their structure.

For this aim achievement the following tasks have been resolved: to search the initial thiol obtaining with the necessary triazol- and xanthinesyntones and also further chemical

conversions; to study the structure and capabilities of practical application of the synthesized compounds.

Materials and methods

The study of physical-chemical properties of the obtained compounds has been carried out using methods listed in the State Pharmacopoeia of Ukraine. The melting point was determined using capillary method on Stanford Research Systems Melting Point Apparatus 100, America. The structure of the compounds was confirmed with elemental analysis on Elemental Vario EL cube (Elementar Analysensysteme, Germany), IR spectra (4000 – 400 cm^{-1}) were taken off the module ALPHA-T of Bruker ALPHA FT-IR spectrometer (Bruker optics, Germany). Gear Liquid Chromatography System with Mass spectrometric detector (Agilent Technologies, USA): Agilent 1260 Infinity HPLC System (degasser, binary pump, autosampler, thermostat Column, diode-array detector); single quadrupole mass spectrometer Agilent 6120 with electrospray ionization (ESI); Open LAB CDS Software. Terms of HPLC-MS study: 1) binary gradient – A: H_2O (0.1% solution of HCOOH), B: CH_3CN (0,1% solution of HCOOH); 2) Column: Zorbax SB-C18; 30 mm × 4,6 mm × 1.8 mm; 3) column temperature: 40°C; 4) DAD: 210, 254 nm; 5) ion source: API-ES; 6) scanning range m/z: 160-1000; 7) fragmentor: 10V; 8) positive polarity; 9) nitrogen temperature – 300°C; 10) Nebulizer pressure 40 psig; 11) the rate of drying gas (nitrogen) – 10 l/min.

Prop-1-yl-2- (3'-methylxanthine-7'-yl)ethanoat. To 0.055 mol $NaHCO_3$ in 150 ml of DMFA 0.05 mole of 3-methylxanthine was added and heat for 10 minutes. To the reaction mixture 0.055 mol of prop-1-ylmonochlorethanoate was added and boiled for 2 hours. After cooling the equal amount of water was added to the reaction mixture. The residue was dissolved, then falls again. Ester precipitate was filtered, washed with water and dried. The white crystalline substance, practically insoluble in water, soluble in organic solvents (alcohol, 1,4-dioxane, DMFA, DMSO). For the analysis was purified from mixture water - 1,4-dioxane (1: 1). Yield – 82%. Tm. = 247–248°C.

Hydrazide of 2-(3'-methylxanthine-7'-yl)acetic acid. To the heated solution of 0.05 mol prop-1-yl-2-(3'-methylxanthine-7'-yl)ethanoate in 200 ml of ethanol 0.5 mol of hydrazine hydrate was added. Heat for 1 hour. Cool. The precipitate was filtered, washed with water and dried. White, amorphous substance, practically insoluble in water, acetone, soluble in alcohol, 1,4-dioxane, soluble in DMFA, DMSO. Crystallized from the mixture water – DMFA (1 : 1). Yield – 83%. Tm. = 210–212°C.

7'-((3-thio-4-ethyl-4H-1,2,4-triazole-5-yl) methyl)-3'-methylxanthine. 0.05 mol of hydrazide 2-(3'-methylxanthine-7'-yl)acetic acid, 150 ml of 1,4-dioxane and 60 ml of water were heated up to the initial material dissolution. The equivalent amount of ethylisothiocyonate was added to the obtained solution, boil for 30 minutes, cool, add 100 ml of water, the precipitate was filtered, washed with water, propane-2-ol and dried. The white crystalline substance, practically insoluble in water and alcohol, soluble in 1,4-dioxane. Crystallized from a mixture water –1,4-dioxane (1 : 3). Yield – 79%. Tm. > 300°C.

2-((5-((3'-methylxantine-7'-yl)methyl)-4-ethyl-4H-1,2,4-triazole-3-yl)-thio)acetic acid *(Tab. 1).* To the aqueous solution of sodium salt of 7'-((3-thio-4-ethyl-4*H*-1,2,4-triazole-5-yl)methyl)-3'-methylxanthine (0.01 mol) an equivalent amount of aqueous solution of sodium monochloracetate was added. Heat up to boiling for 1 hour. Cool. Neutralize by acetic acid. The precipitate was filtered, washed with water and dried. Recrystallized from propane-1-ol. Yield – 73%. Tm. = 203–205°C. IR-spectra, *v, cm*$^{-1}$: 2988 (ν_{OH}), 2879 (νCH_2, alyphatic), 1735 ($\nu_{C=O}$), 1653 ($\nu_{C=O}$), 1608 ($\nu_{C=N}$), 1553 ($\nu_{C=N}$), 1500 ($\nu_{C=N}$), 1475 (δCH_2), 920 (δ_{O-H}), 746(ν_{C-S}). ^{1}H NMR (DMSO-d_6, 400 MHz), δ/ppm: 1,27 (t, 3H, -N^{4}CH$_2$C$\underline{H}_3$), 3,12 (s, 3H, -N$^{3'}$CH$_3$), 3,65 (s, 2H, -SCH$_2$-), 3,95 (q, 2H, CH$_3$C$\underline{H}_2$), 5,50 (s, 2H, -N$^{7'}$CH$_2$), 8,42 (s, 1H, CH), 12,0 (s, 1H, COOH).

Salts of 2-((5-((3'-methylxantine-7'-yl)methyl)-4-ethyl-4H-1,2,4-triazole-3-yl)thio)acetic acid with organic bases *(Tab. 1).* Mixture of 0.01 mol initial carboxylic acid, 35 ml of ethanol and 0.011 mol of the corresponding organic base (methylamine, ethylamine, ethanolamine, diethanolamine, dimethylethanolamine, morpholine, piperidine, piperazine) heated during 1 hour on a water bath, the solvent was evaporated. Obtained white crystalline substances are soluble in water, soluble in diethyl ether and chloroform. For analysis compounds were recrystallized from ethanol or propane-1-ol.

Sodium, zinc salts of 2-((5-((3'-methylxanthine-7'-yl) methyl)-4-ethyl-4H-1,2,4-triazole-3-yl)thio)acetic acid *(Tab. 1).*

A mixture of 0.01 mol of the initial carboxylic acid and 0.01 mol of sodium hydroxide or 0.02 mol of zinc oxide in 30 ml of water was heated on a water bath for 15-30 minutes. Evaporated up to the 1/3 from the original volume and precipitated, adding acetone. Filtered. Received white crystalline substance, soluble in water. For the analysis compounds recrystallized from ethanol.

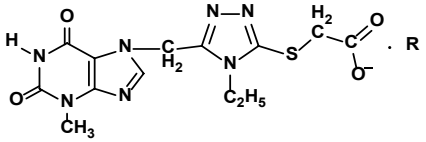
Results and discussion

On the first stage of work optimal conditions of the reception of 7'-((3-thio-4-ethyl-4*H*-1,2,4-triazole-5-yl) methyl)-3'-methylxanthine have been determined. Synthesis was performed through several stages: complex ester reception, its hydrazynolysis, interaction with ethyl isothiocyanate with intramolecular cyclization. Corresponding carboxylic acid has been obtained by interaction of the obtained thiol with monochloracetate acid in aqueous solution with double amount of alkali and the following neutralization by acetic acid *(Fig. 1)*.

In a strong part of the magnetic field of ^{1}H NMR spectrum of the obtained acid available protons of CH_2 group that resonate as a triplet at 3.65 ppm (-SCH$_2$-), quadruplet at 3.95 ppm (-N^{4}C$\underline{H}_2$CH$_3$) and singlet at 5.50 ppm (-N$_7$'CH$_2$). Signals of CH_3-groups protons also manifested by intense singlet at 3.12 ppm (-N$_3$'CH$_3$) and triplet (-N$_4$CH$_2$CH$_3$) at 1.27 ppm. Proton of the CH-fragment is characterized by a signal at 8.42 ppm. Broadened proton signal of COOH group is fixed at 12.0 ppm.

Table 1

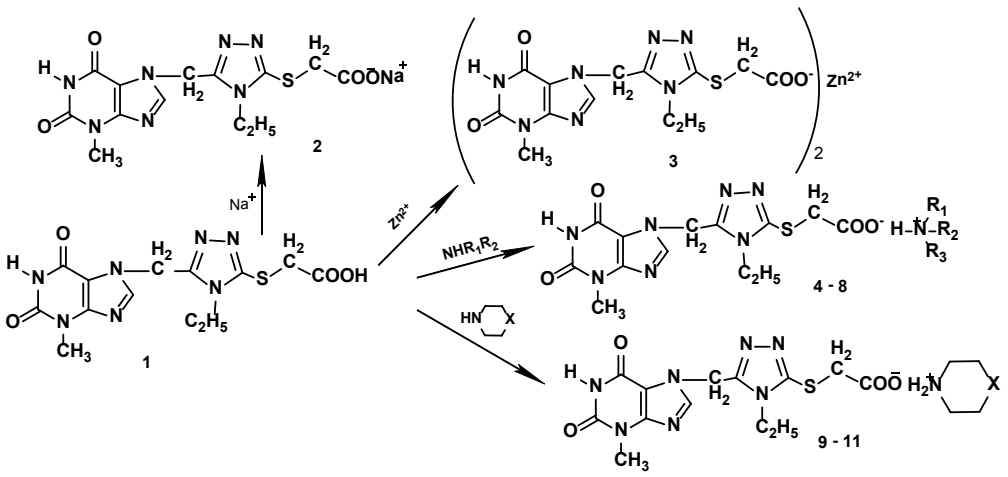
Physic-chemical properties of the synthesized compounds



№ c/c	R	$T_{m.}$	Yield, %	Empiric formula
1	H	203 - 205	75	$C_{13}H_{15}N_7O_4S$
2	Na^+	259 - 261	79	$C_{13}H_{14}N_7NaO_4S$
3	Zn^{2+}	191 - 193	72	$C_{26}H_{28}N_{14}O_8S_2Zn$
4	$H_3N^+CH_3$	230 - 232	81	$C_{14}H_{20}N_8O_4S$
5	$H_3N^+C_2H_5$	225 - 227	79	$C_{15}H_{22}N_8O_4S$
6	$H_3N^+C_2H_4OH$	216 - 218	67	$C_{15}H_{22}N_8O_5S$
7	$H_2N^+(C_2H_4OH)_2$	262	66	$C_{17}H_{26}N_8O_6S$
8	$HN^+(CH_3)_2C_2H_4OH$	202 - 205	83	$C_{19}H_{30}N_8O_5S$
9	piperidinium	237 - 239	82	$C_{18}H_{25}N_8O_4S$
10	morpholinium	189 - 191	84	$C_{18}H_{26}N_8O_4S$
11	piperazinium	220 - 222	76	$C_{17}H_{24}N_9O_4S$

Cont. table 1

№ c/c	Found, %				Calculated, %			
	C	H	N	S	C	H	N	S
1	42.73	4.14	26.84	8.78	42.62	4.15	26.78	8.80
2	40.31	3.64	25.31	8.28	40.41	3.63	25.37	8.30
3	39.32	3.55	24.69	8.08	39.41	3.56	24.64	8.06
4	42.42	5.09	28.27	8.09	42.31	5.11	28.33	8.07
5	43.89	5.40	27.30	7.81	44.00	5.39	27.37	7.79
6	42.25	5.20	26.28	7.52	42.36	5.18	26.35	7.50
7	43.40	5.57	23.82	6.82	43.51	5.56	23.88	6.80
8	47.29	6.27	23.22	6.64	47.41	6.25	23.28	6.62
9	48.10	5.61	24.93	7.13	48.22	5.60	24.99	7.11
10	47.99	5.82	24.87	7.12	48.11	5.81	24.93	7.10
11	45.32	5.37	27.98	7.12	45.43	5.36	28.05	7.10



X = CH_2, NH, O; $R_1 = R_2 = R_3$ = H, CH_3, C_2H_5, C_2H_5OH

Fig. 1. Synthesis of salts of 2-((5-((3-methylxantine-7'-yl)methyl)-4-ethyl-4*H*-1,2,4-trazole-3-yl)thio)acetate acid

IR-spectra of the obtained acid is characterized by polygonal deformation vibrations of C-H fragment in the ranges 1240–1018 cm^{-1} (band of weak intensity at 1194 cm^{-1}, 1154 cm^{-1}, 1132 cm^{-1}, 1087 cm^{-1}) out planar deformation vibrations of CH-fragment at 993 - 643 cm^{-1} (band of strong intensity at 781 cm^{-1}, 761 cm^{-1}, 744 cm^{-1}, 715 cm^{-1}) valence vibrations of C=N-fragment in the cycle in ranges 1557–1484 cm^{-1}. There are also an intense absorption bands at 1741 and 1681 cm^{-1}, due to valence vibrations of C=O groups.

The formation of salts has been confirmed by signals of

corresponding protonated amines. For example, in the ^{1}H NMR spectrum of the morpholinium salt there is a set of signals of the protonated morpholine as two multiplets at 3.23 ppm and 3.85 ppm and the singlet at 8.95 ppm. Piperazine cation is described by the presence of singlet protons at 2.73 ppm and 3.40 ppm. Piperidinium salt is characterized by signals of organic base protons as a multiplet at 1.65 ppm and at 2.70 ppm and the singlet at 7.13 ppm

Conclusions

It has been established that the reaction of interaction of hydrazide 2-(3'-methylxanthine-7'-yl)acetic acid with ethylizotiocyonate finds its continuation in intra molecular heterocyclization. The optimal conditions for the salts obtaining with inorganic and organic bases have been determined.

It has been proved that the largest outputs of products of the salt formation reactions of 2-((5-((3'-methylxanthine-7'-yl)methyl)-4-ethyl-4*H*-1,2,4-triazole-3-yl)thio) acetic acid are observed at using water as a solvent (receipt inorganic salts) and ethanol with its replacement on acetone (organic salts receipt).

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