Anthraquinonylhydrazones of α-Active Ketones and β-Carbonyl-containing Compunds: Synthesis and Antioxidant Activity

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Abstract – ***An effective method for the synthesis of 1-anthraquinonyl hydrazones containing the acyl- and/or ethoxycarbonyl, carbo- and heterocyclic fragments in the ylidene moiety has been shown, which are convenient reagents for further chemical transformations. Investigation of the antioxidant activity of hydrazones has allowed to identify promising compounds that can be suggested for further research as antioxidant substances.***

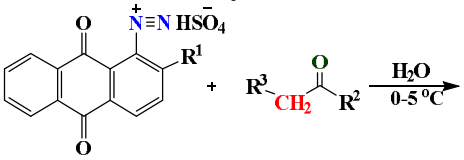
Keywords – 9,10-anthraquinone, diazonium salt, hydrazone, α-active ketones, β-carbonylcontaining compunds, antioxidant activity.

I. Introduction

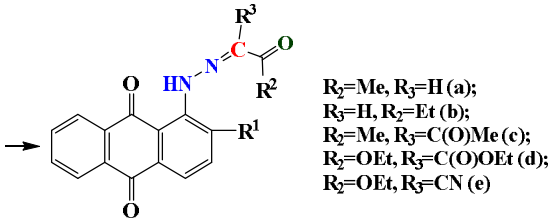
Hydrazones as functional derivatives of the hydrazine are widely used in the synthesis of heterocyclic compounds [1]; some hydrazones exhibit a broad spectrum of biological activity [2]. Compounds of the 9,10-anthraquinone series are known to possess a combination of practically important properties [3]; they have been shown to be promising for various applications, in particular for use as medicinal agents [4]. The anthraquinone ring system is an important scaffold for the design of new biologically active compounds, which strongly stimulates synthesis of new derivatives. Syntheses of anthraquinone hydrazones from the anthrone and its derivatives have been reported in [5–7]. Vorob'eva et al. [8] developed a procedure for the synthesis of ethyl pyruvate anthraquinonylhydrazone via the Japp–Klingemann reaction of 9,10-anthraquione-2-diazonium chloride with ethyl methylacetoacetate in acid medium. However, anthraquinonylhydrazones have not been reported, presumably due to their ability to readily undergo intramolecular cyclization [9].

II. Results and discussion

Herein we propose an efficient method for the synthesis of previously unknown 1-anthraquinonylhydrazones containing in the ylidene moiety acyl and/or ester fragments (Eq. (1)). The reactions of freshly prepared 9,10-dioxo-9,10-dihydroanthracene-1-diazonium hydrogen sulfates **1**, **2** [10] with acetone **3a**, butan-2-one **3b**, acetylacetone **3c**, diethyl malonate **3d**, and ethyl acetoacetate **3e** at a ratio of 1 : 3 in water at 0–5°C in the absence of a base afforded hydrazones **4a–e, 5a-e** in 62–71% yields.



1 (R_1=H), **2** (R_1=COOH) **3a-e**



R_2=Me, R_3=H (a);
R_3=H, R_2=Et (b);
R_2=Me, R_3=C(O)Me (c);
R_2=OEt, R_3=C(O)OEt (d);
R_2=OEt, R_3=CN (e)

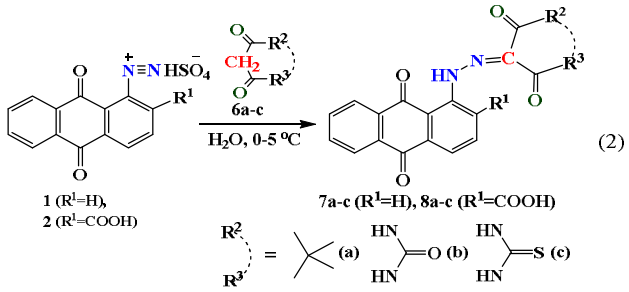
(1)

4a-e (R^1=H), **5a-e** (R^1=COOH)

The reaction time depended on the initial carbonyl compound. The reactions with less acidic ketones **3a** and **3b** were completed in 40–45 min, and with 1,3-dicarbonyl compounds **3c**–**3e** in 10–15 min.

The formation of hydrazones **4a-e**, **5a-e** is confirmed by the data of the ^{1}H and ^{13}C NMR spectra, as well as the presence of the corresponding molecular peaks in the LC-MS spectra. The signal of the ylidene proton in compounds **4a,b** and **5a,b** are superimposed with protons of the anthracenedione fragment and are located within the range of 7.71-7.92 ppm. The signal of proton in the amino group of anthraquinonylhydrazones **4a-e**, **5a-e** with acyl substituents in the ylidene moiety is resonated as a broad singlet within the range of 12.29-12.79 ppm, and for compounds **4d,e** the chemical shift increse to the region of the weak field at 14.28-14.48 ppm. In the IR spectra of hydrazons there are absorption bands of the secondary amino group at 3310-3370 cm^{-1}.

In order to modify the anthraquinonylhydrazones by new pharmacophores, in particular, carbonic and heterocyclic fragments, reactions of the 1-amino-9.10-anthracenedione **1** and **2** diazonium salt with cyclic β-dicarbonyl compounds **6a-c** – 5,5-dimethyl-1,3-cyclohexanedione, 2,4,6-pyrimidintrione, 2-thioxopyrimidine-4,6-dione (Eq. (2)). The analysis of the ^{1}H and ^{13}C NMR spectra of the obtained hydrazons **7a-c**, **8a-c** allowed to establish the following: the 5,5-dimethyl-1,3-cyclohexanedione fragment in anthraquinonyl-hydrazone **7a** in DMSO-d_6 solution exists exclusively in a ketone form. A similar situation is observed for hydrazone **8a**. In the ^{1}H NMR spectra of compounds **7b,c** and **8b,c** in DMSO-d_6, in addition to the NH signal of the hydrazinyl moiety in the weak field, the signals of exchange protons were observed, which is evidence of the formation of keto-enol tautomeric forms.



(2)

Antioxidant activity

Antioxidant capacity of the synthesized compounds were determined by comparing with Trolox as the standard reference compound using CUPRAC assay (at room temperature) [11]. The CUPRAC molar absorption coefficient (ε) of the tested compound divided by that of TR under the same conditions gave the TEAC-CUPRAC values (Fig. 1).

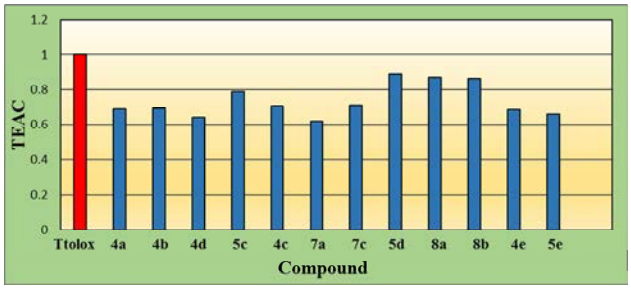


Fig. 1. The TEAC coefficients of the hydrazones with respect to the CUPRAC assay

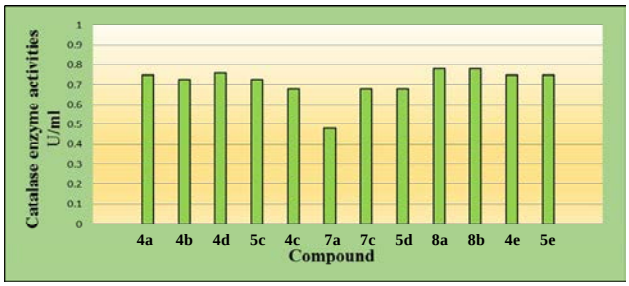


Fig. 2. Catalase enzyme activities (U mL^{-1}) of hydrazones

Amongst the compounds screened for a antioxidant capacity, **5d, 8a** and **8b** exhibited the highest antioxidant capacities and the TEAC coefficients of these compounds were TEAC = 0.86, 0.89, 0.87 (Fig. 1). Also, studies on the effect of catalase activity, which is an integral part of antioxidant protection in cells, were carried out using the CUPRAC method [12]. The results (Fig. 2) showed that the highest activity was characteristic of compound **8b** (0.89 U/ml), and the lowest – hydrazone of dimetidon **7a** (0.48 U/ml).

Conclusion

A convenient way of obtaining a number of new anthraquinonylhydrazones by combining diazonium salt with α-active ketones and β-dicarbonyl compounds in an aqueous medium under mild conditions is proposed. All the synthesized compounds were tested for their antioxidant capacity and for inhibitory activities against catalase enzyme using the CUPRAC method. The synthesized compounds 5d, 8a and 8b exhibited better antioxidant capacity than the other compounds. The results revealed that 8b exhibited high CAT inhibition activity compared to the other compounds.

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