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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-functionalyzed derivatives of **1**, including epoxy compounds, were prepared.

From blue polyps of deep sea gorgonian, Scheuer[2)] 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 oxidation[4)] 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 mesurement 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 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)

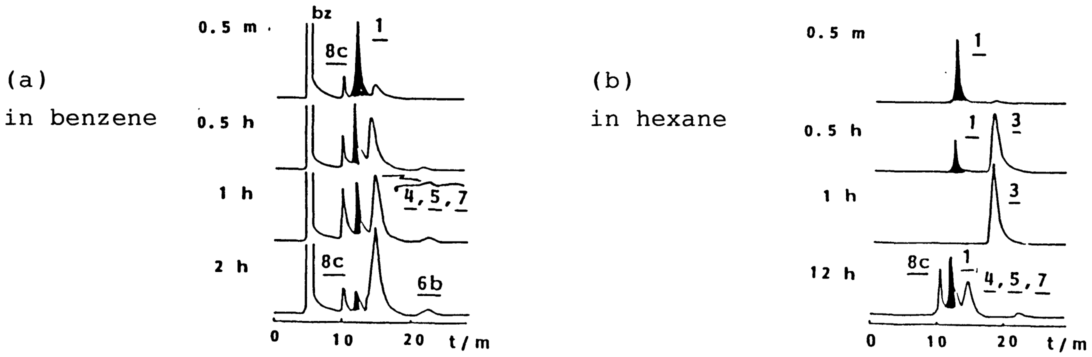
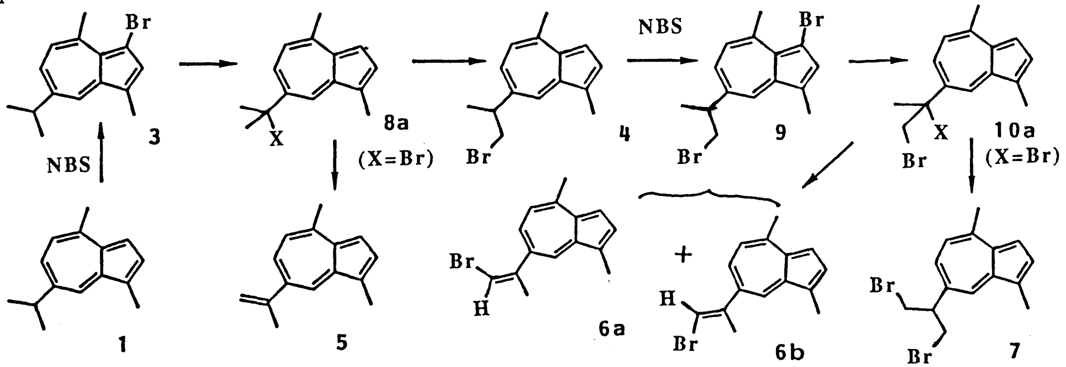


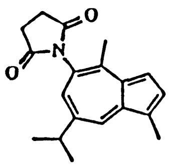
Fig. 1. Time-dependent HPLC diagrams of reaction of **1** with NBS.

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.



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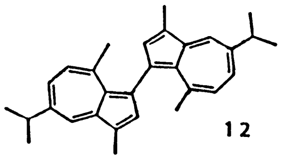

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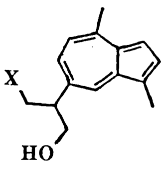
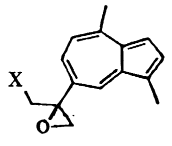
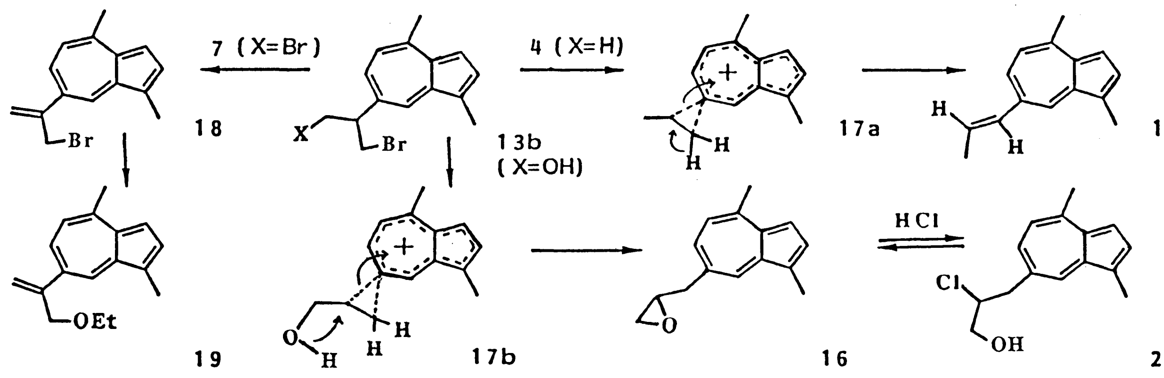


13a; X=H
b; X=Br
c; X=OH



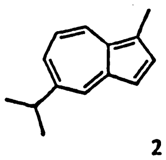
14a; X=H
b; X=Br

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-ethoxylactaroazulene (**19**)[15] under the same conditions (Scheme 2). Namely, in the case of **4** and **13b** solvolysis is assisted by two methyl groups in guaiazulene 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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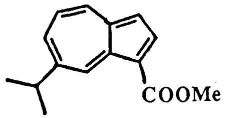

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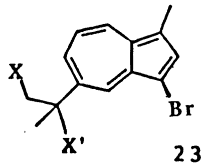

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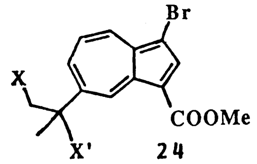

24

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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);
b) Private communication of Professor Scheuer; see also S. Imre, R. H. Tomson, and B. Jahli, Experientia, 39, 442 (1981).

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 λmax (MeOH) 244, 290, 352, 369, and 600 nm; ^{1}H 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, $C\underline{H}HBr$), 3.37 (2H, dd, J=10.3 and 6.8 Hz, $CH\underline{H}Br$), 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 ($M^{+\cdot}$).

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 λmax 290, 370, 400, 435, and 500-700 nm.

12) **14b**: blue oil; ^{1}H NMR (270 MHz, benzene-d_6) δ=2.54 (6H, s, Me-1,4), 3.34 (2H, s, $C\underline{H}_2Br$), 3.48 (2H, s, $-C\underline{H}_2-O$), 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 ($M^{+\cdot}$), 290 ($M^{+\cdot}$).

13) **15**: blue oil; UV λmax 242, 290, 360(sh), 381, and 613 nm; ^{1}H NMR (270 MHz, benzene-d_6) δ=1.74 (3H, dd, J=6.6 and 1.5 Hz, $=CH-\underline{Me}$), 2.56 (3H, s, Me-1), 2.57 (3H, s, Me-4), 6.04 (1H, dq, J=15.4 and 6.6 Hz, $=C\underline{H}-Me$), 6.46 (1H, dd, J=15.4 and 1.5 Hz, $-C\underline{H}=$), 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 ($M^{+\cdot}$).

14) **16**: blue oil; UV λmax 244, 285, 304, 350, 367, and 603 nm; ^{1}H NMR (270 MHz, benzene-d_6) δ=2.13 (1H, dd, J=5.1 and 2.4 Hz, $C\underline{H}H$), 2.32 (1H, dd, J=5.1 and 3.8 Hz, $C\underline{H}H$), 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 ($M^{+\cdot}$).

15) **19**: blue oil; UV λmax (MeOH) 246, 291, 377, and 603 nm; ^{1}H NMR (270 MHz, benzene-d_6) δ=1.07 (3H, t, J=7.0 Hz, $CH_2-C\underline{H}_3$), 2.56 (6H, d, J=1.8 Hz, Me-1,4) 3.35 (2H, q, J=7.0 Hz, $C\underline{H}_2-CH_3$), 4.28 (2H, s, $=C-C\underline{H}_2$), 5.41 (2H, s, $=C\underline{H}_2$), 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 ($M^{+\cdot}$).

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