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Synthesis and Antioxidant Activity of 2-amino-5-R-1,3,4-oxadiazoles with Hindered Phenol Fragments †

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Abstract: Compounds with hindered phenolic moiety are known to be effective inhibitors of oxidative processes in different materials, moreover a number of phenols found to show wide spectrum of biological activity. At the same time, five-membered heterocycles exhibit unique properties, including antioxidant activity. One of the ways to create new effective antioxidants with a set of useful properties is to combine hindered phenol and a heterocyclic fragment in one molecule. In this work new 1-acyl-4-R-thiosemicarbazides were obtained during the reaction between 3-(4-hydroxy-3,5-di-tert-butylphenyl)propanoic acid hydrazide and a number of isothiocyanates. 2-Amino-5-R-1,3,4-oxadiazoles were prepared in good yelds by heterocyclization of 1-acyl-4-R-thiosemicarbazides in presence of iodoxybenzoic acid and triethylamine. The antioxidant activity of 1,3,4-oxadiazoles was studied in vitro and was found to be higher than that of 4-methyl-2,6-di-tert-butylphenol.

Keywords: 2.6-di-tert-buthylphenol; heterocycles; antioxidant activity; IBX; hypervalent iodine

1. Introduction

All organic substances undergo oxidative degradation under the influence of reactive oxygen species (ROS) such as hydroxyl $HO^{\bullet}$, superoxide $O_2^{\bullet}$, peroxide $ROO^{\bullet}$, alkoxyl $RO^{\bullet}$ and nitroxyl $NO^{\bullet}$ radicals [1]. ROS induce oxidative damage of cell membranes, lipids, proteins, and DNA repair system breakdown, that is connected with many degenerative diseases, such as cancer, atherosclerosis, Alzheimer's disease [2–4]. Antioxidants aim to scavenge free radicals and inhibit oxidative stress processes, because of their ability to inhibit the chain process of free radical oxidation and play crucial role in conserving finest cellular functions [5]. A wide number of natural antioxidants as well as synthetic ones have been found. Natural antioxidants include endogenous enzymatic (glutathione peroxidase, superoxide dismutase and catalase) [6], non-enzymatic (uric acid, lipoic acid, bilirubin, glutathione, metatonin) [7] and exogenous (carotenoids, vitamin E, A and C, natural flavonoids) [8]. Synthetic antioxidants are represented by a wide range of classes of organic compounds, such as amines [9], benzotriazole derivatives [10], alkylaminothiadiazoles [11] and others, but the most common structures in synthetic antioxidants are flavonoids [12,13], coumarins [14,15], and hindered phenols [16,17]. Despite the fact that the mechanism of oxidation, as well as the mechanism of action of antioxidants, has been studied for several decades, there is no universal approach to the creation of new antioxidants. The most rational way to obtain new antioxidants is to combine in one structure a fragment known for its antioxidant properties, for example, hindered phenol and structures with functional groups of various nature or heterocycles [18]. Thus, it was shown that chalcon derivatives with di-tert-butylphenol fragments are effective antioxidants [14]. Also, an increase in the antioxidant properties of phenols under some conditions was achieved by introducing a sulfur atom into the structure of an oxidation inhibitor [19,20]. Antioxidants containing

heterocyclic fragments in their structure are of considerable interest [21,22]. Such compounds are able to act by several mechanisms at once: inhibit free radical processes, decompose hydroperoxides, and chelate metals [23].

In continuation of our previous studies [24,25], in this work we combined in one structure a fragment of 2,6-di-tert-butylphenol and 2-alkyl/arylamino-1,3,4-oxadiazole and studied the antioxidant properties of the synthesized structures.

2. Results and Discussions

2.1. Synthesis

Preparation of the target compounds is outlined in the Scheme 1. Initially, 1-acylthiosemicarbazides **1a-c** were obtained by the reaction between 3-(4-hydroxy-3,5-di-tert-butylphenyl)propanoic acid hydrazide with a number of isothiocyanates. The reaction was carried out by boiling of the starting reagents in isopropanol for 5 h. The yields of thiosemicarbazides were 77–95%. The ^{1}H NMR spectra of the obtained compounds show peaks in the region of 9.5–10 ppm, corresponding to the protons of the NH-NH fragment.

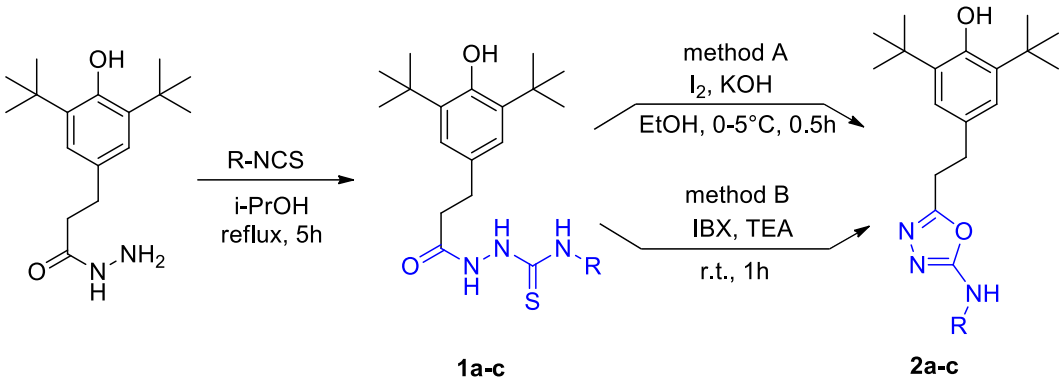
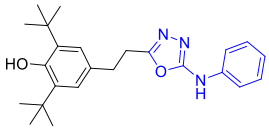
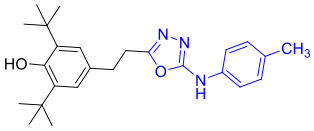
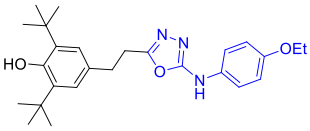


Figure 1. Scheme of preparation of oxadiazoles **2a-c.**

In accordance with the convenient method [27], the reaction was carried out in an alcoholic alkali solution with the presence of iodine at 0 °C. N-substituted 2-amino-1,3,4-oxadiazoles were obtained in 48–58% yield, with a strong resinification of the reaction mixture, which made it difficult to isolate the products. It was also not possible to achieve complete conversion of the starting 1-acylthiosemicarbazides even by boiling of the reaction mixture. In this regard, the method of applied cyclization proposed by the author of [26] has been applied: the reaction was carried out in chloroform in the presence of 2-iodoxybenzoic acid and triethylamine at room temperature. The yields of the target compounds increased to 74–80% (Table 1).

Table 1. The yields of oxadiazoles **2a-c**.

Methods	**2a**	**2b**	**2c**
			
Method A	58%	56%	48%
Method B	74%	80%	75%

In the ^{1}H NMR spectra of compounds **2a-c** all peaks, corresponding to phenol fragment are observed: the singlet peak near 6.71 ppm is attributed to the O–H of the hindered phenol, peaks at 7.42–7.54 ppm with the integration of two protons was assigned to the two symmetrical aromatic ring

protons. In addition, singlet peaks in the range of 9.23–10.36 ppm, corresponding to the protons of the secondary amino group were observed.

2.2. Antioxidant Properties

The antioxidant properties of the obtained **2a-c** compounds were tested in a model reaction of oleic acid oxidation. The oxidation of oleic acid was investigated at 65 °C using a thermostated apparatus upon bubbling of air into a cell for the oxidation at a constant rate of 2—4 mL min^{-1}. The level of lipid peroxidation was estimated on the concentration of primary oxidation products, hydroperoxides (LOOH) and secondary carbonyl products, which form complexes with thiobarbituric acid (TBARS, thiobarbituric acid reactive species) [14]. Butylated hydroxytoluene was used as a standard. The results of antioxidation ability tests are shown on the Figure 1.

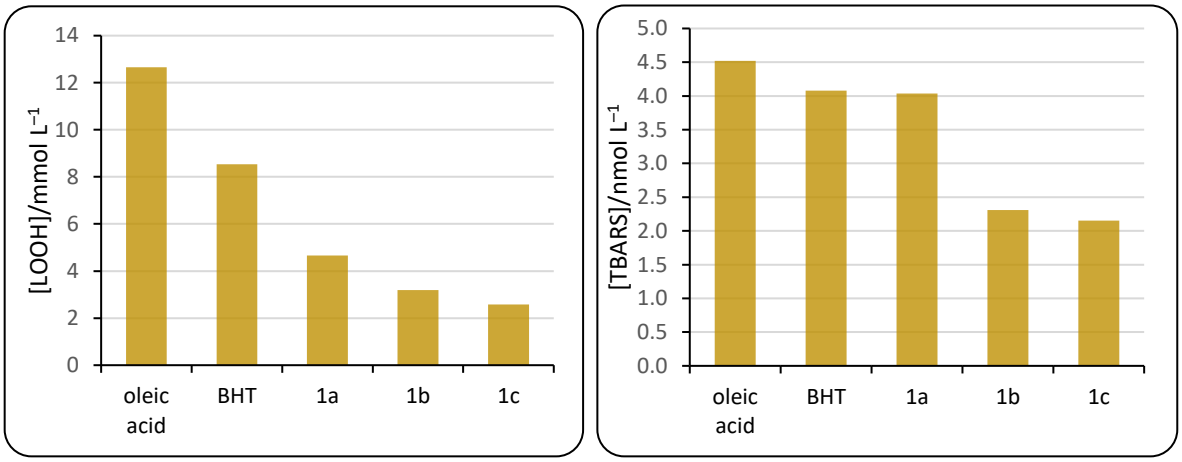


Figure 1. Antioxidant properties of prepeared compounds.

In the presence of compounds **2a-c**, the concentration of both hydroperoxides and secondary oxidation products decreases. All compounds have a significant effect on the concentration of hydroperoxides, according to this parameter, the activity of the synthesized substances significantly exceeds activity of BHT. In the presence of **2c** and **2c**, the concentration of TBARS also significantly decreases, compound **2a** exhibits an efficiency comparable to that of BHT.

3. Materials and Methods

3.1. General Information

NMR ^{1}H and ^{13}C spectra of solutions in DMSO-d_6 were recorded on a Bruker AM-300 spectrometer. All experiments were performed according to the standard methods of Bruker. Chemical shifts were reported relative to Me_4Si. The values of SSCCs are given in Hz. The mass spectra were recorded on an MS-30 Kratos device (Eu, 70 eV). A peak of the molecular ion M^+ was observed for all synthesized compounds. The melting points of the compounds obtained were determined in an open capillary. Elemental analysis carried out using Elemental analyzer Vario micro cube. The course of reactions and purity of the compounds obtained was monitored by TLC on silica gel plates in a 10:1 toluene-ethanol solvent system.

3.2. Synthesis and Analytical Data of Preparated Compounds

3.2.1. Synthesis of Compounds **1a-c**

A mixture of 20 mmol of hydrazide and 20 mmol of isothiocyanate in 70 mL of propanol-2 was stirred and refluxed for 5 h. The reaction mixture was cooled to room temperature, the precipitate formed was filtered off and recrystallized from a suitable solvent.

1-[2-(4-hydroxy-3,5-di-tert-butylphenyl)ethyl]-4-phenylthiosemicarbazide ***1a***. Yield 85%. M.p = 165–167 °C (ethanol: water 70:30). ^{1}H NMR (DMSO-d$_6$, δ, ppm): 1.36 s (18H, t-Bu), 2.34–2.62 m (4H, CH_2CH_2), 6.68 s (1H, HO), 7.05 s (2H, Har), 7.15 -7.44 m (5H, Har), 9.56 br.c. (2H, NH), 10.02 s (1H, NH). MS: (M^+) m/z 427. Calculated,%: C 67.41; H 7.78; N 9.83; S 7.50; found,%: C 67.26; H 7.98; N 9.68; S 7.35.

1-[2-(4-hydroxy-3,5-di-tert-butylphenyl)ethyl]-4-(4-methylphenyl)thiosemicarbazide ***1b***. Yield 77%. Mp = 203–204 °C (isopropanol: water 1: 1).). ^{1}H NMR (DMSO-d6, δ, ppm): 1.35 s (18H, t-Bu), 2.31 s (3H, CH_3), 2.44 t (J = 7.3, 2H, CH_2), 2.75 t (J = 7.2, 2H, CH_2), 6.71 s (1H, OH), 6.97 s (2H, Nar), 7.14 d (2H, Nar), 7.30 d (2H, Nar), 9.48 br.s (2H, NH), 9.86 s (1H, NH). MS: (M^+), m/z 444. Calculated,%: C 67.99; H 7.99; N 9.51; S 7.26; found,%: C 67.81; H 7.85; N 9.68; S 7.36;

1-[2-(4-Hydroxy-3,5-di-tert-butylphenyl) ethyl]-4-(3-ethoxyphenyl)thiosemicarbazide ***1c***. 80% yield. Mp = 165–167 °C (ethanol: water 1: 1). ^{1}H NMR (DMSO-d6, δ, ppm): 1.35 s (18H, t-Bu), 2.31 t (3H, CH_3), 2.45 t (2H, CH_2), 2.75 t (2H, CH_2), 3.99 m (2H, CH_2), 6.71 s (1H, OH), 6.89 d (2H, Nar.) 6.97 s (2H, Nar), 7.24 d (2H, Nar), 9.45 br.s (2H, NH), 9.88 s (1H, NH). MS: (M^+) m/z 471. Calculated,%: C 66.21; H 7.91; N 8.91; S 6.80; C found,%: 66.02; H 7.91; N 8.91; S 6.80;

3.2.2. Synthesis of Compounds **2a-c**

Method A: To a suspension of 14 mmol of 1-acylthiosemicarbazide in ethanol 0.7 mL of 4N NaOH solution was added. The reaction mixture was cooled and I_2 in an aqueous solution of KI was added dropwise at the temperature of 0–5 °C until a non-fading color of iodine appears. The reaction mixture цwas heated to boiling point, then cooled, poured into 200 mL of ice water, the precipitate was filtered off and the product was crystallized from a suitable solvent.

Method B: To 113 mmol of 1-acylthiosemicarbazide in chloroform 113 mmol of triethylamine and 23 mmol of iodoxybenzoic acid (IBX) were added. Reaction mixture was stirred at room temperature for 2.5 h. A solution of K_2CO_3 was added to reaction mixture, the target substance was extracted from the aqueous layer with chloroform, then the resulting extracts were dried over calcined Na_2SO_4. The solvent was evaporated, threated with cold water and the product was filtered off and crystallized from a suitable solvent.

2-N-(phenyl)amino-5-[2- (4-hydroxy-3,5-di-tert-butylphenyl) ethyl]-1,3,4-oxadiazole ***2a***. Yield 58% (Method A), 74% (Method B), mp. 186–188 °C, (ethanol: water 5: 1). ^{1}H NMR (DMSO-d6, δ, ppm): 10.36 s (1H, NH), 7.54 d (J = 8.2 Hz, 2H, Har), 7.34 t (J = 7.6 Hz, 1H, Har), 6.91 s (2H, Har), 6.76 s (1H, OH), 3.01 t (J = 7.0 Hz, 2H, CH_2-CH_2), 2.90 t (J = 7.3 Hz, 2H, CH_2-CH_2), 1.35 s (18H, t-Bu). MS: (M^+) m/z 393. Calculated,%: C 73.25; H 7.94; N 10.68; found,%: C 73.11; H 8.13; N 10.52.

2-N-(4-methylphenyl)amino-5-[2-(4-hydroxy-3,5-di-tert-butylphenyl) ethyl]-1,3,4-oxadiazole ***2b***. Yield 56% (Method A), 80% (Method B), mp. 172–174 °C, (ethanol: water 3: 1). ^{1}H NMR (DMSO-d$_6$, δ, ppm): 10.23 s (1H. NH), 7.42 (d, J = 8.1 Hz, 2H, Har), 7.14 (d, J = 8.2 Hz, 2H, Nar), 6.91 s (2H, Har), 6.76 s (1H, OH), 2.89 (t, J = 7.0, 2H, CH_2-CH_2), 2.99 t (J = 6.8, 2H, CH_2-CH_2), 1.35 s (18H, t-Bu). MS: (M^+) m/z 437. Calculated,%: C 73.68; H 8.16; N 10.31; found,%: C 73.79; H 8.33; N 10.15.

2-N-(4-ethoxyphenyl)amino-5-[2-(4-hydroxy-3,5-di-tert-butylphenyl)ethyl]-1,3,4-oxadiazole ***2c***. Yield 48% (Method A), 75% (Method B), mp. 179–181 °C, (ethanol: water 3: 1). ^{1}H NMR (DMSO-d$_6$, δ, ppm): 9.33 s 1H, NH), 7.42 (s 2H, Har), 6.90 s (2H, Har), 6.51 s (1H, OH), 3.97, br. s (2H, CH_2), 2.8–3.07 m (2H, CH_2-CH_2), 1.35 br s (18H, t-Bu). MS: (M^+) m/z 438. Calculated,%: C 71.37; H 8.06; N 9.60; found,%: C 71.25; H 8.18; N 9.80.

3.2. Antioxidant Properties of Preparated Compounds

Determination of the concentration of LOOH in oleic acid.

0.5 Ml of oleic acid, 9 mL of glacial acetic acid, 6 mL of chloroform, and 0.5 mL of a saturated freshly prepared KI solution were placed in a flask. The flask was shaken for 2 min, then 50 mL of distilled water and 0.5 mL of 1% starch solution were poured into it. Thereafter, they were immediately titrated with 0.01 N $Na_2S_2O_3$ solution. The LOOH concentration was calculated according to the following formula:

$$[LOOH] = [(V - V_0) \bullet 0.001269K \bullet 100]/m \quad (1)$$

V is the volume of 0.01 N $Na_2S_2O_3$ solution, consumed during the titration of working sample, mL; V_0 is the volume of 0.01 N $Na_2S_2O_3$ solution, consumed during the titration of control sample, mL; K is the conversion factor to the exactly 0.01 N $Na_2S_2O_3$ solution; m is the mass of studied oleic acid; 0.001269 is the amount of I_2 expressed in g, equivalent to 1 mL of 0.01 N $Na_2S_2O_3$ solution. The [LOOH] content equal to 1% corresponds to 78.7 mM of active O_2 per 1 L of lipids (mmol L^{-1}).

Determination of the concentration of TBARS in oleic acid

The studied compounds (1 mmol L^{-1}) were added to oleic acid and thermostated at the 65 °C for 6 h. After cooling, samples (0.01 mL) of oleic acid were taken from the thermostat and put into a test tube. A mixture of phosphate buffer (0.8 mL), distilled water (1.2 mL), and freshly prepared thiobarbituric acid solution (0.8%, 1 mL) were added; the tube was heated for 10 min in a boiling water bath, and after cooling, the absorption of the samples was measured in comparison with that of control at λ = 532 nm. The concentration of carbonyl compounds was calculated according to the formula:

$$[TBARS] = (E \bullet 3)/0.156 \quad (2)$$

[TBARS] is the content of carbonyl compounds, nmol L^{-1}; E is the absorbance of a sample relative to the control (mixture without oleic acid); 3 is the sample volume, mL; and 0.156 is the extinction of malondialdehyde (1 nmol) dissolved in 1 mL at λ = 532 nm [14].

4. Conclusions

In this study the synthesis and antioxidant activity of three 2,6-di-tert-buthylphenol derivatives linked to 2-amino-5-R-1,3,4-oxadiazoles is described. Carrying out the cyclization of 1-acylthiosemicarbazides by the action of iodoxybenzoic acid made it possible to increase the yields of the target compounds in comparison with the convinient method. All investigated substances exhibit antioxidant capacity superior or comparable to those of BHT. 2-N-(4-ethoxyphenyl)amino-5-[2-(4-hydroxy-3,5-di-tert-butylphenyl)ethyl]-1,3,4-oxadiazole **2c** possesses the best antioxidant properties among the studied oxadiazoles.

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