

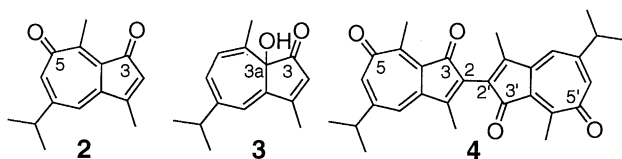
X-Ray Crystal Structure of Guaiazulenequinone and the Structures of Two New Guaiazulene Derivatives¹

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The first X-ray crystallographic analysis on azulenequinones is reported for 3,5-guaiazulenedione. Two unique azulene derivatives, 3a-hydroxy-3(3aH)-guaiazulene and 2,2'-bi-3,5-guaiazulenedione, are obtained by the autoxidation of 5,5'-biguaiazulene-3,3'(5H,5'H)-dione in pyridine at 25 °C. The possible reaction pathways for these azulene formation are discussed.

We have discovered that 5,5'-biguaiazulene-3,3'(5H,5'H)-dione (biguaiazulene, **1**) obtained exclusively by the peracid oxidation of guaiazulene in hexane turned out to be a highly important key intermediate for the various autoxidation products of guaiazulene.^{2,3} For example, autoxidation of **1** in pyridine at 25 °C provides as high as 46% yield of 3,5-guaiazulenedione (guaiazulenequinone, **2**), which has been found to exhibit some anticarcinogenic activity.⁴ We wish to report herein on the crystal structure of quinone **2** as the first example obtained for azulenequinones and also on two, unique guaiazulene derivatives obtained by autoxidation of **1** in pyridine.



Guaiazulenequinone **2**⁵ was recrystallized from hexane (several times) to provide a suitable specimen for the X-ray analysis.⁶ As a result, two different conformational analyses of **2** were found to exist in the asymmetric unit cell of this crystal: Namely, two rotamers in which the isopropyl group at the C-7 position is rotated at 180°. The ORTEP drawing of **2** (one molecule of the two rotamers) is illustrated in Fig. 1 together with the bond distances, which clearly indicate the bond alteration between single and double bonds. The distances corresponding to the four double bonds in **2** are within a close range of their average lengths (1.364 Å), which is slightly longer than the distances observed for C₂=C₃ of *p*-benzoquinone (1.344 Å) and 1,4-naphthoquinone (1.341 Å). However, the distances corresponding to the single bonds in **2** appreciably varies between 1.413 and 1.529 Å; in particular, the C₃-C_{3a} distance (1.529 Å) is characteristically longer than the average of the seven single bond distances (1.459 Å), which is slightly shorter than C₁-C₂ of *p*-benzoquinone (1.481 Å) and 1,4-naphthoquinone (1.474 Å). The C₃=O (1.225 Å) and C₅=O (1.231 Å) distances coincide with the C=O distances of *p*-benzoquinone (1.225 Å) and 1,4-naphthoquinone (1.232 Å).

Autoxidation of **1** was studied in detail in pyridine at 25 °C (for 24 h), and two, new compounds **3**⁷ and **4**⁸ were isolated after careful chromatographic purification at a low temperature (5-10 °C). The structures of 3a-hydroxy-3(3aH)-guaiazulene and 2,2'-bi-3,5-guaiazulenedione were respectively assigned to compounds **3** and **4** on the basis of their spectral data. Although TLC monitoring of the reaction products obviously indicated its formation in a much larger proportion, compound **3** was isolable only in a low yield (1.2%) apparently because of the instability during the repeated purification. Indeed, when **3** was dissolved in an organic solvent (e.g., MeOH, CH₂Cl₂, or CHCl₃) and

allowed to stand at 25 °C for 24 h, it was converted almost quantitatively into 5-isopropylidene-3,8-dimethyl-1(5H)-azulene (**5**),^{2,9} which gradually yielded several 1-indenone derivatives on exposure to air.² The oxidative dimer **4** showed rather low values of three half-wave potentials ($E_1 = -1.02$, $E_2 = -1.18$, and $E_{3,4} = -1.47$ V, see Fig. 2), which can be rationalized in terms of the azulenequinone structure, taking into account the reported values of the monomer **2** ($E_1 = -1.13$ and $E_2 = -1.52$ V).⁵

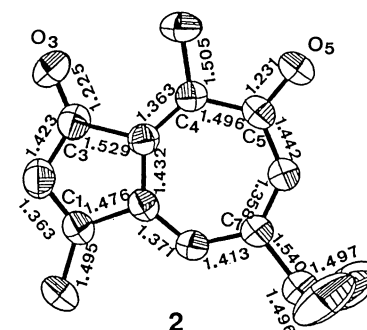


Figure 1. An ORTEP drawing of **2** with the numbering scheme and the bond distances (Å).

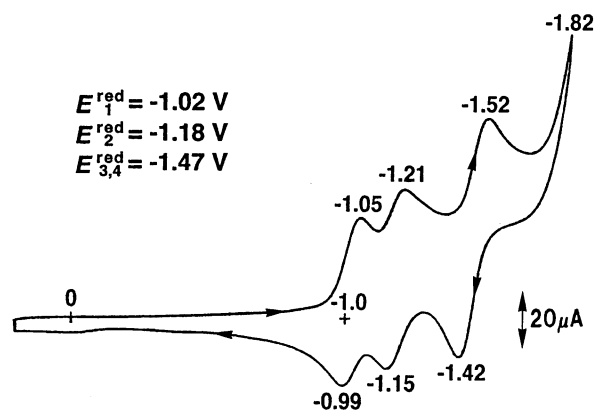
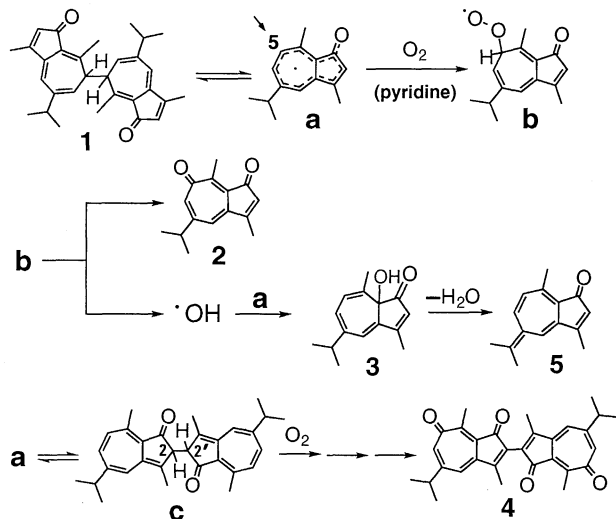


Figure 2. Cyclic voltammogram (reduction potentials) of **4**. Conditions: E/V vs SCE, 0.1 mol·dm⁻³ Et₄NClO₄ in MeCN, Pt wire electrodes, scan rate 100 mV/s, at 25 °C.

Reaction pathways of biguaiazulene **1** have now become considerably clarified by the isolation of an important missing intermediate **3** and a new dimeric azulenequinone **4**, as shown in Scheme 1. Compound **1** is in an equilibrium with the monomeric 3-guaiazulene radical **a**, from which various types of products are obviously derived. An attack of oxygen at the C-5 position gives the peroxy radical **b**, which leads to the formation of guaiazulenequinone **2**; a coupling of **a** with the liberated hydroxyl radical would then give 3a-hydroxy-3(3aH)-guaiazulene **3**.

Quinonemethide **5** has now become apparent to be derived from the unstable precursor **3** upon dehydration, whereas the dimeric guaiazulenequinone **4** is most likely derived from the 2,2'-coupling dimer **c** partly formed in an equilibrium with the divergent radical **a**, followed by aerobic oxidation at the C-5 position and the subsequent transformation similar to the conversion of **b** to **2**.



Scheme 1. Possible reaction pathways for the formation of **2-5** (from **1**).

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References and Notes

- Partly presented at the 7th International Symposium on the Chemistry of Novel Aromatic Compounds, July 1992, Victoria, Canada, Abstr. Poster 104.
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- Against P388; ID₅₀ values (μg/mL) obtained by *in vitro* screening was approximately 1/10 that of adriamycin: Y. Matsubara, *J. Synth. Org. Chem. Jpn.*, **50**, 963 (1992).
- Y. Matsubara, S. Takekuma, K. Yokoi, H. Yamamoto, and T. Nozoe, *Bull. Chem. Soc. Jpn.*, **60**, 1415 (1987). Although ¹³C NMR data (50 MHz, CDCl₃) was reported in this Ref, a better resolved ¹³C NMR parameters (125 MHz, acetone-d₆) have been obtained for the purpose of comparison with those of **4** (see Ref 8): δ 197.1(C-3), 189.2(C-5), 166.4(C-1), 155.9(C-7), 148.4(C-4), 145.1(C-8a), 133.4(C-6), 133.4(C-3a), 131.9(C-8), 125.4(C-2), 38.3(Me-4), 22.6(Me₂CH-7), and 14.2(Me-1); the carbon signals of Me₂CH-7,7' were included in the methyl carbon signals (δ 30-29) of acetone-d₆.
- Yellow needles (from hexane), mp 94 °C (lit,⁵ mp 94 °C); the crystal size, 0.6 x 0.4 x 0.3 mm. Crystal data, C₁₅H₁₆O₂ (MW = 228.29); space group, triclinic P1; lattice constants (Å, degrees), a=11.911(1), b=15.656(1), c=7.071(1), α=95.58(1), β=89.75(2), γ=104.96(1); cell volume (Å³), V=1268; formula units/cell, Z=4; D_{obsd} (g/cm³), 1.196. A total of 3459 reflections with ω-2θ > 126° were collected on a RIGAKU AFC-5R automated four-circle diffractometer, using graphite (010) monochromated CuKα radiation (rotating anticathode: 50 kV, 60 mA). The structure was solved by the direct method (MULTAN 78) and refined by a block-diagonal least-squares program. The R factor was 0.0926 for 3459 observed reflections.
- 3**: Pale yellow prisms (from hexane), 1.2% isolated yield, mp 131 °C; R_f = 0.13 on silica-gel TLC (AcOEt/hexane = 15/85); UV λ_{max} (MeOH) nm (log ε) 247(4.21), 310(3.83), and 360(3.75). The IR (KBr) spectrum indicates the presence of -OH (ν_{max} 3417 cm⁻¹) and C=O group (1705). The molecular formula C₁₅H₁₈O₂ was determined by the EI mass spectrometry [m/z 230(M⁺, 30%), 215(39), 213(3), 212(3), 201(45), 197(4), 187(100), 172(9), 159(22), 145(7), 141(6), 128(11), and 115(12)] and by the exact EI-MS spectrum. Found: m/z 230.1286. Calcd for C₁₅H₁₈O₂: M⁺ 230.1307. The 500 MHz ¹H NMR (acetone-d₆) spectrum showed signals at δ 1.16, 1.20 (3H each, 2d, J=7.0 Hz, i-Pr-7), 1.74(3H, d, J=1.0 Hz, Me-4), 2.26(3H, d, J=1.5 Hz, Me-1), 2.68(1H, sept, J=7.0 Hz, HC-7), 2.80(>1H*, HO-3a), 6.03(1H, q, J=1.5 Hz, H-2), 6.20(1H, dq, J=7.0, 1.0 Hz, H-5), 6.46(1H, dd, J=7.0, 1.0 Hz, H-6), and 6.57(1H, d, J=1.0 Hz, H-8). *including the moisture signal in the solvent.
- 4**: Yellow prisms (from hexane), 1.0% isolated yield, mp 223 °C; R_f = 0.13 on silica-gel TLC (AcOEt/hexane=15/85); UV-vis λ_{max} (MeOH) nm (log ε) 234(4.56), 262(4.46), 318 (4.24), and 408(3.84). The IR (KBr) spectrum suggests the presence of two different C=O groups (ν_{max} 1701 and 1583 cm⁻¹). The molecular formula C₃₀H₃₀O₄ was determined by the EI mass spectrometry [m/z 454 (M⁺, 31%), 426(22), 398(100), 383(15), 355(18), and 44(30)] and by the exact EI-MS spectrum. Found: m/z 454.2102. Calcd for C₃₀H₃₀O₄: M⁺ 454.2144. The 500 MHz ¹H NMR (acetone-d₆) spectrum showed signals at δ 1.29 (12H, d, J=7.0 Hz, i-Pr-7, 7'), 2.31(6H, s, Me-1,1'), 2.57(6H, s, Me-4, 4'), 2.87(2H, sept, J=7.0 Hz, HC-7, 7'), 6.70(2H, d, J=2.0 Hz, H-8, 8'), and 7.04(2H, d, J=2.0 Hz, H-6, 6'). The 125 MHz ¹³C NMR (acetone-d₆) spectrum exhibited signals at δ 194.5(C-3,3'), 189.1(C-5,5'), 164.8(C-1,1'), 156.1(C-7,7'), 149.0(C-4,4'), 144.4(C-8a,8a'), 134.1(C-6,6'), 133.5(C-3a,3a'), 132.8(C-8,8'), 125.9(C-2,2'), 38.4(Me-4,4'), 22.7(Me₂CH-7,7'), and 14.3(Me-1,1'); the carbon signals of Me₂CH-7,7' were included in the methyl carbon signals (δ 30-29) of acetone-d₆.
- Structure of the compound **5** was established on the basis of TLC, GC-MS, and ¹H NMR spectral data.²

