Isolation, structure, and properties of quinone-aci tautomer of a phenol-nitro compound related to eugenoxyacetic acid

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A B S T R A C T
Treatment with excess nitric acid in acetic acid revealed that eugenoxyacetic acid underwent an unexpected ether cleavage, a normal nitration, and then an unexpected electrophilic addition to the double bond of the side chain that led to the formation of a dinitro compound which subsequently converted to a sensitive, reactive quinone-aci compound. The structure of the quinone-aci compound (1) and its derivatives (2–6) was established by 1D-, 2D NMR, MS spectra, and chemical methods. In addition, the XRD structure of compound 2 derived from 1 was established. A double tautomerization of 1 in solution was studied by the LC−UV−MS method.

1. Introduction
Eugenoxyacetic acid, 2-methoxy-4-(2-propenyl)phenoxyacetic acid, is known to be a beneficial food additive. It is an odorless and tasteless compound with good antioxidant power and is considered to be nontoxic [1]. Eugenoxyacetic acid, 5-nitrougenoxyacetic acid, and their methyl, ethyl esters are known to exhibit hypolipidaemic and antiplatelet activity and thus appear to be promising for the treatment of human hyperlipidaemia and thrombotic diseases [2–4]. In addition, several modified side chain eugenoxyacetic acids have been shown to exhibit antiviral and antimycobacterial activities [5,6].

Recently, in order to prepare a precursor of quinoline derivatives, a nitration of eugenoxyacetic acid in acetic acid with excess of nitric acid was carried out and a dinitro compound was obtained as main product; however, the compound was comprised of a molecular structure distinct from that obtained by Clauser [7]. In the dinitro compound was obtained by Robert Clauser, as the formula $\text{C}_9\text{H}_5\text{C}_4\text{H}(\text{OH})(\text{NO}_2)_2\text{OCH}_2\text{COOH}$ shown, two nitro groups were both bound with the benzene ring, whereas in the recently obtained dinitro compound, one nitro group is attached to the side chain. Also, this compound particularly exists in quinone-aci form, which is considered as a reactive and unstable intermediate in the thermal decomposition of explosives [8,9]. The versatility of nitro compounds in organic synthesis is largely owing to their easy availability and transformation into a variety of diverse functionalities [10–14]. In spite of the increasing importance of nitro compounds, until now no other work has mentioned about the dinitro compound derived from eugenoxyacetic acid. In this study, the isolation and structure of the quinone-aci and some dinitro compounds related to eugenoxyacetic acid are described.

2. Experimental section
2.1. Preparation

Compound 1 was obtained when treating eugenoxyacetic acid with excess of nitric acid in acetic acid. In order to convert quinone-aci form into more stable phenol-nitro form, compound 1 was treated with sulfuric acid in acetic anhydride, and then with water to obtain compound 2 as the main product and compound 3 as the byproduct (Scheme 1, the numeration is done specially for NMR analysis).

Compound 2 is transformed into esters 4, 5, and 6 as shown in Scheme 2.

2.1.1. Quinone-aci compound 1
To a solution of 22.2 g (0.1 mol) of eugenoxyacetic acid in 100 mL of glacial acetic acid was slowly added 20 mL of HNO3 ($D = 1.41$ g/mL). The reaction mixture was allowed to stand at $-5$ to $0 \degree C$ for 4 h and at room temperature for additional 4 h. The yellow solid was collected and washed with dried ethyl acetate, dried diethyl ether and then was dried in vacuum at $40 \degree C$ for...
2.1.2. 2-Hydroxy-4-(2-hydroxy-3-nitropropyl)-5-nitrophenoxyacetic acid (2) and 2-Hydroxy-4-(2-acetoxy-3-nitropropyl)-5-nitrophenoxyacetic acid (3)

A mixture of 1.8 g (5 mmol) of 1 in 6 mL of acetic anhydride was slowly added a solution of 0.2 mL of H$_2$SO$_4$ in 4 mL of acetic anhydride. The reaction mixture was shaken and then refluxed at 55–60 °C for 2 h. The received solution was poured into 10 mL of cooled water. A small amount of solid was filtered out and recrystallized from 50% by volume aqueous EtOH to afford 0.18 g (10%) of 2. The filtrate was allowed to stand at room temperature for 3 days. The resulting precipitate was collected, washed with water, recrystallized with 1.5 water molecules melting at 123–124 °C. IR (KBr), cm$^{-1}$: 3304 (O–H); 3075, 2988, 2938 (C–H); 1750, 1715 (aromatic C=O); 1600, 1560 (aromatic C=C). Anal. Calcd. for C$_{13}$H$_{14}$N$_2$O$_{10}$: C, 45.00; H, 3.91; N, 7.82. Found: C, 43.82; H, 4.22; N, 7.58.

The filtrate was allowed to stand at room temperature for 3 days. The resulting precipitate was collected, washed with water, recrystallized from 50% by volume aqueous EtOH to give 0.79 g (50%) of 2 (crystallized with 1.5 water molecules) melting at 110–111 °C. IR (KBr), cm$^{-1}$: 3304 (O–H); 3096, 2931 (C–H); 1717 (C=O); 1590, 1519 (aromatic C=C). Anal. Calcd. for C$_{13}$H$_{13}$N$_2$O$_{10}$·1.5H$_2$O: N, 8.16. Found: N, 7.87.

2.1.3. 2-Acetoxy-4-(2-acetoxy-3-nitropropyl)-5-nitrophenoxyacetic acid (4)

A mixture of 343 mg (1 mmol) of 2 in 4 mL of acetic anhydride and 1 drop of H$_2$SO$_4$ was refluxed at 50–60 °C for 2 h. The received solution was poured into 5 mL of cooled water. The precipitate was filtered out and recrystallized from 50% by volume aqueous EtOH to afford 262 mg (66%) of 4 melting at 111–113 °C. IR (KBr), cm$^{-1}$: 3134 (O–H); 3062, 2941 (C–H); 1782, 1738 (C=O), 1562, 1526 (aromatic C=C). Anal. Calcd. for C$_{13}$H$_{16}$N$_2$O$_{11}$·1: C, 45.00; H, 4.00; N, 7.00. Found: C, 45.31; H, 4.17; N, 7.3.

2.1.4. Ethyl 2-hydroxy-4-(2-acetoxy-3-nitropropyl)-5-nitrophenoxyacetate (5)

A mixture of 686 mg (2 mmol) of 2 in 5 mL of EtOH and 2 drop of H$_2$SO$_4$ was refluxed for 12 h. The received solution was allowed to cool to room temperature. The precipitate was filtered out and recrystallized from 50% by volume aqueous EtOH to afford 443 mg (64%) of 5, melting at 95–97 °C. IR (KBr), cm$^{-1}$: 3318, 3103 (O–H); 3053, 2924 (C–H); 1726 (C=O), 1571, 1531 (aromatic C=C). Anal. Calcd. for C$_{13}$H$_{16}$N$_2$O$_{11}$·1: C, 45.35; H, 4.65; N, 8.14. Found: C, 45.57; H, 4.85; N, 8.44.

2.1.5. Ethyl 2-acetoxy-4-(2-acetoxy-3-nitropropyl)-5-nitrophenoxyacetate (6)

A mixture of 344 mg (1 mmol) of 5 in 4 mL of acetic anhydride and 1 drop of H$_2$SO$_4$ was refluxed at 50–60 °C for 2 h. The received solution was poured into 5 mL of cooled water. The precipitate was filtered out and recrystallized from 50% by volume aqueous EtOH to afford 254 mg (60%) of 6 melting at 123–124 °C. IR (KBr), cm$^{-1}$: 3075, 2988, 2938 (C–H); 1784, 1736 (C=O), 1561, 1522 (aromatic C=C). Anal. Calcd. for C$_{13}$H$_{12}$N$_2$O$_{11}$·1: C, 47.66; H, 4.67; N, 6.54. Found: C, 47.93; H, 4.26; N, 6.74.

2.2. Physical measurements

2.2.1. Elemental analysis

C, H and N were analysed on a LECO CHNS model 932 elemental analyser.

2.2.2. X-ray measurements

Single-crystal X-ray diffraction is recorded on a Bruker SMART6000 diffractometer (fine-focus sealed tube, Cu Kα radiation, crossed Göbel mirrors) at 100 K. A total of 18,874 reflections were measured of which 5086 independent. The intensity data were corrected for Lorentz and polarization effects, and for absorption (SADABS) [15]. The structure was solved by direct methods (SHELXS-97) [16] and refined by full-matrix least-squares based on $F^2$ using SHELXL-97 [17] (448 parameters). Hydrogen atoms were located in the calculated positions.

2.2.3. IR and LC–UV–MS spectra

The IR spectra were recorded on an IMPACK-410 NICOLET spectrometer in KBr discs in the range 400–4000 cm$^{-1}$. LC–UV–MS were recorded on an Agilent LC–MSD-Trap-SL series 1100, column: C18 150 × 3.0, solvent: MeOH – H$_2$O, gradient: 30% MeOH – 100% MeOH.

2.2.4. NMR data

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. The $^1$H- and $^{13}$C NMR data are listed in Tables 1 and 2.

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Scheme 1. Conversion of quinone-aci form into phenol-nitro form.

Scheme 2. The esters derived from 2.
3. Results and discussion

3.1. Isolation of the quinone-aci 1

Eugenoxycetic acid (1 mol) was treated with excess of nitric acid (3 mol) in acetic acid at -5 to 0 °C, and the ready formation of a yellow solid was observed. The solid was washed with water and ethanol 96°, and then dried in vacuum at 50 °C. By the 1H NMR and the 13C NMR spectra in the solid above none of compounds contained methoxy group as eugenoxycetic acid. When using dried ethyl acetate and dried diethyl ether instead of water, the solid proved to be unsuccessful. By the use of chemical and physical methods (shown below), it was demonstrated that the second yellow solid is an individual compound having quinone-aci structure.

3.2. Structure of compound 2

The structure of compound 2 on the basis of XRD with the numbering scheme is depicted in Fig. 1.

The asymmetric unit consists of two molecules, named A (numbered from C1 to O22) and B (numbered from C31 to O52), and three water molecules. The two molecules differ in configuration of atoms C8 in molecule A (R) and C38 in molecule B (S). A fitting of all non-hydrogen atoms of inverted molecule B on molecule A provides an r.m.s. deviation of 0.176 Å. It can be seen that in both molecules, the nitro group and the carboxymethoxy group attached to the aromatic ring are almost coplanar with this ring, whereas the other nitro group makes an angle of 78.6(2)° (molecule A) or 78.4(2)° (molecule B) with the aromatic ring. As Fig. 1 shown, in 2 one nitro group is bound with C-5 of the benzene ring, the other nitro group is attached to C-9 of the side chain and the -OH group is attached to C-8 of the side chain. This allows to assign the position of the -NO2 group, the -N(O)OH group and the -ONO2 group in 1.

3.3. Spectroscopic studies

The structure of 1–6 was established by IR, NMR, LC–UV and ESI MS methods. The assignment of 1H NMR and 13C NMR signals (Tables 1 and 2) of the reported compounds was based on their chemical shift, spin–spin splitting patterns, and 2D NMR spectra. For example, the HSQC and HMBC spectra of compound 1 were recorded immediately after its dissolution and are presented in Figs. 2 and 3, respectively.

It can be seen that the HSQC spectrum in Fig. 2 allows to assign signals of six carbon atoms attached to nine hydrogen atoms; in particular, the cross peaks a and b indicate that two doublet of doublets at 5.21 and 5.01 ppm belong to two protons attached to one carbon atom (C9).

The data in Table 1 show some distinctive features for the structure of 1 (in quinone-aci form) in comparison to those of 2–6 (in phenol-nitro form). Firstly, it can be seen that the signals of H3, H6 in 1 are shifted by 0.5–1.0 ppm as compared to those in 2–6.

Table 1

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Table 2

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<td>60.75; 13.99</td>
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The signal of H3 in 2–6 is a singlet; however, the signal of H3 in 1 is a triplet with $J = 1.5$ Hz. Secondly, in 2–6, H7a and H7b are non-equivalent and combine with H8 to form an ABC system (H7a, H7b, H8), whereas in 1, H7a and H7b become equivalent and form the B2 part of an AB2C system by involving both H3 and H8, i.e. H3(H7)2H8. Thirdly, the signal of H8 in 1 is found to be significantly different from those in 2, 5; however, it is similar to those in 3, 4, 6. Also, H8, H9a, H9b of 2–6 form an additional ABC system. The alcohol proton (9-OH) in 2 and 5 gives rise to a singlet at 5.57 ppm; the phenol proton (2-OH) in 2, 3, and 5 gives rise to a very weak broadened singlet at 10.7 ppm.

In Table 2, it can be observed that the chemical shift of C1–C6 in 2, 3, and 5 slightly changes from one to another; however, it differs from those in 4 and 6 since the phenol hydroxyl group (2-OH) were replaced by acetoxy group in 4 and 6. The C1–C6 signals of 1 are quite different from those in 2–6; in particular, the C2 signal of 1 is shifted by 26 ppm and the C5 signal of 1 is shifted by –16 ppm when compared to those of 2. This is in good agreement with the quinone-aci structure of 1. The chemical shift of side chain carbons (C7, C8, C9) in 1 was found to be quite different from that in 2. This was because in 1, C7 attaches to a quinone ring, and C8 bonds with –ONO2 group, whereas in 2, C7 attaches to a benzene ring, and C8 bonds with the –OH group.

The behavior of the reported compounds in solution was studied by the LC–UV–MS method. The LC–UV chromatograms of 1 recorded immediately after its dissolution (Fig. 4a) and 6 h after its dissolution (Fig. 4b) indicated that 1 exists in the form of 4 tautomers in solution (Scheme 3), The data are listed in Table 3.

In this study, it was thus reasoned that the unstable quinone-aci forms (1a, 1b) transformed into more stable phenol-nitro forms (1c, 1d) in a double tautomerization as shown in Scheme 3. Since 1a, 1b have quinoid chromophore, they absorb at 368 nm, whereas 1c, 1d bearing benzenoid chromophore absorb at 343–348 nm which is close to p-nitrophenol (at 318 nm). Also, in stable phenol-nitro form, 2–6 do not transform into unstable quinone-aci form. For example, in the LC–UV chromatograms of 2, 3 recorded immediately after its dissolution and 6 h after its dissolution, two peaks were found to be associated with nitro form 2c (R = OH), 3c (R = OAc) and aci form 2d (R = OH), 3d (R = OAc) at the side chain of the compounds (Scheme 4). As a rule 2c, 2d, 3c, and 3d absorb at 348 nm analogous to 1c and 1d (Table 3).

The mass spectra in the positive mode of 1a and 1b showed an absence of molecular ions peak M+1 (m/z 362), but a presence of the base peak at m/z 299. Similarly, mass spectra in the negative mode of 1a, 1b, 1c, and 1d showed an absence of molecular ions peak M–1 (m/z 360), but a presence of the base peak at m/z 297. On the other hand, negative mode mass spectra of 2c, 2d, 3c, and 3d showed molecular ions (M–H)– at m/z 315 and m/z 357 corresponding to molecular mass of 2c, 2d (316 au) and 3c, 3d (358 au), respectively. Probably, 1a, 1b, 1c, and 1d were easily
converted to more stable compounds ($M = 298\text{ au}$) as in the following example for 1a (Scheme 5).

As already seen, the aci form of primary nitroalkanes as 1b and 1d readily converts into the hydroxamic acid one, which is then hydrolyzed to a carboxylic acid [18]. Moreover, quinone-aci tautomers 1a and 1c are reactive and sensitive, and thus, it is not surprising that all attempts to recrystallize 1 were unsuccessful and the above mentioned yellow solid was converted into a mixture after washing in water and ethanol 96.

Considering the formation of 1, it was reasoned that during treatment with excess of nitric acid in acetic acid, eugenoxyacetic acid underwent an ether cleavage, a normal electrophilic aromatic substitution, followed by an unexpected electrophilic addition to the double bond of the side chain that led to a dinitro compound,
which converted to corresponding quinone-aci form as shown in Scheme 6.

It must be noted that the quinone-aci tautomers are usually discussed in theoretical researches [19–21] however, until now their isolation and characterization was not performed, also all our attempts to prepare the compound \( \text{C}_3\text{H}_5\text{A}\text{C}_6\text{H(OH)(NO}_2)_2\text{A}\text{OCH}_2\text{COOH} \) were unsuccessful.

4. Conclusion

A sensitive, reactive quinone-aci compound derived from eugenoxyacetic acid was isolated and transformed into phenol-nitro form and its derivatives. The structure of the quinone-aci and related nitro compounds was established by IR, NMR, LC–UV–MS and XRD methods.

Acknowledgment

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.molstruc.2010.07.005.

References