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СИНТЕЗ И АНТИОКИСЛИТЕЛЬНАЯ АКТИВНОСТЬ ПРОИЗВОДНЫХ 4,5-ДИГИДРО-1,3,4-ТИАДИАЗОЛА С ФРАГМЕНТОМ ЭКРАНИРОВАННОГО ФЕНОЛА

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В настоящей работе был синтезирован ряд 4,5-дигидро-1,3,4-тиадиазола с фрагментом экранированного фенола. Синтез включал конденсацию 4-гидрокси-3,5-ди-трет-бутилбензальдегида с тиосемикарбазидом в растворе уксусной кислоты и этанола в соотношении 1:1, целевой тиосемикарбазон был синтезирован с выходом 63%. Кипячение полученного тиосемикарбазона с ангидридом пропионовой кислоты в тетрагидрофуране в течение 8 ч, а также хлорангидридами бензойной и 2-фурилакриловой кислот в тетрагидрофуране с пиридином в течение 8 ч привело к образованию 4,5-дигидро-1,3,4-тиадиазолов с выходами 64-77%. Структура полученных соединений была подтверждена с помощью ИК-спектрометрии, ^{1}H и ^{13}C ЯМР-спектроскопии. Протонные спектры полученных соединений содержат сигналы протонов CH-N в области 6-7 м.д., что характерно для 4,5-дигидро-1,3,4-тиазольного кольца. ИК спектры полученных веществ содержат полосы поглощения, соответствующие валентным колебаниям O-H при 3551 $см^{-1}$, колебаниям N-H при 3474 $см^{-1}$, валентным колебаниям карбонильных групп при 1699 $см^{-1}$, колебаниям азометинового фрагмента C=N при 1595 $см^{-1}$, а также деформационным колебаниям O-H при 1196 $см^{-1}$. Антиокислительная активность полученных соединений была исследована методом ABTS (2,2'-азино-бис(3-этилбензотиазолин-6-сульфокислота), показывающим способность соединений взаимодействовать с катион-радикалом. В качестве контрольного образца использовали распространенный промышленный антиоксидант – 2,6-ди-трет-бутил-4-метилфенол (Агидол-1). Все синтезированные 4,5-дигидро-1,3,4-тиадиазолы показали более высокую активность в сравнении с Агидолом-1. Соединения, полученные взаимодействием тиосемикарбазона с хлорангидридом бензойной и 2-фурилакриловой кислот, проявили более высокую активность, что может быть связано с их лучшей способностью делокализовывать неспаренный электрон в феноксильном радикале.

Ключевые слова: тиадиазол, 4-гидрокси-3,5-ди-*трет*-бутилбензальдегид, антиоксидантная активность

SYNTHESIS AND ANTIOXIDANT ACTIVITY OF 4,5-DIHYDRO-1,3,4-THIADIAZOLE DERIVATIVES WITH A HINDERED PHENOL MOIETY

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In the present work, a series of 4,5-dihydro-1,3,4-thiadiazoles with a hindered phenol moiety have been synthesized. Condensation of 4-hydroxy-3,5-di-tert-butylbenzaldehyde with thiosemicarbazide in a 1:1 solution of acetic acid and ethanol yielded thiosemicarbazone in 63% yield. Refluxing the resulting thiosemicarbazone with propionic anhydride in tetrahydrofuran for 8 h as well as with benzoic and 2-furylacrylic acid chlorides in tetrahydrofuran with pyridine for 8 h, afforded 4,5-dihydro-1,3,4-thiadiazoles in 64-77% yields. The structure of the resulting compounds was confirmed by IR spectrometry, ^{1}H and ^{13}C NMR spectroscopy. The proton spectra show signals containing CH-N proton signals in the 6-7 ppm region, which is characteristic of the 4,5-dihydro-1,3,4-thiazole ring. The IR spectra contain distributions corresponding to O-H stretching vibrations at 3551 cm^{-1}, N-H vibrations at 3474 cm^{-1}, carbonyl stretching vibrations at 1699 cm^{-1}, C=N azomethine fragment vibrations at 1595 cm^{-1}, and O-H deformation vibrations at 1196 cm^{-1}. Antioxidant activity was determined using the ABTS (2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) assay, which demonstrates the ability of the compound to interact with the cation radical. A common industrial antioxidant, 2,6-di-tert-butyl-4-methylphenol (Agidol-1), was used as a control sample. 4,5-dihydro-1,3,4-thiadiazoles exhibit higher activity in the chain with Agidol-1, forming interactions of thiosemicarbazone with benzoic acid chloride and 2-furylacrylic acid, producing higher activity, which may be due to their better purpose to delocalize the unpaired electron in the phenoxyl radical.

Keywords: thiadiazole, 4-hydroxy-3,5-di-*tert*-butylbenzaldehyde, antioxidant, antioxidant activity

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INTRODUCTION

Oxidative degradation is a process of irreversible destruction of the molecular structure, leading to the loss of their functional properties [1]. In biochemistry the development of destructive processes is directly associated with the activity of free radicals, which have a damaging effect on the organism. The high reactivity of reactive oxygen species (ROS) allows them to react with key biomolecules, including DNA, proteins, lipids, vitamins [2]. It leads to disruption of cellular functions and depletion of cellular energy reserves, ultimately inducing apoptosis [3].

Antioxidants capable of interrupting free radical chain reactions are traditionally used to control undesired oxidation. The basis of this group consists of compounds with a phenolic structure, including flavonoids and carotenoids [4]. However, the significance of the phenolic fragment in the design of biologically active molecules is not limited solely to its antioxidant potential. Numerous studies indicate that phenol itself and its derivatives, especially as part of more complex molecules, exhibit a wide range of biological activities. They possess anti-inflammatory, antimicrobial, and anticancer properties, and also help prevent cardiovascular diseases, diabetes mellitus, and other conditions associated with oxidative stress [5, 6].

Despite the high antioxidant potential, the use of phenolic compounds in their pure form has significant limitations. Currently, the requirements for modern oxidation inhibitors have expanded considerably, particularly regarding their potential for *in vivo* use, for example, in pharmaceuticals. In this case, in addition to high antiradical activity, biocompatibility and safety become crucial criteria. These requirements are met by the strategy of synthesizing hybrid molecules, where the combination of different fragments creates a synergistic effect, allowing the obtainment of compounds with enhanced properties.

Over 75% of pharmaceutical drugs contain heterocyclic fragments incorporating nitrogen and sulfur atoms [7]. Such compounds possess broad therapeutic potential, demonstrating, in particular, antitubercular [8], antimicrobial [9], anti-inflammatory [10], antidiabetic [11], anticancer [12], and antiviral activity [13]. Combination in one molecule of a phenolic fragment

capable of inhibiting radical processes, as well as a heterocycle possessing additional biological activity and/or capable of inhibiting oxidation, makes it possible to create new multipotent antioxidants [14, 15].

Using this strategy, the authors of [16] synthesized 2-amino-1,3,4-thiadiazole **I**, which exhibits both anti-inflammatory properties and high antiradical activity. Unlike 1,3,4-thiadiazoles, the biological activity and antioxidant properties of which have been studied in detail previously [17, 18], their closest structural analogues, thiadiazolines, have not been studied in such detail; however, they have also proven themselves to be promising pharmacophores. Compound **II** – thiadiazoline derivative substituted with N-(2-methylphenyl) acetamide and 2,8-dichloroquinoline fragments was found to exhibit antibacterial activity against *S. aureus* [19], compound **III** with acetoamide fragments showed anticancer properties against prostate tumor cells [20] (Fig. 1).

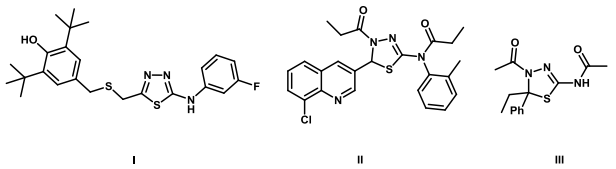

Fig. 1. Thiadiazoline and thiadiazole derivatives
Рис. 1. Производные тиадиазолина и тиадиазола

The synthesis of thiadiazoline derivatives with a phenol fragment is of interest from the point of view of obtaining a potential polyfunctional antioxidant; in addition, an important task is to study the effect of substituents in the heterocyclic ring on the antioxidant activity of the compound, which may further contribute to the development of a strategy for the synthesis of more effective antioxidants.

Thiosemicarbazones are used as convenient synthons for the targeted synthesis of thiadiazolines [21, 22]. This approach, well described in the literature, is based on the high nucleophilicity of the sulfur and nitrogen atoms within the -NHC(=S)NH_2 fragment [23]. The classical method for the synthesis of 4,5-dihydro-1,3,4-thiadiazoles is the acylation of thiosemicarbazones with carboxylic acid derivatives, leading to intramolecular cyclization with the formation of stable carboxamide derivatives [24-26]. Acid anhydrides [27, 28], less commonly the acids themselves (often under activation conditions with PCl_3 or concentrated H_2SO_4) [29, 30], as well as acid halides [31] are traditionally used as acylating agents.

The aim of the present work is to develop methods for the synthesis of thiadiazolines with phenolic fragment and to investigate the influence of structure on their antioxidant properties.

RESULTS AND DISCUSSION

To obtain thiadiazolines containing the 2,6-di-*tert*-butylphenol moiety, thiosemicarbazone **1** was prepared at the first stage by reaction of 4-hydroxy-3,5-di-*tert*-butylbenzaldehyde with thiosemicarbazide. Subsequently, the thiosemicarbazone was reacted with propionic anhydride in tetrahydrofuran, as well as with the acid chlorides of benzoic and 2-furylacrylic acids in tetrahydrofuran in the presence of pyridine. The mixture was refluxed for 8 hours, after which the precipitate of acylpyridinium chloride was filtered off, and the target products were isolated from the filtrate. As a result, the thiadiazolines were obtained in good yields of 64-77% (Fig. 2).

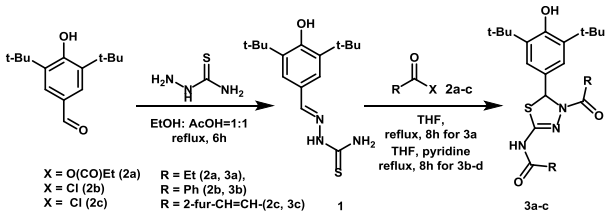

Fig. 2. Synthesis of thiadiazolines **3a-c**
Рис. 2. Схема синтеза тиадиазолинов **3a-c**

The IR spectrum of product **3a**, which is typical for the obtained thiadiazolines, exhibits absorption bands corresponding to O-H stretching vibrations at 3551 cm^{-1}, N-H stretching vibrations at 3474, 3205, 3140 cm^{-1}, stretching vibrations of *tert*-butyl groups at 2930-2850 cm^{-1}, carbonyl stretching vibrations at 1699 cm^{-1}, benzene ring bending vibrations at 1611 cm^{-1}, stretching vibrations of the azomethine C=N fragment at 1595 cm^{-1} as well as O-H bending vibrations at 1196 cm^{-1}. ^{1}H NMR spectra of the synthesized compounds contain a singlet for the amide N-H proton in the downfield region at 9.0 ppm, a singlet for the thiadiazoline ring proton at 6.8 ppm, which is consistent with literary data [32], and all signals characteristic of the phenolic fragment: a singlet of 18 protons in a strong field at 1.41 ppm, a singlet of two aromatic protons in the region of 7.1 ppm and a phenolic OH proton in the region of 5.3 ppm. The proton spectrum of compound 3a contains signals of protons of two propionyl fragments: 2 quadruplets for 2 protons at 2.25-2.34 and 2.53-2.72 ppm, as well as 2 triplets for 3 protons in the region of 1.09-1.38 ppm. In the spectrum of compound 3b signals of two benzoyl fragments are observed in the region of aromatic protons: multiplets at 7.32-7.47 and 7.67-7.84 ppm. In the proton spectrum of com-

pound 3c, doublets of 4 protons of CH=CH fragments are observed in the region of 6.6 and 7.3 ppm, as well as signals of protons of two furan rings at 6.4 and 7.4 ppm.

The ABTS method was used to study the ability of the compounds to interact with cation radicals (Fig. 3). The antioxidant interacts with the deeply colored $ABTS^{+}$, inhibiting it and causing decolorization of the solution.

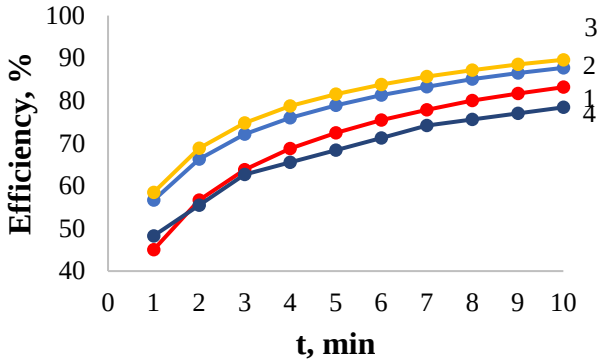

Fig. 3. Results of the antioxidant activity by ABTS method
1 – **3a**, 2 – **3b**, 3 – **3c**, 4 – BHT
Рис. 3. Результаты исследования антиокислительной активности по методу ABTS
1 – **3a**, 2 – **3b**, 3 – **3c**, 4 – BHT

All synthesized compounds showed better activity than BHT, compounds with a phenyl and ethylenylfuryl fragment showed the best activity, which may be due to their better ability to delocalize an unpaired electron in the phenoxyl radical. Thiadiazolines with propanoyl substituents showed lower efficiency.

EXPERIMENTAL PART

Melting points were determined using a Stuart SMP30 apparatus. IR spectra were recorded using an Agilent Carry 600 spectrometer equipped with an attenuated total reflectance (ATR) device. ^{1}H and ^{13}C NMR spectra were recorded at room temperature on a Bruker Avance II 300 spectrometer (^{1}H, 300 MHz; ^{13}C, 75 MHz); Me_4Si was used as an internal standard. Antioxidant activity was determined using a PE-2201 UV-VIS spectrophotometer. Mass spectra were obtained using a Bruker FTICR Apex Ultra Fourier transform ion cyclotron resonance mass spectrometer in positive ionization mode using an electrospray ion source (ESI).

Preparation of thiosemicarbazone of 4,6-di-tert-butyl-2,3-dihydroxybenzaldehyde ***1***

Thiosemicarbazide (8,5 mmol) was added to a solution of 4-hydroxy-3,5-di-*tert*-butylbenzaldehyde (8,5 mmol) in 40 ml of a mixture of AcOH:EtOH = 1:1. The mixture was refluxed with stirring for 6 hours. After completion of the reaction, the mixture was poured into water. Then the resulting precipitate was filtered off. The product was obtained with a yield of 62%, white powder, m.p. 183-184 °C [33].

^{1}H NMR (DMSO-d_6, δ, ppm, $^{3}J_{HH}$, Hz): 11.19 s (1H, NH), 7.94 s (1H, CH), 7.41 s (2H, Har), 7.33 s (1H, OH), 1.37 s (18H, t-Bu). ^{13}C NMR (DMSO-d_6, δ, ppm): δ 177.7 (NH_2-C=S), 156.5, 144.6, 139.6, 139.1, 127.35, 125.7,124.5, 35.0 ($(CH_3)_3C$), 30.7 ($(CH_3)_3C$). IR, ν, cm^{-1}: ν_{O-H} – 3624, ν_{N-H} – 3453, 3236, 3155, $\nu_{C=N\ Ar}$ – 1604, $\nu_{C=C\ Ar}$ – 1533, ν_{C-N} –1294, $\nu_{C-H\ Ar}$ – 889, 837.

Preparation of thiadiazole N-(5-(3,5-di-tert-butyl-4-hydroxyphenyl)-4-propionyl-4,5-dihydro-1,3,4-thiadiazol-2-yl)propionamide ***3a***

Thiosemicarbazone **2** (1,5 mmol) was dissolved in 20 ml of THF and 1.5 mmol of propionic anhydride were added. The mixture was refluxed with stirring for 8 h. The reaction progress was analyzed by TLC. After which the reaction mixture was cooled, THF was evaporated and the residue was poured into water. Purification of the compounds was performed by recrystallization from ethanol. The product was obtained with a yield of 77%, yellow crystals, m.p. 150-152 °C.

NMR ^{1}H ($CDCl_3$, δ, ppm, J_{HH}, Hz): 9.03 (1H, NH), 7.00 (2H, Ar), 6.86 (1H, CH-S), 5.22 (1H, OH), 2.56 (m, 2H, CH_2), 2.31 (q, 2H, CH_2), 1.38 (18H, t-Bu), 1.20 (3H, CH_3), 1.09 (3H, CH_3). ^{13}C NMR ($CDCl_3$, δ, ppm): 172.29, 153.97, 146.89, 136.17, 131.10, 121.91, 68.08, 34.32, 30.14, 29.35, 27.76, 8.81. IR, ν, cm^{-1}: ν_{O-H} – 3551, ν_{N-H} – 3474, 3205, 3140, ν_{C-H} – 2955, $\nu_{C=O}$ – 1699, $\nu_{C=C\ Ar}$ – 1611, $\nu_{C=N}$ – 1595. HRMS (ESI-) for $C_{22}H_{33}N_3O_3S$, *m/z*: calcd for $[M-H]^-$ 418.2170, found 418.2158.

Preparation of thiadiazole ***3b,c***

Thiosemicarbazone **2** (1,5 mmol) was dissolved in 20 ml of THF and 1.5 mmol of corresponding acyl chloride and a few drops of pyridine were added. The mixture was refluxed with stirring for 8 h. The reaction progress was analyzed by TLC. After which the reaction mixture was cooled, THF was evaporated and the residue was poured into water. Purification of the compounds was performed by recrystallization from an appropriate solvent.

3b: *N-(4-benzoyl-5-(3,5-di-tert-butyl-4-hydroxyphenyl)-4,5-dihydro-1,3,4-thiadiazol-2-yl)benzamide.* Yellow crystals. Yield 74%, m.p. 107-109 °C (Ethanol: H_2O, 1:1).

NMR ^{1}H ($CDCl_3$, δ, ppm, J_{HH}, Hz): 9.30 s (1H, NH), 7.84-7.67 m (4H, Har), 7.47-7.32 m (6H, Har), 7.34 s (2H, Har), 7.10, s (1H, CH-S), 5.27 s (1H, OH), 1.41 (18H, t-Bu). ^{13}C NMR (75 MHz, $CDCl_3$): 165.10, 154.20, 136.29, 134.57, 133.25, 131.33, 130.88, 130.59, 130.09, 128.91, 128.39, 127.81, 127.59, 122.59, 34.37,

30.18. IR, ν, cm: ν_{O-H} – 3630, ν_{N-H} – 3414, 3233, 3140, $\nu_{C-H\ Ar}$ – 3061, ν_{C-H} – 2959, $\nu_{C=C\ Ar}$ – 1611, $\nu_{C=O}$ – 1676, $\nu_{C=N}$ – 1601, 1632, $\nu_{C=C\ Ar}$ – 1480. HRMS (ESI+) for $C_{30}H_{33}N_3O_3S$, *m/z*: calcd for $[M+H]^+$ 516.2242, found 516.2315.

3c: *N-(5-(3,5-di-tert-butyl-4-hydroxyphenyl)-4-(-3-(furan-2-yl)acryloyl)-4,5-dihydro-1,3,4-thiadiazol-2-yl)-3-(furan-2-yl)acrylamide*. Yellow crystals. Yield 64%, m.p. 194-196 °C (Acetonitrile).

NMR ^{1}H (300 MHz, $CDCl_3$) δ 9.47 s (1H, NH), 7.46 d (1H, fur), 7.43 d (1H, Fur), 7.43 d (1H, CH=) 7.27 d (1H, CH=), 7.11 s (2H, Ar), 6.98 s (1H, CH CH-S), 6.63 d (1H, CH=), 6.53 d (1H, CH=), 6.48-6.40 m (4H, fur), 5.21 s (1H, OH), 1.37 s (18H, t-Bu). ^{13}C NMR (75 MHz, $CDCl_3$): 163.94, 154.03, 151.77, 150.77, 147.33, 145.10, 144.19, 136.14, 131.04, 129.25, 122.36, 116.17, 115.61, 114.39, 112.61, 112.23, 68.69, 58.41, 34.29, 30.11. IR, ν, cm: $\nu_{O-H,\ N-H}$ – cm 3460, ν_{N-H} – 3208, $\nu_{C=O}$ – 1641, $\nu_{C=N,\ C=C\ acryl}$ – 1605, $\nu_{C=C\ furan}$ – 1410, $\nu_{C-O-C\ furan}$ – 1017.

HRMS (ESI+) of **3c**: $C_{30}H_{33}N_3O_3S$, *m/z*: calcd for $[M+H]^+$ 548.2141, found 548.2212.

Antioxidant activity by the ABTS method [34]

2,2'-Azinobis(3-ethylbenzothiazoline-6-sulfonic acid) (Sigma) radical cation ($ABTS^{+}$) was prepared by mixing 7 mM aqueous potassium persulfate solution and 2.45 mM ABTS ammonium salt solution. The resulting solution was kept in the dark at room temperature for 12-16 h before use. The working solution was prepared by diluting the previous volume of solution in ethanol until its absorbance at 734 nm was 0.70 ± 0.02. To 2.7 ml of the working solution, 300 μl of 250 mmol solution of the prepared compounds in DMSO were added. After 10 min, the absorbance at 734 nm was measured using a spectrophotometer. Percent inhibition calculated as ABTS (%) = (AbsControl − Abssasment)/AbsControl, where AbsControl is the absorbance of the ABTS radical in ethanol; Abssasment is the absorbance of the ABTS solution mixed with the sample/standard extract. All determinations were performed in triplicate.

CONCLUSIONS

New 4,5-dihydro-1,3,4-thiadiazole derivatives containing a hindered phenol moiety were synthesized via acylation of the corresponding thiosemicarbazone with propionic anhydride and the corresponding acid chlorides. The yields were 64-77%. The structures of the obtained compounds were proven by IR, ^{1}H and ^{13}C NMR spectroscopy. All synthesized compounds showed a higher ability to interact with cation radicals compared to BHT. Compound **3c** with 2-furylethenyl fragment demonstrated the highest antioxidant activity.

Авторы заявляют об отсутствии конфликта интересов, требующего раскрытия в данной статье.

The authors declare the absence of a conflict of interest warranting disclosure in this article.

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