Reaction of Guaiazulene with Bromine in Hexane and in Aqueous Tetrahydrofuran[1]

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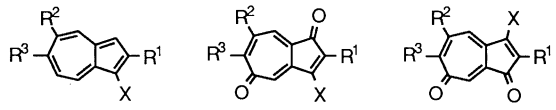
3-Bromoguaiazulenium bromide and 3,3-dibromo guaiazulenium bromide were obtained respectively from the reaction of guaiazulene and its 3-bromo compound with 1 equivalent of bromine in hexane at -20 °C. The former compound afforded in methanol a mixture of guaiazulene, 3,3'-biguaiazulene, and oligomers, 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 the side-chain to give various brominated and debrominated compounds, along with 3,3'-biguaiazulene (**3**) and its 13,14'-isomer.[2-3] Very recently we have discovered[4] that 1,5- and 1,7-azulenequinones (**5** and **6**: X=Br, alkyl or phenyl, R^1, R^2, R^3=H, alkyl or phenyl) were formed in one-pot procedures and in high yield when azulene and its derivatives **4** (R^1-R^3: 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.



4 **5** **6**

Treatment of **1** with 1 equiv. of bromine in hexane at -20 °C afforded a pale yellow solid **7**,[5] which gave **2**[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.[2-3] 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,[6] which with one more equiv. of bromine in 25% aqueous THF, followed by evaporation of THF in vacuo, afforded 2-6% of guaiazulenequinone (**9**),[7] 10-15% of 3-bromo-1-hydroxyguaiazulen-5-one (**10a**,[8] 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,[9] 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,[10] 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**,[11] 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,[12] and ORTEP[13] diagram is shown in Figure 1.

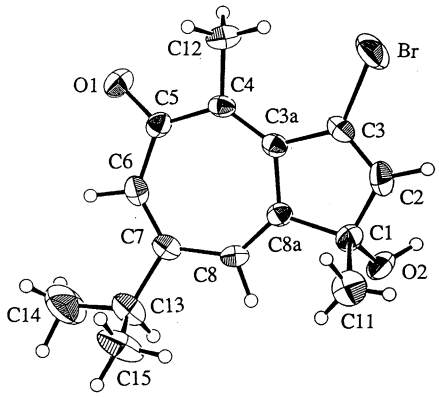


Figure 1. An ORTEP drawing for **10a**. Selected bond distances (Å) C1-C2 1.462(8), C2-C3 1.326(8), C3-C3a 1.488(7), C3a-C4 1.368(7), C4-C5 1.469(7), C5-C6 1.456(7), C6-C7 1.336(8), C7-C8 1.420(7), C8-C8a 1.340(7), C8a-C1 1.541(7), C3a-C8a 1.464(6), C1-C11 1.521(9), C1-O2 1.432(7), C3-Br 1.881(5), C4-C12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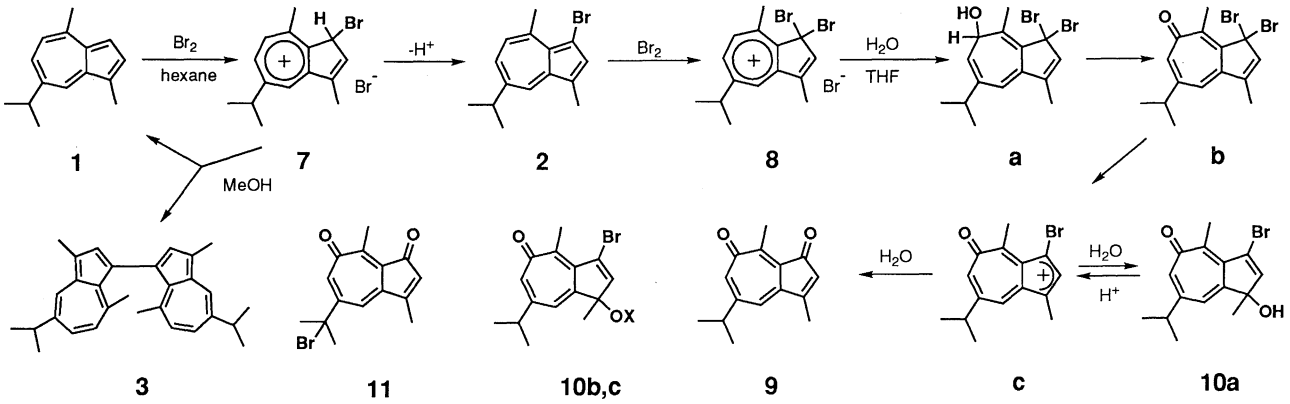

Scheme 1.

References and Notes

1 Partly presented by T. Nozoe, at 4th Towa University International Symposium, Fukuoka, Nov. 1994, Abstr. pp.13-18; T. Nozoe, presented at 24th Symposium on Structural Organic Chemistry, Kiryu, Oct., 1993, Abstr. p. 1A07; T. Nozoe, H. Wakabayashi, K. Shindo, and M. Kageyama, 65th Symposium on Organic Synthesis, Tokyo, June, 1994, Abstr. p. 21.

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3 K. Shindo, H. Wakabayashi, S. Ishikawa and T. Nozoe, at 9th Symposium on Fundamental Structural Chemistry, Oct., 1988, Abstr. p. 393; K. Shindo, S. Ishikawa, and T. Nozoe, unpublished results.

4 T. Nozoe, H. Wakabayashi, K. Shindo, T. Kurihara, S. Ishikawa, and M. Kageyama, *Chem. Lett.*, **1995**, 25; T. Nozoe, H. Wakabayashi, K. Shindo, and M. Yasunami, *Chem. Lett.*, **1995**, 439.

5 Compound **7** is rather unstable in solution even at -45 °C. **7**: ^{1}H NMR (400 MHz, CD_3CN, -45.2 °C) δ = 1.39 (6H, d, *J*=6.7 Hz, iPr-CH_3), 2.34 (3H, s, 1-CH_3), 2.95 (3H, s, 4-CH_3), 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).

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**: ^{1}H NMR (400 MHz, CD_3CN) δ = 1.42 (6H, d, *J*=6.7 Hz, iPr-CH_3), 2.41 (3H, s, 1-CH_3), 3.25 (3H, s, 4-CH_3), 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); ^{13}C NMR (100 MHz, CD_3CN) δ = 13.04 (1-CH_3), 23.21 (iPr-CH_3), 27.04 (4-CH_3), 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).

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8 **10a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.22 (6H, d, *J*=6.7 Hz, iPr-CH_3), 1.51 (3H, s, 1-CH_3), 2.62 (3H, s, 4-CH_3), 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); ^{13}C NMR (125 MHz, $CDCl_3$) 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 $C_{15}H_{17}O_2Br$: M, 310.0391.

9 **10b**: ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.21 (3H, d, *J*=6.9 Hz, iPr-CH_3), 1.24 (3H, d, *J*=6.9 Hz, iPr-CH_3), 1.46 (3H, s, 1-CH_3), 2.71 (3H, s, 4-CH_3), 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).

10 **10c**: ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.21 (3H, d, *J*=6.7 Hz, iPr-CH_3), 1.22 (3H, d, *J*=6.7 Hz, iPr-CH_3), 1.65 (3H, s, 1-CH_3), 2.04 (3H, s, $COCH_3$), 2.70 (3H, s, 4-CH_3), 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 **11**: ^{1}H NMR (500 MHz, $CDCl_3$) δ = 2.12 (6H, s, iPr-CH_3), 2.34 (3H, d, *J*=1.5 Hz, 3-CH_3), 2.62 (3H, s, 8-CH_3), 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).

12 Crystal data for **10a**: monoclinic, space group $P2_1/n$, *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 Rw=0.074.

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