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Aci-Quinone Compounds from Eugenoxyacetic Acid and Methyleugenol: Preparation and Reaction

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Abstract: A new aci-quinone compound, 4-(*aci*-nitro)-2-(methoxy)-5-(3-nitro-2-(nitrooxy)propyl)-cyclohexa-2,5-dienone (**2**), an analog to 4-(*aci*-nitro)-2-(carboxymethoxy)-5-(3-nitro-2-(nitrooxy)propyl)-cyclohexa-2,5-dienone (**1**), was successfully synthesized and fully characterized by spectroscopic methods. The reactions of **1** and **2** with various reagents such as hydroxylamine, acetic anhydride, semicarbazide and thiosemicarbazide were examined. The structure of 11 obtained new compounds was established by IR, ^{1}H NMR, ^{13}C NMR, HMBC and MS spectra. It was shown that the unstable, sensitive aci-quinone structure of compounds **1** and **2** can exist in anhydrous organic solvents such as AcOEt, EtOH but in the presence of water, H^{+}, HO^{-} or at high temperatures, the aci-quinone structure of both **1** and **2** tendentiously transformed into the more stable nitro-phenol form.

Keywords: Aci-nitro, aci-quinone, nitrophenol, eugenol, semicarbazone, thiosemicarbazone.

1. INTRODUCTION

l-Hydroxy-2-methoxy-4-allylbenzene, also known as eugenol, the active constituent in *Ocimum sanctum L.* oil, and tulsi oil, has been found to be largely responsible for the therapeutic potentials of the plants in traditional medicines [1]. The condensation of eugenol and monochloroacetic acid in alkaline medium affords eugenoxyacetic acid (2-methoxy-4-(2-propenyl)phenoxyacetic acid). Eugenoxyacetic acid is known to be a beneficial food additive since it is an odorless, tasteless and non-toxic compound with good antioxidant [2]. It has been reported that eugenoxyacetic acid, 5-nitroeugenoxyacetic acid, their methyl, and their ethyl esters exhibit hypolipidaemic and antiplatelet activity, thus they appear to be potential for the treatment of human hyper-lipidaemia and thrombotic diseases [2-5]. Methyleugenol (4-allyl-1,2-dimethoxybenzene) is a natural constituent of a number of plants such as cinnamomum cordatum, nutmeg, pimento, lemongrass, tarragon, holy basil, star anise and fennel. It is easily prepared by methylation of eugenol. Methyleugenol is used in perfumery and flavoring [6], in formulating insect attractants, and as UV absorbers, analgesics, biocides [7-9] and psychotropic drugs [10].

Aci-nitro tautomerism are well known, azo-quinone hydrazone tautomers are also studied in several works [11-13]. Aci-quinone tautomers have been discussed in theoretical researches [14-17] as very unstable intermediates in explosion of nitrophenols. However, until now, their isolation, characterization and name were almost not performed.

In our previous work [18] the isolation, structure and double tautomerization of an aci-quinone compound, 4-(*aci*-nitro)-2-(carboxymethoxy)-5-(3-nitro-2-(nitrooxy)propyl)-cyclohexa-2,5-dienone (**1**) related to eugenoxyacetic acid have been reported. The aci-quinone **1** was used as the key compound for the synthesis of novel polysubstituted quinolines [19]. Herein another aci-quinone compound, 4-(*aci*-nitro)-2-(methoxy)-5-(3-nitro-2-(nitrooxy) propyl)-cyclohexa-2,5-dienone (**2**), was prepared from methyleugenol. Several reactions of **1** and **2** were concomitantly studied as well. The products of these reactions can be used for the preparation of aza- and sulfur-heterocycles.

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2. RESULTS AND DISCUSSION

Aci-quinone **2** was prepared by treatment of methyleugenol with excess nitric acid in the acetic acid according to the procedure described for the preparation of aci-quinone **1** [18]. The formation of aci-quinone **2** can be briefly explained as shown in Scheme **1**. The numeration in the formulas is given specially for NMR analysis only.

As known, aci-quinone structure is very unstable [14-17]. It was surprising that after reflux of an ethanol solution of aci-quinone **1** for an hour we obtained both **3**, an ethyl ester in aci-quinone form (Scheme **2**) in 30% yield, and **3a**, an ethyl ester in nitro-phenol form in 23% yield. When an ethanol solution of **3** and $N_2H_4.H_2O$ was refluxed for an hour, we obtained only hydrazide **4** in nitrophenol form in 42% yield. When **1** was stirred in aqueous solution of $HONH_2.HCl$ and AcONa, we obtained **5**, a product of the replacement of $-ONO_2$ by –NHOH instead of an oxime of the aci-quinone (Scheme **2**).

The convincing evidences for aci-quinone structure of **2** and **3** are as follows: The medium absorption bands at 1632, 1640 cm^{-1} in IR spectra of **2**, **3**, respectively, and the ^{13}C signals at 178.4, 178.2 ppm in the spectra of **2**, **3**, respectively, show the presence of the quinone carbonyl group in **2** and **3**; the absorption band at 364 nm (ε = 8250) in UV-Vis spectrum of **2** (whereas *p*-nitrophenol absorbs at 318 nm) indicates a quinoid chromophore; the strong upfield shift of H-3 and H-6 in **2** and **3** as compared to those in **4** – **12** (Tables **1** and **2**) is consistent with the quinoid structure in **2** and **3** and the benzenoid structure in **4** – **12**. In the negative mode ESI MS of **2** there is no [M-H^{+}] peak at m/z 317 au but there is [M-HNO_3-H^{+}] peak at 253 au as the base peak. It is possible that **2** was converted into the more stable form (a nitrophenol conjurated with the side chain) and the phenolic proton was lost as shown in Scheme **3**. In addition, the similarity in ^{1}H NMR spectra of **2**, **3** and **1** (previously reported [18]) indicates that they have the same aci-quinone structure.

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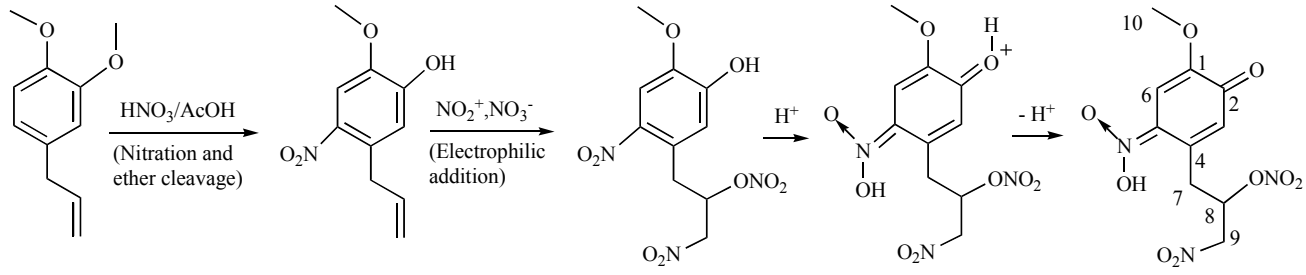
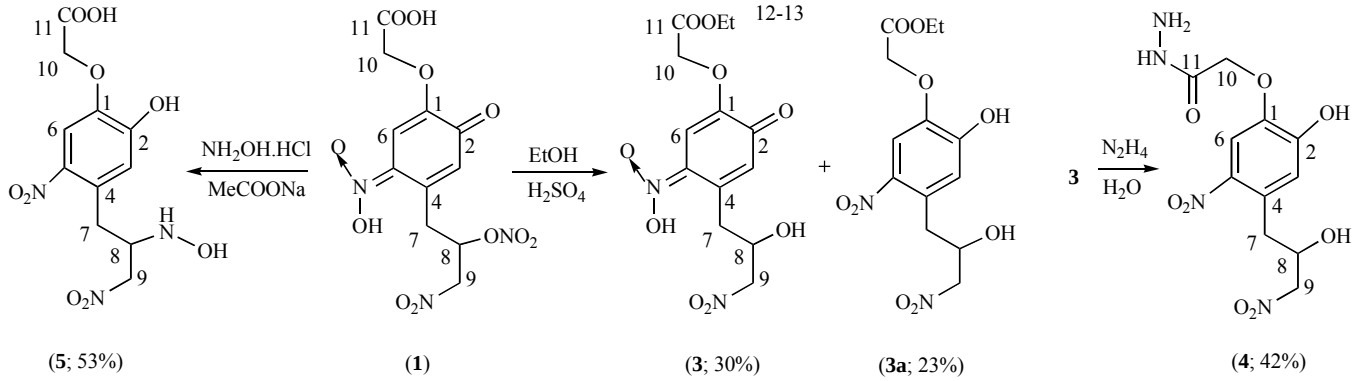
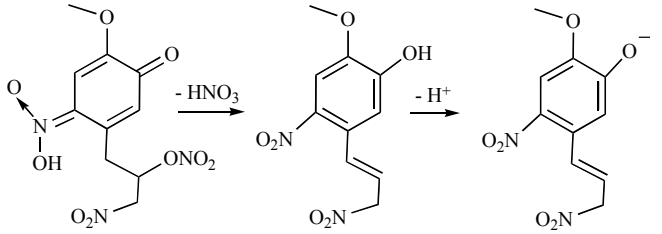


Scheme 1. The formation of aci-quinone **2** from methyleugenol.



Scheme 2. Transformation of aci-quinone **1** into aci-quinone **3**, hydrazide **4** and hydroxyamino **5**.



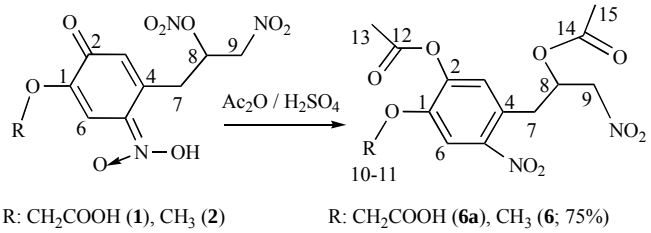
Scheme 3. Transformation of **2** into more stable compound and it's deprotonation.

The absence of the signals of the ethyl group, the presence of the broadened signal of the NH_2 group in ^{1}H NMR spectrum of **4** (Table **1**) and the strong decrease in the frequency of carbonyl group of **4** (1699 cm^{-1}) in comparison with that of **3** (1752 cm^{-1}) are clear evidences for the formation of hydrazide **4**.

The strong upfield shift of H-8 in **5** as compared to that in **4** and **6** by 0.71 and 2.07 ppm (Table **1**), the strong upfield shift of C-8 in **5** as compared to that in **4** and **6** by about 8 ppm (see Experimental) associate with the HC-8 attached to NOH group in **5** and HC-8 attached to OH in **4** and to OAc in **6**. In addition, the molecular mass of **5** from ESI MS accords with the calculation (see Experimental).

Reaction of Aci-quinones 1 and 2 with Acetic Anhydride

It has been reported that 1,4-benzoquinone reacts with acetic anhydride and sulfuric acid to give the triacetate of hydroxyquinol [20]. Being heated in acetic anhydride and concentrated H_2SO_4, **1** and **2** were transformed into the corresponding nitro-phenol compounds. Subsequently, the phenolic hydroxyl group was acylated, followed by the replacement of the nitrate group to give **6a** and **6**, respectively (Scheme **4**).



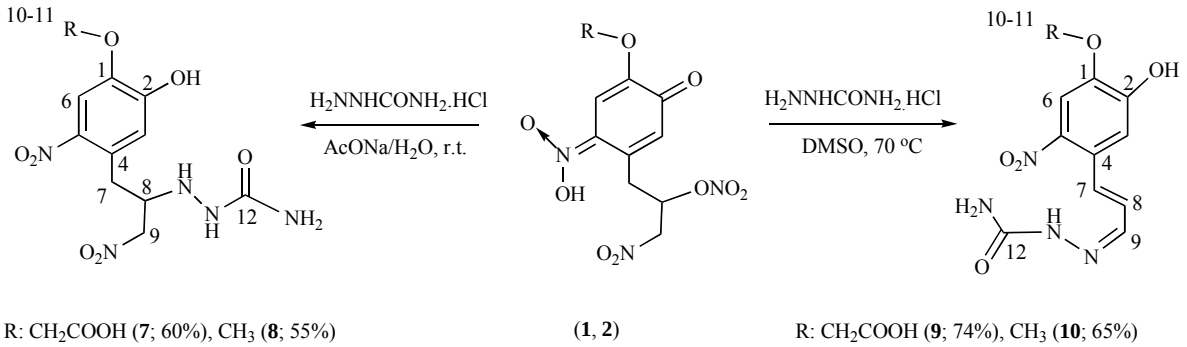
Scheme 4. Acylation of aci-quinones **1** and **2**.

Compound **6a** was identified as 2-acetoxy-4-(2-acetoxy-3-nitropropyl)-5-nitrophenoxyacetic acid, which had been isolated and characterized [18]. The structure of compound **6** was examined by IR and NMR spectroscopic methods (see Experimental section and Table **1**). For instance, in the IR spectrum of **6** there are two bands at 1742 and 1750 cm^{-1} for two ester C=O groups, in the ^{13}C NMR of **6** there are four characteristic signals of two acetoxy groups: the first at 168.0 (C=O), 20.1 (CH_3) and the second at 169.1 (C=O), 20.3 (CH_3) ppm.

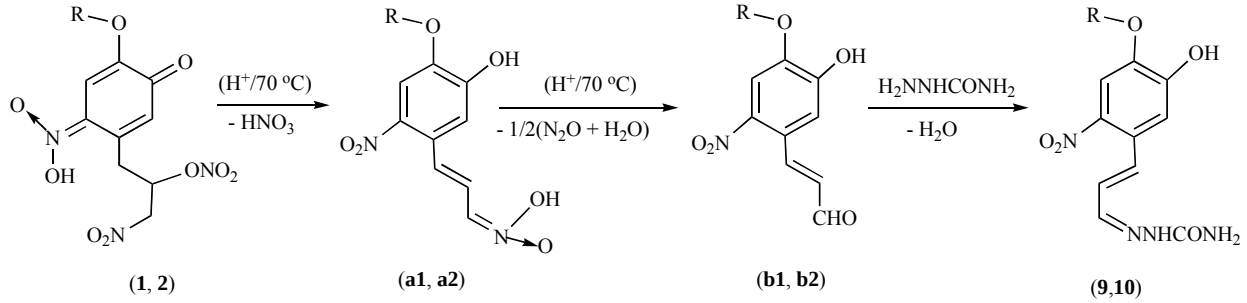
Reactions of Aci-quinones 1 and 2 with Semicarbazide

It is known that the formation of oximes, phenyl-hydrazones, and semicarbazones are common to ketones and quinones. When stirring **1** and **2** in aqueous solution of $H_2NNHCONH_2$.HCl and AcONa at room temperature, instead of semicarbazones of the aci-quinones, we received compounds **7** and **8**, respectively, with the replacement of $-ONO_2$ by $-NHNHCONH_2$. On the other hand, when heating DMSO solutions of **1** and **2** with $H_2NNHCONH_2$.HCl at 70 ^oC, we received compounds **9** and **10**, respectively (Scheme **5**).

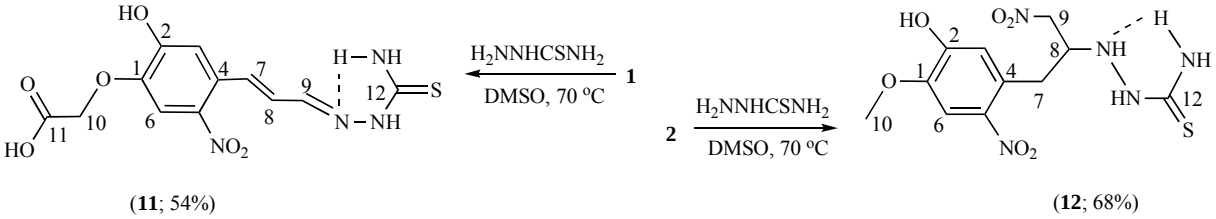
The NMR data show some distinctive features for compounds **9** and **10** in comparison to those of **7** and **8**. Firstly, in the ^{1}H NMR spectra of **7** and **8**, there are five protons H-7a, H-7b, H-8, H-9a and H-9b attached to the three carbon atoms of the propyl side chain, whereas the ^{1}H NMR spectra of **9** and **10** show only three protons H-7, H-8 and H-9 (Table **2**). Secondly, the three carbon signals in



Scheme 5. Reaction of aci-quinone **1** and **2** with semicarbazide.



Scheme 6. Chemical transformation of aci-quinones **1** and **2** into aldohydrazones **9** and **10**.



Scheme 7. Reaction of aci-quinones **1** and **2** with thiosemicarbazide.

the side chain (C-7, C-8, C-9) of **7** and **8** lie in the sp^3-carbon region (smaller than 80 ppm), whereas the three carbon signals in the side chain of **9** and **10** lie in the sp^2-carbon region (greater than 110 ppm) (see Experimental section). In particular, in the HMBC (Heteronuclear Multiple Bond Correlation) spectrum of **9** as well as in the HMBC spectrum of **10** there is a cross peak between proton HN and C9. This indicates that the semicarbazide moiety is bound up with C-9 to the side chain of **9** and **10**.

The presence of $–NHNHCONH_2$ at C-8 in **7** and **8** is shown by the appearance of three proton signals of CO-NH, C8-NH and CO-NH_2 (see Table **2**). The presence of $=NNHCONH_2$ at C-9 in **9** and **10** is shown by the appearance of two proton signals of CO-NH, CO-NH_2 (see Table **2**).

The formation of **9** and **10** can be explained as follows: When being heated with $H_2NNHCONH_2.HCl$, HNO_3 was eliminated from the molecules of **1** and **2**, resulting in the formation of the corresponding aci-compounds **a1** and **a2**. These two compounds undergo the Nef reaction to give the unisolated intermediate aldehydes **b1** and **b2**. The following condensation of **b1** and **b2** with semicarbazide afforded the aldohydrazones **9** and **10** as shown in Scheme **6**.

Reaction of Aci-quinones 1 and 2 with thiosemicarbazide

By heating DMSO solutions of **1** or **2** and $H_2NNHCSNH_2$ at 70 °C, we obtained compounds **11** and **12**, respectively (Scheme **7**).

In the IR spectra of **11** and **12**, there are narrow bands at 3320, 3177 and 3330, 3175 cm^{-1}, respectively, showing the presence of NH groups. The ^1H and ^{13}C signals of **11** and **12** were assigned using their HMBC spectra. The chemical shift and multiplicity of the resonance signals of H3, H6, H7, H8, H9, H10 and NH of **11** and **12** are similar to those of **9** and **8**, respectively (see Table **2**). The two protons of the H_2N-C=S group of **11** and **12** become non-equivalent (Table **2**) since one of them forms intramolecular hydrogen bond with =N-C9 and NC-8, respectively (see Scheme **7**).

The formation of **11** and **12** can be explained as follows: The -OCH_2COOH group of **1** affords enough H^+ as the catalyst for the elimination of HNO_3, for the Nef reaction in the side chain and for the condensation of the generated aldehyde with thiosemicarbazide, leading to the formation of **11** (similarly in Scheme **6**). Whereas in the absences of H^+, thiosemicarbazide, a nucleophile, replaces the nitrate group in the side chain of **2** to give **12**.

The typically high coupling constant of the two protons H-7 and H-8 ($^3J_{H7,H8}$ = 16 Hz) in **9**, **10** and **11** (Table **2**) reveals the *trans*-configuration of the C-7=C-8 double bond in these compounds.

3. EXPERIMENTAL

General

Melting points were measured using a Galenkamp capillary melting point apparatus and are not corrected. C, H and N were

Table 1. ^{1}H NMR signals of compounds 2 - 6, δ (ppm), J_{HH} (Hz).

	H-3	H-6	H-7a	H-7b	H-8	H-9a	H-9b	H-10	Others
2	6.31 s	6.68 s	3.06 m	3.04 m	5.65 m	5.21 dd, ^2J 15, ^3J2	5.02 dd, ^2J 15, ^3J 9	3.77 s, 3H	-
3	6.33 s	6.69 s	3.05 d, ^3J 6.5	3.05 d, ^3J 6.5	5.67 m	5.22 dd, ^2J 15, ^3J 2	5.01 dd, ^2J 15, ^3J 9	4.86 s, 2H	H-12: 4.18 q, ^3J 7; H-13: 1.22 t, ^3J 7
4	6.37 s	7.65 s	3.03 dd, ^2J 15, ^3J 5	2.88 dd, ^2J 15, ^3J 7	4.36 m	4.58 dd, ^2J 12, ^3J 3	4.41 dd, ^2J 12, ^3J 9	4.49 s, 2H	NH_2: 5.5 (broadened)
5	6.81 s	7.63 s	3.01 dd, ^2J 14, ^3J 6	2.97 dd, ^2J 14, ^3J 8	3.65 m	4.69 dd, ^2J 13, ^3J 8	4.54 dd, ^2J 13, ^3J 5	4.41 s, 2H	-
6	7.28 s	7.74 s	3.33 dd, ^2J 14, ^3J 4	3.03 dd, ^2J 14, ^3J 9	5.72 m	5.02 dd, ^2J 14, ^3J 3	4.75 dd, ^2J 14, ^3J 9	3.87 s, 3H	H-13: 2.31 s, 3H H-15: 1.84 s, 3H

Table 2. ^{1}H NMR signals of compounds 7 - 12, δ (ppm), J_{HH} (Hz).

	H-3	H-6	H-7a	H-7b	H-8	H-9a	H-9b	H-10	Others
7	6.79 s	7.64 s	3.09 dd, ^2J 14, ^3J 7	2.95 dd, ^2J 14, ^3J 7	3.54 m	4.62 dd, ^2J 13, ^3J 7	4.48 dd, ^2J 13, ^3J 5	4.45 s, 2H	HNCO: 7.35 s; NH_2: 5.76 s; HNC-8: 4.93 s
8	6.84 s	7.62 s	3.09 dd, ^2J 14, ^3J 7	2.94 dd, ^2J 14, ^3J 7	3.53 m	4.65 dd, ^2J 13, ^3J 7	4.47 dd, ^2J 13, ^3J 5	3.85 s, 3H	HNCO: 7.38 s; NH_2: 5.72 s; HNC-8: 4.95 s
9	7.11 s	7.55 s	7.23 d, ^3J 16	-	6.68 dd, ^3J 16, ^3J 9	7.70 d, ^3J 9	-	4.82 s, 2H	NH: 10.25 s NH_2: 6.34 s
10	7.08 s	7.61 s	7.23 d, ^3J 16	-	6.66 dd, ^3J 16, ^3J 9	7.69 d, ^3J 9	-	3.88 s, 3H	OH: 10.68 s; NH: 10.26 s; NH_2: 6.35 s
11	7.11 s	7.57 s	7.35 d, ^3J 16	-	6.67 dd, ^3J 16, ^3J 9	7.89 d, ^3J 9	-	4.84 s, 2H	NH: 11.43 s NH_2: 8.21 s, 7.68 s
12	6.83 s	7.61 s	3.14 dd, ^2J 14, ^3J 6	2.96 dd, ^2J 14, ^3J 7	3.59 m	4.65 dd, ^2J 13, ^3J 7	4.49 dd, ^2J 13, ^3J 6	3.84 s, 3H	OH: 10.63 s; HN-CS: 9.00 s; NH_2: 7.84 s, 7.67 s; HNC-9: 5.33 d , ^3J 7

analyzed on a LECO CHNS model 932 elemental analyser. The IR spectra were recorded on an IMPACK-410 NICOLET spectrometer, in KBr plates, in the range 400 - 4000 cm^{-1}. The UV-Vis spectra were recorded on a UV-Vis spectrophotometer 2800. MS spectra were acquired on a LC/MS/MS Waters-API-ESI. The NMR spectra were recorded on a Bruker AVANCE 500 MHz, all at 298 - 300 K, in d_6-DMSO, with TMS as the internal standard.

Preparation

4-(*aci*-nitro)-2-(carboxymethoxy)-5-(3-nitro-2-(nitrooxy)-propyl)cyclohexa-2,5-dienone (1). This compound was obtained by treating eugenoxyacetic acid with excess amounts of nitric acid in acetic acid [18].

4-(*aci*-nitro)-2-(methoxy)-5-(3-nitro-2-(nitrooxy)-propyl)-cyclohexa-2,5-dienone (2). To a solution of methyleugenol (17.8 g, 0.1 mol) in glacial acetic acid (50 mL) was slowly added HNO_3 (20mL, D = 1.41 g/mL). The reaction mixture was allowed to stand at -5 ÷ 0 ^oC for 4 h and at room temperature for additional 4 h. The yellow solid was collected by filtration, washed with ethyl acetate, diethyl ether and then dried under reduced pressure at 40 ^oC for 2 h to give 15.8 g of **2** in 50% yield, **2** was not melt but decomposed at 160 ^oC. The yellow color of **2** slowly changed on standing in air. IR (cm^{-1}): 3505 (O-H); 3031, 2954 (C-H); 1632 (quinone C=O); 1604 (quinone C=C), 1600, 1520 (N=O). ^{1}H NMR see Table **1**. ^{13}C NMR, δC (asigned according to the HMBC spectrum): 154.2 (C-1); 178.4 (C-2); 123.7 (C-3); 133.8 (C-4); 123.7 (C-5); 100.6 (C-6); 26.8 (C-7); 78.8 (C-8); 75.6 (C-9); 55.8 (C-10). UV spectrum, λ_{max}(nm)/ε: 248/2337; 364/8250. ESI –MS, *m/z* (%) = 253 (M-HNO_3 and H, 100). Anal. Calcd for $C_{10}H_{11}N_3O_9$ (317.21): C, 37.86; H, 3.50; N, 13.25. Found: C, 38.12; H, 3.27; N, 13.54.

Reaction of 1 with ethanol. A mixture of **1** (3.61 mg, 1 mmol) in absolute ethanol (5 mL) and H_2SO_4 (1 drop) was refluxed for 1 h. The precipitate was filtered out and recrystallized from EtOH/H_2O 1:1 (by volume) to afford **3a**, yield 23 %, 80 mg. This compound was identified as ethyl 2-hydroxy-4-(2-hydroxy-3-nitropropyl)-5-nitrophenoxyacetate, which was identical to the one reported [18]. The filtrate was allowed to stand at room temperature for 24 h. The resulting yellow crystals were collected and washed with ethyl acetate and diethyl ether to give 4-(*aci*-nitro)-2-(carbethoxymethoxy)-5-(3-nitro-2-(nitrooxy)propyl)cyclohexa-2,5-dienone (**3**), yield 30%, 104 mg, decomposed at 150 ^oC. IR (cm^{-1}): 3452 (O-H); 3074, 3046, 2932 (C-H); 1752 (ester C=O); 1640 (quinone C=O); 1600 (quinone C=C); 1565, 1517 (N=O). ^{1}H NMR see Table **1**. ^{13}C NMR, δC (asigned according to the HMBC spectrum): 152.5 (C-1); 178.2 (C-2); 123.7 (C-3); 133.8 (C-4); 123.5 (C-5); 102.1 (C-6); 26.8 (C-7); 78.9 (C-8); 75.6 (C-9); 64.9 (C-10); 168.5 (C-11); 60.8 (C-12); 14.0 (C-13). Anal. Calcd. for $C_{13}H_{16}N_2O_9$ (344.27): C, 45.35; H, 4.68; N, 8.14. Found: C, 45.72; H, 4.34; N, 7.88.

Reaction of 3 with hydrazine. A mixture of **3** (361 mg, 1 mmol) and EtOH (6 mL) and 80% $N_2H_4.H_2O$ (0.5 mL) was re-

fluxed for 2 h. The solution was allowed to cool to room temperature. The resulting yellow crystals were collected and washed with EtOH and diethyl ether to give 2-hydroxy-4-(2-hydroxy-3-nitropropyl)-5-nitrophenoxyacetohydrazide (**4**), yield 42%, 139 mg, mp 135-137 ^{o}C. IR (cm^{-1}): 3350 (O-H); 3296, 3152 (N-H); 3002, 2940 (C-H); 1699 (amide C=O), 1624 (δ_{NH2}); 1600, 1530 (aromatic C=C). ^{1}H NMR see Table **1**. ^{13}C NMR, δC (assigned according to the HMBC spectrum): 146.7 (C-1); 164.1 (C-2); 122.1 (C-3); 131.9 (C-4); 132.2 (C-5); 112.5 (C-6); 39.0 (C-7); 68.4 (C-8); 81.4 (C-9); 68.5 (C-10); 167.1 (C-11). Anal. Calcd. for $C_{11}H_{14}N_4O_8$ (330.25) C, 40.01; H, 4.27; N, 16.96. Found: C, 39.76; H, 4.01; N, 17.23.

Reaction of 1 with hydroxylamine. To a solution of $NH_2OH.HCl$ (139 mg, 2 mmol) and CH_3COONa (164 mg, 2 mmol) in H_2O (3 mL) was slowly added **1** (361 mg, 1 mmol)**.** The resulting solution was stirred for 2 h at room temperature. The precipitate was filtered out and recrystallized from EtOH/H_2O 6:1 (by volume) to afford 2-hydroxy-4-(2-hydroxyamino-3-nitropropyl)-5-nitrophenoxy-acetic acid (**5**), yield 53%, 176 mg, light yellow crystals, mp 178-179 ^{o}C. IR (cm^{-1}): 3416 (O-H); 3293, 3215 (N-H); 3009, 2926 (C-H); 1750 (C=O); 1570, 1585 (aromatic C=C). ^{1}H NMR see Table **1**. ^{13}C NMR, δC (assigned according to the HMBC spectrum): 146.20 (C-1); 156.0 (C-2); 120.5 (C-3); 130.6 (C-4); 138.9 (C-5); 115.4 (C-6); 32.6 (C-7); 60.4 (C-8); 77.0 (C-9); 70.6 (C-10); 172.9 (C-11). ESI –MS, *m/z* (%) = 330 (M-H, 100). Anal. Calcd. for $C_{11}H_{13}N_3O_9$ (331.24): C, 39.89; H, 3.96; N, 12.69. Found: C, 39.67; H, 4.05; N, 12.96.

Reaction of 2 with acetic anhydride. To a solution of **2** (317 mg, 1 mmol) in Ac_2O (3 mL) was slowly added a mixture of H_2SO_4 (0.2 mL) in Ac_2O (1.5 mL). The reaction mixture was stirred for 4 h at 50 ^{o}C and then poured into ice-water (10 g). The mixture was allowed to stand at room temperature for 48 h. The precipitate was filtered out, washed with cold water and recrystallized from H_2O/EtOH 1:1 (by volume) to afford 5-(2-acetoxy-3-nitropropyl)-2-methoxy-4-nitrophenyl acetate (**6**), yield 75%, 267 mg, colorless needles, mp 146-148 ^{o}C. IR (cm^{-1}): 3106, 3057, 2900 (C-H); 1750, 1742 (C=O); 1571, 1529 (aromatic C=C). ^{1}H NMR see Table **1**. ^{13}C NMR, δC (assigned according to the HMBC spectrum): 147.1 (C-1); 150.3 (C-2); 123.3 (C-3); 127.2 (C-4); 142.4 (C-5); 109.4 (C-6); 33.1 (C-7); 69.0 (C-8); 77.2 (C-9); 56.5 (C-10); 168.0 (C-11); 20.1 (C-12); 169.1 (C-13); 20.3 (C-14). Anal. Calcd. for $C_{14}H_{16}N_2O_9$ (356.28): C, 47.20; H, 4.53; N, 7.86. Found: C, 46.92; H, 3.28; N, 8.12.

Reaction of 1 with semicarbazide in water. To a solution of $NH_2CONHNH_2.HCl$ (223 mg, 2 mmol) and CH_3COONa (164 mg, 2 mmol) in H_2O (3 mL) was slowly added **1** (361 mg, 1 mmol). The reaction mixture was stirred for 2 h at room temperature. The precipitate was filtered out and recrystallized from H_2O to afford 4-(2-(2-carbamoyl-hydrazinyl)-3-nitropropyl)-2-hydroxy-5-nitrophenoxyacetic acid (**7**) yield 60%, 224 mg, white crystals, decomposed at 170 ^{o}C. IR (cm^{-1}): 3462 (O-H); 3320, 3215, 3190 (N-H); 3050, 2926 (C-H); 1750 (acid C=O), 1680 (amide C=O); 1599, 1530 (aromatic C=C). ^{1}H NMR see Table **2**. ^{13}C NMR, δC (assigned according to the HMBC spectrum): 146.0 (C-1); 155.6 (C-2); 120.1 (C-3); 130.1 (C-4); 138.6 (C-5); 115.6 (C-6); 33.9 (C-7); 59.4 (C-8); 77.1 (C-9); 69.7 (C-10); 171.7 (C-11); 160.3 (C-12). UV spectrum, λ_{max}(nm)/ε: 204/8606; 247/4583; 349/2740. ESI –MS, *m/z* (%) = 372 (M-H, 100). Anal. Calcd. for $C_{12}H_{15}N_5O_9$ (373.28): C, 39.61; H, 4.05; N, 18.76. Found: C, 39.87; H, 3.82; N, 19.05.

Reaction of 2 with semicarbazide in water. The reaction was carried out with **2** (317 mg, 1 mmol) according to the procedure described in the preparation of **7** to afford 2-(1-(5-hydroxy-4-methoxy-2-nitrophenyl)-3-nitropropan-2-yl)-hydrazinecarboxamide (**8**), yield 55%, 181 mg, white crystals, mp 172-173 ^{o}C. IR (cm^{-1}): 3448 (O-H); 3342, 3194 (N-H); 3000, 2932 (C-H); 1681 (C=O), 1581, 1511 (aromatic C=C). ^{1}H NMR see Table **2**. ^{13}C NMR, δC (assigned according to the HSQC and HMBC spectra): 146.3 (C-1); 151.9 (C-2); 118.6 (C-3); 127.8 (C-4); 139.8 (C-5); 109.2 (C-6); 33.6 (C-7); 59.6 (C-8); 77.0 (C-9); 56.0 (C-10); 161.0 (C-12). Anal. Calcd. for $C_{11}H_{15}N_5O_7$ (329.27): C, 40.12; H, 4.59; N, 21.27. Found: C, 39.85; H, 4.38; N, 21.56.

Reaction of 1 with semicarbazide in DMSO. A solution of **1** (361 mmg, 1 mmol) and $NH_2CONHNH_2.HCl$ (223 mg, 2 mmol) in DMSO (3 mL) was stirred for 5 h at 70 ^{o}C and then poured into ice-water (20 g). The precipitate was filtered out, washed with cold water and recrystallized from H_2O/EtOH/ dioxan 2:1:1 (by volume) to afford 2-(4-((1*E*)-3-(2-car-bamoylhydrazono)-prop-1-enyl)-2-hydroxy-5-nitrophenoxy)-acetic acid (**9**), yield 74%, 240 mg, a brown solid, decomposed at 170 ^{o}C. IR (cm^{-1}): 3454 (O-H); 3334, 3195 (N-H); 3100, 2923 (C-H); 1736 (acid C=O); 1673 (amide C=O); 1615 (ethylenic C=C); 1508, 1426 (aromatic C=C). ^{1}H NMR see Table **2**. ^{13}C NMR, δC (assigned according to the HMBC spectrum): 146.0 (C-1); 152.4 (C-2); 113.6 (C-3); 127.2 (C-4); 138.6 (C-5); 110.6 (C-6); 131.3 (C-7); 128.9 (C-8); 141.4 (C-9); 65.7 (C-10); 169.9 (C-11); 156.5 (C-12). Anal. Calcd. for $C_{12}H_{12}N_4O_7$ (324.25): C, 44.45; H, 3.73; N, 17.28. Found: C, 44.72; H, 3.92; N, 18.56.

Reaction of 2 with semicarbazide in DMSO. The reaction of **2** (317 mg, 1 mmol) and $NH_2CONHNH_2.HCl$ (223 mg, 2 mmol) was carried out according to the procedure described in the preparation of **9** to afford 2-((*E*)-3-(5-hydroxy-4-methoxy-2-nitrophenyl) allylidene)hydrazinecarboxamide **(10)**, yield 65%, 183 mg, a brown solid, mp 172-173 ^{o}C. IR (cm^{-1}): 3448 (O-H); 3342, 3194 (N-H); 3080, 3000, 2932 (C-H); 1681 (amide C=O); 1581, 1511 (aromatic C=C). ^{1}H NMR see Table **2**. ^{13}C NMR, δC (assigned according to the HMBC spectrum): 147.5 (C-1); 151.8 (C-2); 112.9 (C-3); 123.3 (C-4); 138.9 (C-5); 108.7 (C-6); 131.1 (C-7); 128.6 (C-8); 141.2 (C-9); 56.1 (C-10); 156.3 (C-12). Anal. Calcd. for $C_{11}H_{12}N_4O_5$ (280.24): C, 47.15; H, 4.32; N, 19.99. Found: C, 47.42; H, 4.06; N, 19.69.

Reaction of 1 with thiosemicarbazide in DMSO. A solution of **1** (361 mg, 1 mmol) and $NH_2CSNHNH_2$ (182 mg, 2 mmol) in DMSO (3 mL) was stirred for 5 h at 70 ^{o}C and then poured into ice-water (20 g). The precipitate was filtered out, washed with cold water and recrystallized from H_2O to afford 2-(4-((1*E*)-3-(2-carbamothioylhydrazono)-prop-1-enyl)-2-hydroxy-5-nitrophenoxy) acetic acid (**11**), yield 54%, 184 mg, a brown solid, decomposed at 170 ^{o}C. IR (cm^{-1}): 3428 (O-H); 3320, 3177 (N-H); 3100, 2955 (C-H); 1733 (acid C=O); 1591, 1523 (aromatic C=C). ^{1}H NMR see Table **2**. ^{13}C NMR, δC (assigned according to the HSQC and HMBC spectra): 146.2 (C-1); 152.3 (C-2); 113.7 (C-3); 126.9 (C-4); 138.7 (C-5); 110.7 (C-6); 133.8 (C-7); 128.3 (C-8); 144.1 (C-9); 65.7 (C-10); 169.8 (C-11); 178.02 (C-12). *Anal.* Calcd. for $C_{12}H_{12}N_4O_6S$ (340.31): C, 42.35; H, 3.55; N, 16.46. Found: C, 42.63; H, 3.32; N, 16.21.

Reaction of 2 with thiosemicarbazide in DMSO. The reaction was carried out with **2** (317 mg, 1 mmol) and $NH_2CSNHNH_2$ (182 mg, 2 mmol) according to the procedure described in the preparation of **11** to afford 2-(1-(5-hydroxy-4-methoxy-2-nitrophenyl)-3-nitropropan-2-yl)hydrazinecarbothioamide (**12**), yield 68%, 235 mg, a yellow solid, mp 178-179 ^{o}C. IR (cm^{-1}): 3450 (O-H); 3330, 3175 (N-H); 3050, 2950, 2890 (C-H); 1594, 1550, 1528 (aromatic C=C). ^{1}H NMR see Table **2**. ^{13}C NMR, δC (assigned according to the HMBC spectrum): 146.4 (C-1); 151.9 (C-2); 118.5 (C-3); 127.4 (C-4); 139.6 (C-5); 109.2 (C-6); 33.7 (C-7); 58.7 (C-8); 76.8 (C-9); 50.0 (C-10); 181.8 (C-12). Anal. Calcd. for $C_{11}H_{15}N_5O_6S$ (345.33): C, 38.26; H, 4.38; N, 20.28. Found: C, 38.53; H, 4.22; N, 19.98.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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REFERENCES

[1] Prakash, P.; and Gupta, N. Therapeutic uses of Ocimum sanctum linn (Tulsi) with a note on eugenol and its pharmacological actions: A short review. *Indian J. Physiol. Pharmacol.* **2005**, *49*, 125-131.

[2] Pages, N.; Maurois, P.; Bac, P.; Vanden Eynde, J. J.; Tamariz, J.; Labarios, F.; Chamorro, G.; Vamecq, J. The α-asarone/clofibrate hybrid compound, 2-methoxy-4-(2-propenyl)phenoxy-acetic acid (MPPA), is endowed with neuroprotective and anticonvulsant potentialities. *Biomedicine and Aging Pathology* **2011**, *1*, 210-215.

[3] Perez-Pasten, R.; Garcia, R.V.; Garduno, L.; Reyes, E.; Labarrios, F.; Tamariz, J.; Chamarro, G. Hypolipidaemic and antiplatelet activity of phenoxyacetic acid derivatives related to α-asarone. *J. Pharm. Pharmacol.* **2006**, *58*, 1343-1349.

[4] Labarrios, F.; Garduno, L.; Vidal, M. R.; Garcia, R.; Salazar, M.; Martinez, E.; Diaz, F.; Chamarro, G. and Tamariz, J. Synthesis and hypolipidaemic evaluation of a series of α-asarone analogues related to clofibrate in mice *J. Pharm. Pharmacol*. **1999**, *51*, 1-7.

[5] Garduno-Siciliano, L.; Labarrios, F.; Tamariz, J.; Moreno, M.G.; Chamarro, G. and Muriel, P. Effect of α-asarone and a derivative on lipids, bile flow and Na+/K+-ATPase in ethinyl estradiol-induced cholestasis in the rat. *Fundam. Clin. Pharmacol*. **2007**, *21*, 81-88.

[6] Ford, R. A.; Domeyer, B.; Easterday, O.; Maier, K.; and Middleton, J. Criteria for Development of a Database for Safety Evaluation of Fragrance *Regulatory Toxicology and Pharmacology* **2000**, *31*, 166-181.

[7] Darshan, S.; and Doreswamy, R. Patented antiin ammatory plant drug development from traditional medicine. *Phytotherapy Research* **2004**, *18*, 343-357.

[8] Yan, H.; Shuit-Hung H.; Hsien-Chieh Lee and Yen-Ling, Y. Insecticidal properties of eugenol, isoeugenol and methyleugenol and their effects on nutrition of *Sitophilus zeamais* Motsch. (Coleoptera: Curculionidae) and *Tribolium castaneum* (Herbst) (Coleoptera: Tenebrionidae). *Journal of Stored Products Research,* **2002**, *38*, 403-412.

[9] Todd, E. S.; James, E.; Elaine, P.; Suk, L. W. and Ritsuo, N. Re-examining the relationship between sexual maturation and age of response to methyl eugenol in males of the oriental fruit fly. *Entomologia experimentalis et applicata* **2008**, *128*, 380-388.

[10] Freeman, S.; Alder, J. F. Arylethylamine psychotropic recreational drugs: a chemical perspective. *Eur. J. Med. Chem.* **2002**, *37*, 527-539.

[11] Antonovhttp://www.sciencedirect.com/science/article/pii/0143720894000 76E - COR1, L.; Stoyanov, S. Azo-quinonehydrazone tautomerism in 2-phenylazo-1-naphtol. *Dyes and Pigments* **1995**, *28*, 31-39.

[12] Traven, Valery F. Dihydrofurocoumarinones - new useful intermediates for substituted and condensed furocoumarins. *Arkivoc* **2000**, (*iv*), 523-560.

[13] Mohindra Chawla, H.; Meenakshi N. New hydrogen bond assisted synthesis of calixarene quinone-hydrazones. *Arkivoc* **2003**, (*iii*), 171-175.

[14] Chen, P. C.; Lo, W.; Tzeng, S. C. Molecular structures of mononitrophenols and their thermal decomposition tautomers. *J. Mol. Struct. (Theochem)* **1998**, *428*, 257-266.

[15] Politzer, P.; Seminario, J. M.; Bolduc, P. R. A proposed interpretation of the destabilizing effect of hydroxyl groups on nitroaromatic molecules. *Chemical Physics Letters* **1989**, *158*, 463-469.

[16] Lammertsma, K.; and Bharatam, B. V. Keto ⇌ Enol, Imine ⇌ Enamine, and Nitro ⇌ *aci*-Nitro Tautomerism and their interrelationship in substituted nitroethylenes. Keto, imine, nitro, and vinyl substituent effects and the importance of H-bonding. *J. Org. Chem.* **2000**, *65*, 4662-4670.

[17] Bharatam, B. V.; Lammertsma, K. aci-nitro Tautomerism in high-energetic nitro compounds. *Theoretical and Computational Chemistry* **2003**, *12*, 61-89.

[18] Dinh, N. H.; Huan, T. T.; Toan, D. N.; Kimpende, P. M.; Meervelt, L. V. Isolation, structure, and properties of quinone-aci tautomer of a phenol-nitro compound related to eugenoxyacetic acid. *J. Mol. Struct*. **2010**, *980*, 137-142.

[19] Dinh, N. H.; Co, L. V.; Tuan, N. M.; Hai, L. T. H.; Meervelt, L. V. New route to novel polysubstituted quinolines starting with eugenol, the main constituent of Ocimum sanctum L. oil. *Heterocycles* **2012**, *85*, 627-637.

[20] Vliet, E. B. Hydroquinone Triacetate. *Org. Synth.* **1925**, *4*, 35-38.

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