

OXIDATION OF AZULENE DERIVATIVES. AUTOXIDATION OF
 GUAIAZULENE IN A POLAR APROTIC SOLVENT¹⁾

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Autoxidation of guaiazulene at 100 °C in *N,N*-dimethylformamide afforded twenty-three separable products including seven known compounds. Most of these new compounds possess highly interesting structures of azulenoquinone, inden-1-one, benzocyclobutadiene, naphthoquinone, and dimeric forms.

Azulenenes have been regarded as one of the representative examples of non-benzenoid aromatic hydrocarbons, which usually do not undergo Diels-Alder-type addition reactions but are easily susceptible to many electrophilic substitution reactions (normally at the 1- and/or 3-position).²⁾ As for oxidation of azulenes it has been briefly reported that the treatment of naturally occurring guaiazulene (**1**) with KMnO₄ or SeO₂ in acetone gave the oxidized products **K** and **O** (see later), aldehyde **L**, and 3,3'-diguaiazulenylacetone,³⁾ whereas on exposure to air **1** produced 3,3'-biguaiazulene **B** and two indenones for which structures **2** and **3** were presented.⁴⁾ We wish to report in this paper the first detailed study on autoxidation of an azulene derivative **1** in an aprotic solvent, that resulted in the formation of a wide variety of products which were fully characterized.

Thus, a solution of **1** (1.00 g) in 20 ml of *N,N*-dimethylformamide (DMF) was subjected to autoxidation by bubbling oxygen in a pyrex flask at 100 °C. Periodical checking of the reaction mixture by silica-gel TLC (with hexane/AcOEt, 85:15) and the reversed-phase HPLC (PSG-100, with methanol) (Fig. 1) showed that

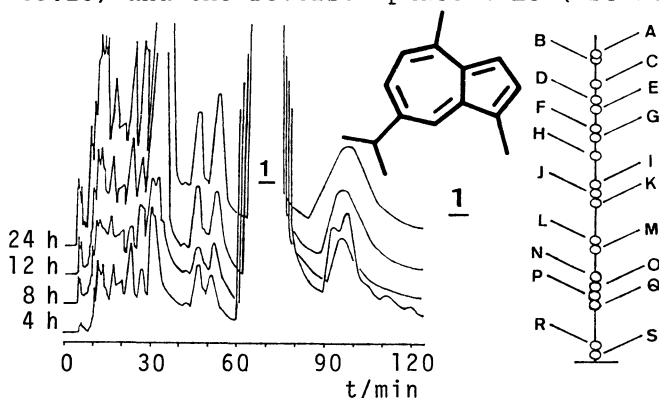
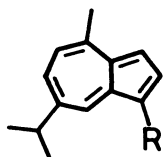


Fig. 1. Time-dependent HPLC diagram of autoxidation of **1**, and TLC of the products.

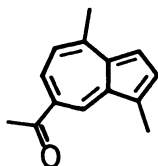
more than twenty kinds of products were formed simultaneously over a period of 24 hours, by which about a half of **1** was consumed. The reactants were then carefully separated by silica-gel column chromatography, TLC, and HPLC, thus affording twenty-three products as pure compounds, which will be referred to as Substances **A-S** according to their decreasing *R_f*

values; band A contained at least five compounds A₁-A₅, among which A₁ was the recovered 1. Structures of these products, explicitly established by spectroscopy,⁵⁾ are presented here (with isolated yields) after having been divided into four groups according to the site of the oxidation.

Group 1: Oxidation products of the side-chain.

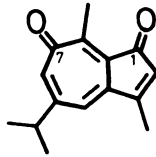


K* R=CHO (5.0%)³⁾
Q* R=COOH (1.0%)³⁾

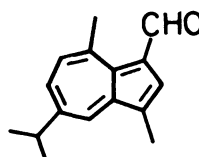


J (0.2%)⁶⁾

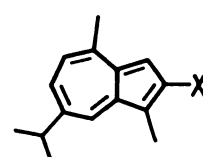
Group 2: Oxidation and substitution products of the nucleus.



Q (1.0%)⁷⁾

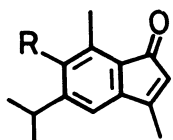


L* (1.0%)³⁾

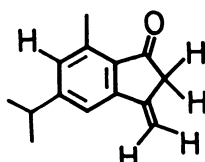


S (0.5%)⁸⁾
 X=CH₂NMeCHO

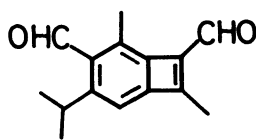
Group 3: Monomeric, oxidative-rearrangement products.



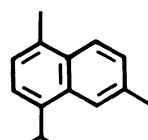
E R=H (1.0%)⁹⁾
I R=CHO (2.0%)¹⁰⁾



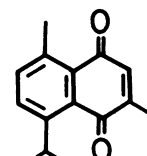
G (0.5%)¹¹⁾



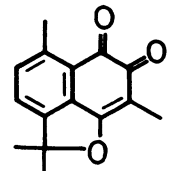
N (0.2%)¹²⁾



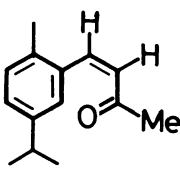
A₅* (0.5%)¹³⁾



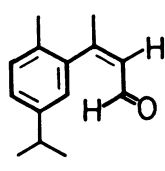
D (3.5%)¹⁴⁾



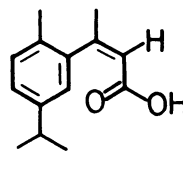
R (0.5%)¹⁵⁾



F₁ (1.0%)¹⁶⁾

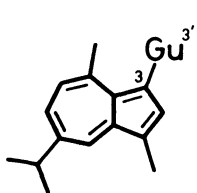


F₂ (1.0%)¹⁷⁾

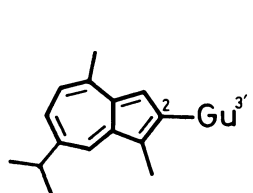


P (1.5%)¹⁸⁾

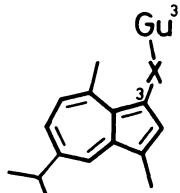
Group 4: Dimeric oxidation products.



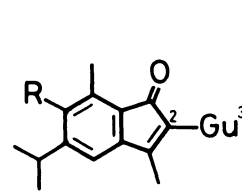
B* (3.5%)¹⁹⁾



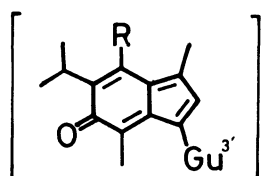
A₃ (0.5%)²⁰⁾



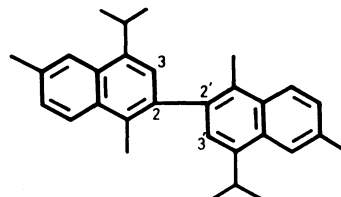
A₂* X=CH₂ (5.0%)²¹⁾
M* X=CO (1.0%)²²⁾



C R=H (1.3%)²³⁾
H R=CHO (1.3%)²⁴⁾



2 R=H⁴⁾
3 R=CHO⁴⁾



A₄ (0.1%)²⁵⁾

*Previously known compound. Gu^{3'}: 3-Guaiazulenyl.

It is noteworthy that this autoxidation directly gave a 1,7-azulenoquinone derivative Q as a minor product, since azulenoquinones are currently drawing an increasing interest.²⁶⁾ In contrast with the efficient preparation of acetyl derivatives from isopropylbenzenes by the similar autoxidation,²⁷⁾ 1 afforded only a small amount of 7-acetyl compound J. Most of the indenones obtained here were rather unstable; e.g. an equilibrium ($\approx 1:1$) gradually reached between E and G in CHCl_3 at 25 °C, and finally colorless dimers were produced from this mixture.²⁸⁾ Interestingly, the formyl compound I was observed to rearrange to a unique benzocyclobutadiene N even on standing at 25 °C and was then gradually converted into four colorless dimers.²⁸⁾ Substances C and H appeared to be spectroscopically identical with the reported compounds 2 and 3, respectively.⁴⁾ Their structures, however, are now revised to the isomeric forms C and H, which are more in conformity with the spectral data.

Although a precise mechanistic study with regard to this highly intricate, competitive oxidation reaction using various other azulene derivatives is now in progress, the present work clearly demonstrates a diversity of autoxidation of azulenes, which produce a wide variety of very interesting compounds, some of which are apparently difficult to prepare by alternative methods.

References

- 1) Presented at 16th Symposium of the Chemistry of Nonbenzenoid Aromatic Compounds, Urawa, 1983, Abstr. Nos. A2-25 and A2-26.
- 2) See e.g. T. Nozoe and S. Ito, *Fortschr. Chem. Org. Naturst.*, **19**, 33 (1961); D. Lloyd, "Carbocyclic Non-benzenoid Aromatic Compounds," Elsevier, Amsterdam (1966).
- 3) K. Kohara, *Bull. Chem. Soc. Jpn.*, **42**, 3229 (1969); W. Treibs, *Chem. Ber.*, **90**, 761 (1957); **92**, 2152 (1959).
- 4) M. Pailer and H. Lobenwein, *Monatsh. Chem.*, **102**, 1558 (1971).
- 5) ^1H NMR (200 MHz; in CDCl_3), ^{13}C NMR, MS (high-resolution EI or chemical ionization), IR, and UV (only the longest wavelength absorption maxima in MeOH being shown here) data were in agreement with the structures of the products described in this paper. These data and the reaction mechanism will be discussed in full paper (in preparation).
- 6) J: Violet crystals, mp 55 °C; UV λ_{max} 575 nm ($\log \epsilon$ 2.72); IR (KBr) 1670 cm^{-1} ; CI-MS m/e 199 ($M+1$); ^1H NMR δ 2.74 (6H, s, Me-1 and Ac-7), 2.87 (3H, s, Me-4), 7.04 (1H, d, $J=11.0$ Hz, H-5), 7.50 and 7.66 (both 1H, d, $J=4.0$ Hz, H-3 and 2), 8.18 (1H, dd, $J=11.0$ and 2.0 Hz, H-6), and 8.98 (1H, d, $J=2.0$ Hz, H-8).
- 7) Q: Yellow needles, mp 94 °C; UV λ_{max} 398 nm ($\log \epsilon$ 3.95); IR (KBr) 1680 and 1590 cm^{-1} ; EI-MS m/e 228 (M^+); ^1H NMR δ 1.26 (6H, d, $J=7.0$ Hz, i-Pr-5), 2.29 (3H, d, $J=1.5$ Hz, Me-3), 2.64 (3H, s, Me-8), 2.76 (1H, sept, $J=7.0$ Hz, Me_2CH -5), 6.23 (1H, qd, $J=1.5$ and 0.5 Hz, H-2), 6.63 (1H, dd, $J=2.0$ and 0.5 Hz, H-4), and 6.76 (1H, d, $J=2.0$ Hz, H-6).
- 8) S: Blue crystals; UV λ_{max} 608 nm ($\log \epsilon$ 2.64); IR (CCl_4) 1665 cm^{-1} ; EI-MS m/e 269 (M^+); ^1H NMR (a) δ 1.32 (6H, d, $J=7.0$ Hz, i-Pr-7), 2.55 (3H, s, Me-1), 2.82 (3H, s, Me-N), 2.88 (3H, s, Me-4), 3.02 (1H, sept, $J=7.0$ Hz, Me_2CH -7), 5.00 (2H, s, CH_2 -2), 6.86 (1H, d, $J=11.0$ Hz, H-5), 7.29 (1H, dd, $J=11.0$ and 2.0 Hz, H-6), 7.38 (1H, s, H-3), 8.05 (1H, d, $J=2.0$ Hz, H-8), and 8.13 (1H, s, N-CHO), (b) δ 1.32 (6H, d, $J=7.0$ Hz, i-Pr-7), 2.55 (3H, s, Me-1), 2.72 (3H, s, Me-N), 2.88 (3H, s, Me-4), 3.02 (1H, sept, $J=7.0$ Hz, Me_2CH -7), 5.11 (2H, s, CH_2 -2), 6.86 (1H, d, $J=11.0$ Hz, H-5), 7.29 (1H, dd, $J=11.0$ and 2.0 Hz, H-6), 7.38 (1H, s, H-3), 8.05 (1H, d, $J=2.0$ Hz, H-8), and 8.13 (1H, s, N-CHO), a and b being a 3:2 mixture due to restricted rotation of the C-N bond in the amide group; cf. A. Mannschreck, *Tetrahedron Lett.*, **1965**, 1341.
- 9) E: Pale yellow oil; UV λ_{max} 337 nm; IR (neat) 1680 cm^{-1} ; CI-MS m/e 201 ($M+1$); ^1H NMR δ 1.23 (6H, d, $J=7.0$ Hz, i-Pr-5), 2.20 (3H, d, $J=1.5$ Hz, Me-3), 2.44 (3H, s, Me-7), 2.88 (1H, sept, $J=7.0$ Hz, Me_2CH -5), 5.61 (1H, q, $J=1.5$ Hz, H-2), 6.79 and 6.83 (both 1H, bs, H-4 and 6).
- 10) I: Yellow crystals, mp 87 °C; UV λ_{max} 340 and 380 nm ($\log \epsilon$ 3.89 and 3.42); IR (KBr) 1700 and 1695 cm^{-1} ; EI-MS m/e 228 (M^+); ^1H NMR δ 1.32 (6H, d, $J=6.9$ Hz, i-Pr-5), 2.26 (3H, d, $J=1.4$ Hz, Me-3), 2.76 (3H, s, Me-7), 3.72 (1H, sept, $J=6.9$ Hz, Me_2CH -5), 5.80 (1H, q, $J=1.4$ Hz, H-2), 7.04 (1H, s, H-4),

- and 10.58 (1H, s, CHO).
- 11) G: Colorless crystals; UV λ_{\max} 330 nm ($\log \epsilon$ 3.79); IR (CCl₄) 1720 cm⁻¹; EI-MS m/e 200 (M⁺); ¹H NMR δ 1.29 (6H, d, J=7.0 Hz, i-Pr-5), 2.62 (3H, s, Me-7), 2.96 (1H, sept, J=7.0 Hz, Me₂CH-5), 3.25 (2H, dd, J=2.0 and 1.8 Hz, 2H-2), 5.24 (1H, t, J=1.8 Hz, (E)-HC-3), 5.78 (1H, t, J=2.0 Hz, (Z)-HC-3), 7.02 (1H, bs, H-6), and 7.43 (1H, bs, H-4).
 - 12) N: Yellow crystals; UV λ_{\max} 418 nm; IR (KBr) 1710 and 1705 cm⁻¹; CI-MS m/e 229 (M + 1); ¹H NMR δ 1.28 (6H, d, J=7.0 Hz, i-Pr-4), 2.68 (3H, s, Me-2), 2.90 (3H, s, Me-6), 3.65 (1H, sept, J=7.0 Hz, Me₂CH-4), 7.02 (1H, s, H-3), 10.56 and 10.68 (both 1H, s, CHO-1 and 5).
 - 13) B. A. Nagasampagi, S. Dev, C. Rai, and K. L. Murthy, *Tetrahedron*, **22**, 1949 (1966).
 - 14) D: Yellow oil; UV λ_{\max} 360 nm ($\log \epsilon$ 3.71); IR (CCl₄) 1645 and 1630 cm⁻¹; CI-MS m/e 229 (M+1); ¹H NMR δ 1.30 (6H, d, J=7.0 Hz, i-Pr-5), 2.16 (3H, d, J=1.5 Hz, Me-3), 2.68 (3H, s, Me-8), 4.12 (1H, sept, J=7.0 Hz, Me₂CH-5), 6.68 (1H, q, J=1.5 Hz, H-2), 7.44 and 7.64 (both 1H, d, J=8.5 Hz, H-6 and 7).
 - 15) R: Orange crystals, mp 220 °C; UV λ_{\max} 440 nm ($\log \epsilon$ 3.73); IR (KBr) 1680 and 1610 cm⁻¹; EI-MS m/e 242 (M⁺); ¹H NMR δ 1.72 (6H, s, Me₂C-5), 1.94 (3H, s, Me-3), 2.70 (3H, s, Me-8), and 7.32 (2H, s, H-6 and 7). Quinoxaline derivative (with o-phenylenediamine): Yellow needles, mp 205 °C; EI-MS m/e 314 (M⁺); for other spectral data, cf. Ref. 5.
 - 16) F₁: Colorless oil; UV λ_{\max} 279 nm ($\log \epsilon$ 4.36); IR (neat) 1680 cm⁻¹; EI-MS m/e 202 (M⁺); ¹H NMR δ 1.21 (6H, d, J=7.0 Hz, i-Pr-5), 1.92 (3H, s, MeCO), 2.26 (3H, s, Me-2), 2.85 (1H, sept, J=7.0 Hz, Me₂CH-5), 6.16 (1H, d, J=11.0 Hz, CH=C-1), 7.03 (1H, bs, H-6), 7.09 (1H, bd, J=8.0 Hz, H-4), 7.13 (1H, d, J=8.0 Hz, H-3), and 7.15 (1H, d, J=11.0 Hz, C=CH-1).
 - 17) F₂: Colorless oil; ¹H NMR δ 1.24 (6H, d, J=7.0 Hz, i-Pr-5), 2.22 (3H, s, Me-2), 2.24 (3H, d, J=1.5 Hz, C=CMe-1), 2.88 (1H, sept, J=7.0 Hz, Me₂CH-5), 6.14 (1H, dq, J=8.2 and 1.5 Hz, CH=C-1), 6.92 (1H, bs, H-6), 7.10 (1H, bd, J=8.0 Hz, H-4), 7.16 (1H, d, J=8.0 Hz, H-3), and 9.20 (1H, d, J=8.2 Hz, CHO).
 - 18) P: Colorless crystals, mp 128 °C; UV λ_{\max} 278 nm ($\log \epsilon$ 4.23); IR (KBr) 3200-2300 and 1680-1660 cm⁻¹; EI-MS m/e 202 (M⁺); ¹H NMR δ 1.21 (6H, d, J=7.0 Hz, i-Pr-5), 2.12 (3H, d, J=1.5 Hz, C=CMe-1), 2.14 (3H, s, Me-2), 2.84 (1H, sept, J=7.0 Hz, Me₂CH-5), 5.92 (1H, q, J=1.5 Hz, CH=C-1), 6.78 (1H, dd, J=2.0 and 0.5 Hz, H-6), 7.05 (1H, dd, J=8.0 and 2.0 Hz, H-4), and 7.08 (1H, dd, J=8.0 and 0.5 Hz, H-3).
 - 19) R. Hagen, E. Heilbronner, and P. A. Straub, *Helv. Chim. Acta*, **51**, 45 (1968).
 - 20) A₃: Green crystals, mp 149 °C; UV λ_{\max} 612 nm ($\log \epsilon$ 2.79); EI-MS m/e 394 (M⁺); ¹H NMR δ 1.38 (12H, d, J=7.0 Hz, i-Pr-7 and 7'), 2.35 (3H, s, Me-1'), 2.48 (3H, s, Me-4'), 2.70 (3H, s, Me-1), 2.81 (3H, s, Me-4), 3.08, 3.10 (1H each, sept, Me₂CH-7 and 7'), 6.89 (1H, d, J=11.0 Hz, H-5'), 7.04 (1H, d, J=11.0 Hz, H-5), 7.35 (1H, dd, J=11.0 and 2.0 Hz, H-6'), 7.35 (1H, s, H-3), 7.36 (1H, dd, J=11.0 and 2.0 Hz, H-6), 7.56 (1H, s, H-2'), 8.18 (1H, d, J=2.0 Hz, H-8'), and 8.20 (1H, d, J=2.0 Hz, H-8).
 - 21) K. Kohara, Y. Ohtani, and N. Sakota, *Nippon Kagaku Kaishi*, **1975**, 139.
 - 22) A. J. Fry, B. W. Bowen, and P. A. Leermakers, *J. Org. Chem.*, **32**, 1970 (1967).
 - 23) C: Red crystals; UV λ_{\max} 520 nm ($\log \epsilon$ 3.51); IR (CCl₄) 1690 cm⁻¹; CI-MS m/e 397 (M + 1); ¹H NMR δ 1.28 and 1.34 (6H each, d, J=7.0 Hz, i-Pr-5 and 7'), 2.08 (3H, s, Me-3), 2.52, 2.62, and 2.64 (3H each, s, Me-1', 4' and 7), 2.89 and 3.04 (1H each, sept, J=7.0 Hz, Me₂CH-5 and 7'), 6.83 (2H, bs, H-4 and 6), 6.90 (1H, d, J=11.0 Hz, H-5'), 7.32 (1H, dd, J=11.0 and 2.0 Hz, H-6'), 7.36 (1H, s, H-2'), and 8.12 (1H, d, J=2.0 Hz, H-8').
 - 24) H: Reddish brown crystals, mp 147 °C decomp; UV λ_{\max} 537 nm ($\log \epsilon$ 3.50); IR (CCl₄) 1690 and 1680 cm⁻¹; CI-MS m/e 425 (M+1); ¹H NMR δ 1.33 and 1.37 (6H each, d, J=7.0 Hz, i-Pr-5 and 7'), 2.14 (3H, s, Me-3), 2.64 (6H, s, Me-1' and 4'), 2.80 (3H, s, Me-7), 3.01 and 3.79 (1H each, sept, J=7.0 Hz, Me₂CH-7' and 5), 6.95 (1H, d, J=11.0 Hz, H-5'), 7.08 (1H, s, H-4), 7.36 (1H, dd, J=11.0 and 2.0 Hz, H-6'), 7.39 (1H, s, H-2'), 8.16 (1H, d, J=2.0 Hz, H-8'), and 10.60 (1H, s, CHO).
 - 25) A₄: Yellow-green oil; UV λ_{\max} 441 nm; EI-MS m/e 394 (M⁺); ¹H NMR δ 1.38 (12H, d, J=7.0 Hz, i-Pr-4 and 4'), 2.55 (6H, s, Me-6 and 6'), 2.64 (6H, s, Me-1 and 1'), 3.72 (2H, sept, J=7.0 Hz, Me₂CH-4 and 4'), 7.22 (2H, s, H-3 and 3'), 7.34 (2H, dd, J=9.0 and 1.7 Hz, H-7 and 7'), 7.90 (2H, d, J=1.7 Hz, H-5 and 5'), and 7.91 (2H, d, J=9.0 Hz, H-8 and 8').
 - 26) T. Morita, F. Ise, and K. Takase, *Chem. Lett.*, **1982**, 1303; L. T. Scott, *Pure Appl. Chem.*, **1983**, 363.
 - 27) H. Iwamuro, M. Kanehiro, and Y. Matsubara, *Yu Kagaku (Oil Chemistry)*, **31**, 222 (1982).
 - 28) Structures of the dimerized products of E, I, and N will be reported elsewhere.

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