

## Reaction of Guaiazulene with Bromine in Hexane and in Aqueous Tetrahydrofuran<sup>1</sup>

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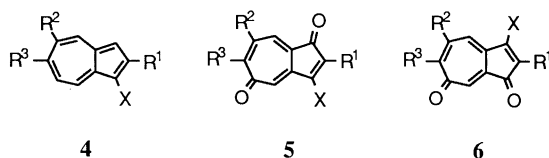
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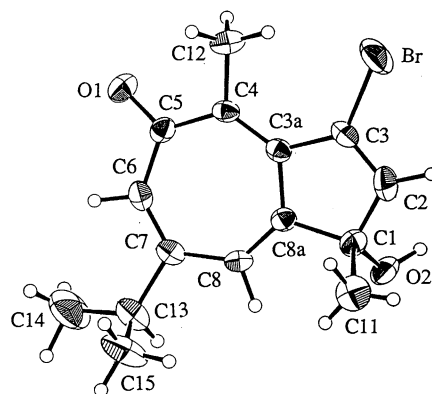
3-Bromoguaiazulenium bromide and 3,3-dibromoguaiazulenium bromide were obtained respectively from the reaction of guaiazulene and its 3-bromo compound with 1 equivalent of bromine in hexane at -20 °C. The former compound afforded in methanol a mixture of guaiazulene, 3,3'-biguaiazulene, and oligomers, and gave 3-bromoguaiazulene quantitatively with alkali. Dibromoguaiazulenium bromide afforded with further moles of bromine in aqueous THF a mixture of guaiazulenequinone, 3-bromo-1-hydroxyguaiazulen-5-one, and a dark blue solid A in different ratios depending on the reaction conditions.

About 12 years ago we started the study of bromination of naturally occurring guaiazulene (**1**). Interestingly we found that the bromine atom of 3-bromoguaiazulene (**2**), which was produced with NBS in hexane, easily shifted intra- and intermolecularly in benzene to give various brominated and debrominated compounds, along with 3,3'-biguaiazulene (**3**) and its 13,14'-isomer.<sup>2-3</sup> Very recently we have discovered<sup>4</sup> that 1,5- and 1,7-azulenequinones (**5** and **6**; X=Br, alkyl or phenyl, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>=H, alkyl or phenyl) were formed in one-pot procedures and in high yield when azulene and its derivatives **4** (R<sup>1</sup>-R<sup>3</sup>: H, alkyl or phenyl) were treated with 3-5 equiv. of bromine in aqueous THF. We now wish to describe here the reaction of guaiazulene **1** with bromine in hexane or in aqueous THF.



Treatment of **1** with 1 equiv. of bromine in hexane at -20 °C afforded a pale yellow solid **7**,<sup>5</sup> which gave **2** quantitatively with alkali. The former compound **7** afforded a mixture of **1** (50% yield), **3** (ca. 20% yield) and unidentified oligomers in methanol at 0 °C, as in the case of **2** in methanol.<sup>2-3</sup> Compound **7** is particularly interesting because this type of compound is generally considered as an important intermediate in aromatic electrophilic substitutions. Similar treatment of **2** in hexane with equiv. mole of bromine easily afforded dibromoguaiazulenium bromide **8** as a pale yellow solid,<sup>6</sup> which with one more equiv. of bromine in 25% aqueous THF, followed by evaporation of THF in vacuo, afforded 2-6% of guaiazulenequinone (**9**),<sup>7</sup> 10-15% of 3-bromo-1-hydroxyguaiazulen-5-one (**10a**,<sup>8</sup> colorless needles or prisms, darken at 95 °C) along with a dark blue solid A. However, if bromination of **1** was carried out with 3.2 equiv. of bromine in acetic acid and aqueous THF at -5 °C and the products

were isolated without removing THF, 8% of **9** and 60% of **10a** were obtained without dark blue solid A. Treatment of **10a** with MeOH in the presence of a trace amount of acetic acid afforded methoxy derivative (**10b**; X=Me,<sup>9</sup> colorless needles; mp 86-88 °C dec, 44% yield) and **9** (33% yield), whereas with acetic anhydride in pyridine **10a** gave acetoxy derivative (**10c**; X=Ac,<sup>10</sup> pale yellow oil) almost quantitatively. Compound **10a**, when dissolved in THF containing a small amount of trifluoroacetic acid, afforded **9** (24% yield) and 5-(1-bromo-1-methylethyl)-3,8-dimethyl-1,7-azulenequinone (**11**,<sup>11</sup> pale yellow needles; mp 76-80 °C dec, 9% yield) along with a dark blue solid A. Structure of **10a** was definitely determined by X-ray crystallographic analysis,<sup>12</sup> and ORTEP<sup>13</sup> diagram is shown in Figure 1.

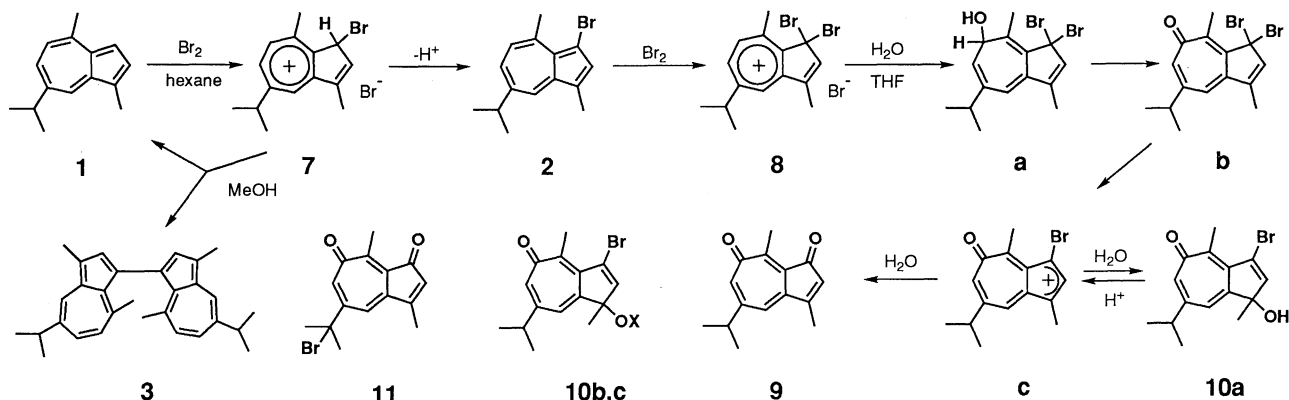


**Figure 1.** An ORTEP drawing for **10a**. Selected bond distances (Å) C1-C2 1.462(8), C2-C3 1.326(8), C3-C3a 1.488(7), C3a-C4 1.368(7), C4-C5 1.469(7), C5-C6 1.456(7), C6-C7 1.336(8), C7-C8 1.420(7), C8-C8a 1.340(7), C8a-C1 1.541(7), C3a-C8a 1.464(6), C1-C11 1.521(9), C1-O2 1.432(7), C3-Br 1.881(5), C4-C12 1.500(7), C5-O1 1.228(6), C7-C13 1.503(7), C13-C14 1.46(1), C13-C15 1.52(1).

Although A is readily available, we could not still determine its structure because mass spectral measurement did not show any peaks and NMR spectra were difficult to assign presumably due to over-crowdedness of alkyl groups. We could not yet obtain single crystals of A for X-ray analysis.

Possible pathways for the formation of the above-mentioned reactants are shown in Scheme 1.

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Scheme 1.

## References and Notes

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- Compound 7 is rather unstable in solution even at -45 °C. 7: <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>CN, -45.2 °C) δ = 1.39 (6H, d, *J*=6.7 Hz, iPr-CH<sub>3</sub>), 2.34 (3H, s, 1-CH<sub>3</sub>), 2.95 (3H, s, 4-CH<sub>3</sub>), 3.51 (1H, sept, *J*=6.7 Hz, iPr-CH), 6.08 (1H, s, H-3), 7.31 (1H, s, H-2), 8.57 (1H, s, H-8), 8.61 (2H, s, H-5,6).
- Solid 8 can be kept unchanged at least for a few days in the refrigerator at -20 °C. The structure of 8 was determined with PFG (Pulsed Field Gradient)-HMBC (36 minutes) and PFG-HMQC (15 minutes) techniques at -35.2 °C. 8: <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>CN) δ = 1.42 (6H, d, *J*=6.7 Hz, iPr-CH<sub>3</sub>), 2.41 (3H, s, 1-CH<sub>3</sub>), 3.25 (3H, s, 4-CH<sub>3</sub>), 3.54 (1H, sept, *J*=6.7 Hz, iPr-CH), 7.55 (1H, s, H-2), 8.54 (1H, s, H-8), 8.64 (1H, d, *J*=11.3 Hz, H-6), 8.71 (1H, d, *J*=11.3 Hz, H-5); <sup>13</sup>C NMR (100 MHz, CD<sub>3</sub>CN) δ = 13.04 (1-CH<sub>3</sub>), 23.21 (iPr-CH<sub>3</sub>), 27.04 (4-CH<sub>3</sub>), 40.84 (iPr-CH), 50.74 (C-3), 140.10 (C-1), 141.59 (C-8), 147.89 (C-6), 151.06 (C-2), 156.22 (C-5), 161.29 (C-4), 161.66 (C-8a), 162.57 (C-3a), 180.21 (C-7).
- T. Nozoe, S. Takekuma, M. Doi, Y. Matsubara, and H. Yamamoto, *Chem. Lett.*, **1984**, 627; Y. Matsubara, S. Takekuma, K. Yokoi, H. Yamamoto, and T. Nozoe, *Bull. Chem. Soc. Jpn.*, **60**, 1415 (1987).
- 10a**: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ = 1.22 (6H, d, *J*=6.7 Hz, iPr-CH<sub>3</sub>), 1.51 (3H, s, 1-CH<sub>3</sub>), 2.62 (3H, s, 4-CH<sub>3</sub>), 2.73 (1H, sept, *J*=6.7 Hz, iPr-CH), 2.91 (1H, br, OH), 6.73 (1H, d, *J*=2.0 Hz, H-6), 6.77 (1H, s, H-2), 6.99 (1H, d, *J*=2.0 Hz, H-8); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ = 17.19, 22.55, 22.71, 26.11, 37.27, 80.68, 123.09, 125.73, 133.35, 141.81, 143.84, 148.91, 153.29, 154.24, 188.40; Found: *m/z* 310.0397. Calcd for C<sub>15</sub>H<sub>17</sub>O<sub>2</sub>Br: M, 310.0391.
- 10b**: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ = 1.21 (3H, d, *J*=6.9 Hz, iPr-CH<sub>3</sub>), 1.24 (3H, d, *J*=6.9 Hz, iPr-CH<sub>3</sub>), 1.46 (3H, s, 1-CH<sub>3</sub>), 2.71 (3H, s, 4-CH<sub>3</sub>), 2.76 (1H, sept, *J*=6.9 Hz, iPr-CH), 3.06 (3H, s, OMe), 6.69 (1H, s, H-2), 6.80 (2H, s, H-6, 8).
- 10c**: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ = 1.21 (3H, d, *J*=6.7 Hz, iPr-CH<sub>3</sub>), 1.22 (3H, d, *J*=6.7 Hz, iPr-CH<sub>3</sub>), 1.65 (3H, s, 1-CH<sub>3</sub>), 2.04 (3H, s, COCH<sub>3</sub>), 2.70 (3H, s, 4-CH<sub>3</sub>), 2.73 (1H, sept, *J*=6.9 Hz, iPr-CH), 6.77 (1H, d, *J*=2.1 Hz, H-6), 6.79 (1H, d, *J*=2.1 Hz, H-8), 7.04 (1H, s, H-2).
- 11**: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ = 2.12 (6H, s, iPr-CH<sub>3</sub>), 2.34 (3H, d, *J*=1.5 Hz, 3-CH<sub>3</sub>), 2.62 (3H, s, 8-CH<sub>3</sub>), 6.27 (1H, q, *J*=1.5 Hz, H-2), 6.85 (1H, d, *J*=2.0 Hz, H-6), 7.17 (1H, d, *J*=2.0 Hz, H-4).
- Crystal data for **10a**: monoclinic, space group *P2<sub>1</sub>/n*, *a* = 7.370(2), *b* = 9.854(2), *c* = 19.096(2) Å, β = 92.65(2)°, *Z* = 4. Data were collected on a Rigaku AFC5R diffractometer using Cu-Kα radiation. Reflections measured: 2362; reflections used: 2273. The final refinement converted with *R* = 0.070 and *R<sub>w</sub>* = 0.074.
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