

Facile Shifts of Bromine Atom on C-3 Position of Guaiazulene
and Synthesis of Variously Functionalized Azulenes Using
These Reactions ¹⁾

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Treatment of guaiazulene (**1**) with NBS in hexane gave exclusively 3-bromo compound, while in benzene it afforded various side-chain-brominated compounds. Shifts of bromine atom catalyzed by succinimide were observed in benzene, presumably via intermolecular radical pathways. Using these reactions, various side-chain-functionalized derivatives of **1**, including epoxy compounds, were prepared.

From blue polyyps of deep sea gorgonian, Scheuer²⁾ and his coworkers isolated guaiazulene (**1**), 3-chloro- (**2**), 3-bromoguaiazulene (**3**), chiral ehuazulene (**4**), linderazulene, guaiazulenequinone,^{2b)} 3-formylguaiazulene, and 3,3'-methylenebis(guaiazulene). The last three compounds, meanwhile, had been isolated by one of us (T.N.) and his coworkers from the autoxidation products,³⁾ as well as from the products of peracetic acid oxidation⁴⁾ of **1**. It should especially be noted that ehuazulene has a bromine atom at the end of the isopropyl side chain instead of the reactive C-3 position and halogeno derivatives **2-4** were reported to be unstable.²⁾ These findings prompted us to study bromination of **1** with N-bromosuccinimide (NBS) in detail and the results are reported herein.

First, we examined reaction of **1** with NBS (1:1 ratio) in benzene. The products were separated by HPLC and TLC and structures of these compounds determined on the basis of spectral data. Surprisingly, the main product was dl-ehuazulene (**4**)⁵⁾ and no 3-bromo compound **3** could be found. Lactaroazulene (**5**),⁶⁾ two isomeric 14-bromolactaroazulenes (**6a,b**)⁷⁾ and 14,15-dibromoguaiazulene (**7**)⁸⁾ were obtained as minor products (see Scheme 1). Although all of these bromo compounds were unstable especially in concentrated solution, most of them afforded stable, deep colored 1,3,5-trinitrobenzene (TNB) complexes. Among the products we also found a small amount of N-(5-guaiazulenyl)succinimide (**11**),⁷⁾ and 13-hydroxy- (**8b**, X=OH)⁷⁾ or 13-methoxyguaiazulene (**8c**, X=OMe);⁷⁾ the latter two compounds are obviously secondary products formed from labile 13-bromoguaiazulene (**8a**) during the HPLC measurement in methanol.

To clarify the formation sequence of these products, we examined the time-dependent HPLC of the reaction of **1** with NBS in benzene at room temperature: peak of **8c** appeared immediately, followed by **4**, **5**, **6a,b**, and **7**, while **1** gradually disappeared (Fig. 1a). When the same reaction was examined in hexane, a sharp single peak of **3** (vide infra) appeared at the expense of **1**. However, when the

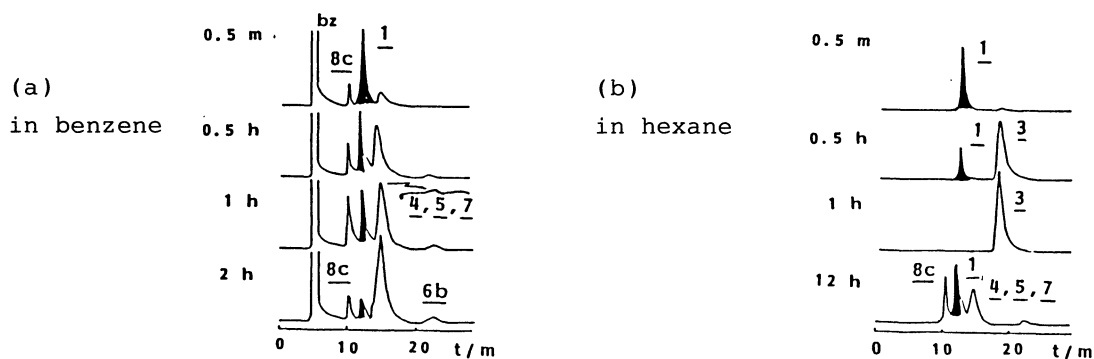
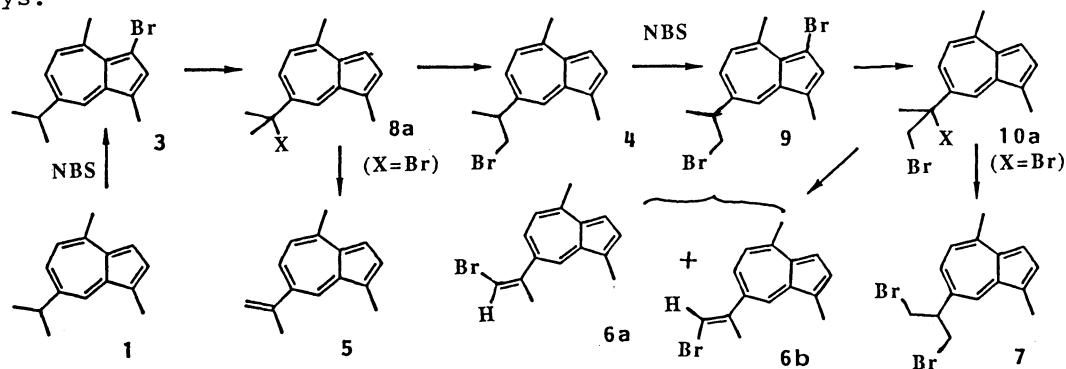


Fig. 1. Time-dependent HPLC diagrams of reaction of **1** with NBS.

solution was allowed to stand for 12 h, the peak of **1** reappeared besides those of **4**, **5**, and **7** (Fig. 1b). Thus, pure 3-bromoguaiazulene (**3**)⁹⁾ was successfully isolated as blue oil.¹⁰⁾

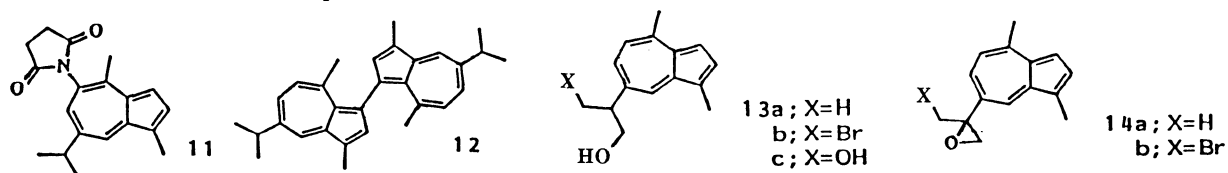
We then examined effect of succinimide on the reaction of **3** in benzene at room temperature. When we examined the time-dependent HPLC chromatograms,⁹⁾ **3** disappeared within 20 min, while **1**, **8b,c**, **4**, **6**, **7**, and a small amount of **12** gradually increased. The following observations are worth noting: (i) bromine-free guaiazulene **1**, dibromo compound **7**, and coupling product **12** are produced from monobromo compound **3**; (ii) compounds **4**, **5**, **6**, and **7** are produced when a chloroform solution of **3** is allowed to stand for a few hours; (iii) these facile shift of Br on C-3 of **3** to the side chain does not take place, if oxygen is absent or hydroquinone is present in the solution. All of these observations strongly suggests that the Br-atom on C-3 migrates to the end of the side chain via unstable C-3 and C-13 brominated intermediates (**8a**, **9**, and **10a**) as illustrated in Scheme 1, and the reaction is presumed to proceed via intermolecular radical pathways.



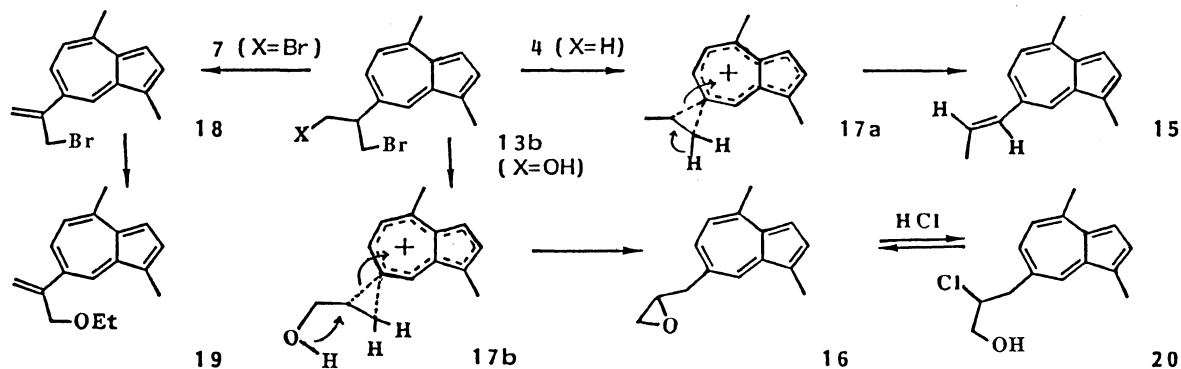
Scheme 1.

3-Bromoguaiazulene (**3**) is stable to alkali but easily affords **1** and its oxidative dimer **12** with acid. **4** and **7** are easily hydrolyzed in warm aqueous

dioxane to give the primary alcohol **13a** ($X=H$),⁷⁾ and **13b,c** ($X=Br$ or OH),⁷⁾ respectively. Treatment of **13a** and **13b** with NBS in benzene afforded epoxy compounds **14a** ($X=H$)¹¹⁾ and **14b** ($X=Br$),¹²⁾ respectively, presumably via unstable C-3 and C-13 bromo compounds.

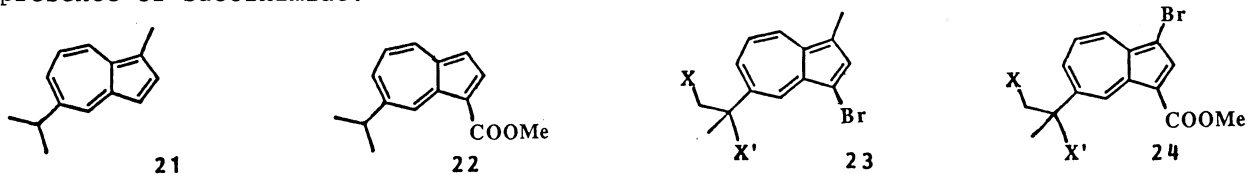


On the other hand, with 3% ethanolic KOH (or even with $NaHCO_3$ in the case of **13b**) at room temperature, **4** and **13b** rearranged quantitatively to 1,4-dimethyl-7-propenylazulene (**15**)¹³⁾ and the epoxide **16**,¹⁴⁾ respectively, presumably via "azulenonium" ion **17a** and **17b**, whereas **7** gives 15-ethoxylactarozulene (**19**)¹⁵⁾ under the same conditions (Scheme 2). Namely, in the case of **4** and **13b** solvolysis is assisted by two methyl groups in guaiiazulene nucleus to form **17a** and **17b** and causing rearrangement, while dibromo compound **7** undergoes dehydrobromination to give **19** via **18**, due to strong electron-withdrawing effect of two bromine atoms. The chlorohydrin **20**⁷⁾ obtained from **16** with warm aqueous dioxane containing HCl, easily reverted back to **16** by alkali.



Scheme 2.

Reaction of **1** with N-chlorosuccinimide was generally similar to the case of NBS but proceeded more slowly. NBS bromination of other azulenes, such as **21** and **22**, under more severe conditions afforded mono-, di-, and tribromo compounds (**23**, **24**: $X=H$ or Br , $X'=OH$ or OMe). Bromine atom of the 3-bromo compounds (**23**, **24**: $X,X'=H$) does not shift to the isopropyl side chain in benzene, even in the presence of succinimide.



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References

- 1) Presented at 56th National Meeting of the Chemical Society of Japan, Tokyo 1988, Abstr. No. 4X1G15 and at 9th Symposium of Fundamental Organic Chemistry, Hiroshima 1988, Abstr. No. O-23.
- 2) a) M. K. W. Li and P. J. Scheuer, *Tetrahedron Lett.*, **25**, 587, 4707 (1984);
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- 3) T. Nozoe, S. Takekuma, M. Doi, Y. Matsubara, and H. Yamamoto, *Chem. Lett.*, **1984**, 627 and the following papers.
- 4) Y. Matsubara, S. Matsui, S. Takekuma, H. Yamamoto, and T. Nozoe, *Nippon Kagaku Kaishi*, **1988**, 1704.
- 5) **4** TNB complex: deep blue needles, mp 97-98 °C.
- 6) F. Sorm, V. Benesnova, and V. Herout, *Collect. Czech. Chem. Commun.*, **19**, 367 (1954); S. Takekuma, Y. Matsubara, H. Yamamoto, and T. Nozoe, *Bull. Chem. Soc. Jpn.*, **61**, 475 (1988).
- 7) Satisfactory spectral (NMR, IR, MS) data were obtained for these new compounds.
- 8) **7**: blue oil; UV $\lambda_{\max}$ (MeOH) 244, 290, 352, 369, and 600 nm; ^1H NMR (270 MHz, benzene- d_6) δ =2.53 (6H, s, Me-1,4), 3.08 (1H, m, J=6.8 Hz, CH), 3.24 (2H, dd, J=10.3 and 6.8 Hz, CHHBr), 3.37 (2H, dd, J=10.3 and 6.8 Hz, CHHBr), 6.65 (1H, d, J=10.8 Hz, H-5), 6.79 (1H, dd, J=10.8 and 1.8 Hz, H-6), 7.29 (1H, d, J=3.7 Hz, H-3), 7.63 (1H, d, J=3.7 Hz, H-2), and 7.88 (1H, d, J=1.8 Hz, H-8); MS m/z 356 (M^+).
- 9) Experimental details will be published elsewhere.
- 10) **3** TNB complex: deep blue needles, mp 123-125 °C.
- 11) **14a**: blue needles, mp 75-76 °C; UV $\lambda_{\max}$ 290, 370, 400, 435, and 500-700 nm.
- 12) **14b**: blue oil; ^1H NMR (270 MHz, benzene- d_6) δ =2.54 (6H, s, Me-1,4), 3.34 (2H, s, CH_2Br), 3.48 (2H, s, $-\text{CH}_2-\text{O}$), 6.63 (1H, d, J=10.8 Hz, H-5), 6.98 (1H, dd, J=10.8 and 2.4 Hz, H-6), 7.29 (1H, d, J=3.6 Hz, H-3), 7.63 (1H, d, J=3.6 Hz, H-2), and 8.01 (1H, d, J=2.4 Hz, H-8); MS m/z=292 (M^+), 290 (M^+).
- 13) **15**: blue oil; UV $\lambda_{\max}$ 242, 290, 360(sh), 381, and 613 nm; ^1H NMR (270 MHz, benzene- d_6) δ =1.74 (3H, dd, J=6.6 and 1.5 Hz, $=\text{CH}-\text{Me}$), 2.56 (3H, s, Me-1), 2.57 (3H, s, Me-4), 6.04 (1H, dq, J=15.4 and 6.6 Hz, $=\text{CH}-\text{Me}$), 6.46 (1H, dd, J=15.4 and 1.5 Hz, $-\text{CH}=\text{}$), 6.74 (1H, d, J=10.8 Hz, H-5), 7.27 (1H, d, J=3.9 Hz, H-3), 7.38 (1H, dd, J=10.8 and 1.5 Hz, H-6), 7.61 (1H, d, J=3.9 Hz, H-2), and 8.37 (1H, d, J=1.5 Hz, H-8); MS m/z=196 (M^+).
- 14) **16**: blue oil; UV $\lambda_{\max}$ 244, 285, 304, 350, 367, and 603 nm; ^1H NMR (270 MHz, benzene- d_6) δ =2.13 (1H, dd, J=5.1 and 2.4 Hz, CHH), 2.32 (1H, dd, J=5.1 and 3.8 Hz, CHH), 2.58 (3H, s, Me-1), 2.59 (3H, s, Me-4), 2.65 (2H, d, J=5.1 Hz, CH_2), 2.82 (1H, m, CH), 6.71 (1H, d, J=10.5 Hz, H-5), 7.16 (1H, dd, J=10.8 and 1.8 Hz, H-6), 7.29 (1H, d, J=3.9 Hz, H-3), 7.66 (1H, d, J=3.9 Hz, H-2), and 8.30 (1H, d, J=1.8 Hz, H-8); MS m/z=212 (M^+).
- 15) **19**: blue oil; UV $\lambda_{\max}$ (MeOH) 246, 291, 377, and 603 nm; ^1H NMR (270 MHz, benzene- d_6) δ =1.07 (3H, t, J=7.0 Hz, CH_2-CH_3), 2.56 (6H, d, J=1.8 Hz, Me-1,4), 3.35 (2H, q, J=7.0 Hz, CH_2-CH_3), 4.28 (2H, s, $=\text{C}-\text{CH}_2$), 5.41 (2H, s, $=\text{CH}_2$), 6.74 (1H, d, J=10.6 Hz, H-5), 7.29 (1H, d, J=3.7 Hz, H-3), 7.54 (1H, dd, J=10.6 and 1.8 Hz, H-6), 7.62 (1H, d, J=3.7 Hz, H-2), and 8.53 (1H, d, J=1.8 Hz, H-8); MS m/z=240 (M^+).

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