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Oxidation of 4,6,8-Trimethylazulene and Guaiazulene with Hydrogen Peroxide in Pyridine[1)]

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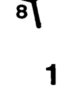
Synopsis. Oxidation of 4,6,8-trimethylazulene (**1**) with hydrogen peroxide in pyridine at 25 °C for 18 h gave 4,6,8-trimethyl-1,5- and -1,7-azulenequinones, their 2-(4,6,8-trimethyl-1-azulenyl) derivatives, and 2,3-dihydro-4,6- and -4,7-dimethyl-2-(4,6,8-trimethyl-1-azulenyl)-1*H*-inden-1-ones in much higher yields than those by autoxidation of **1** in DMF at 120 °C. The same oxidation of guaiazulene afforded sixteen separable products, among which there were three new dimeric condensates.

We have undertaken a systematic investigation on autoxidation of various azulenes for the past several years and isolated a wide variety of interesting products.[2)] Oxidation of guaiazulene (**2**) with peracetic acid was also conducted recently, and three dimeric compounds **3**, **4**, and **5** were isolated in good yields.[3—5)] These compounds were proved to be important intermediates for the autoxidation products of **2**. We now wish to report on oxidation of two representative trialkyl azulene derivatives, 4,6,8-trimethylazulene (**1**) and guaiazulene (**2**), with hydrogen peroxide in pyridine, which has resulted in isolation of several 1,5- and 1,7-azulenequinone derivatives in much higher yields than those by autoxidation, as well as disclosing several new types of reaction pathways in the oxidation of azulenic hydrocarbons.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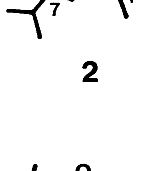
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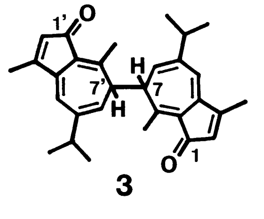
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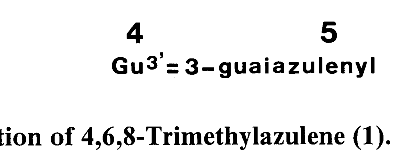

4 **5**

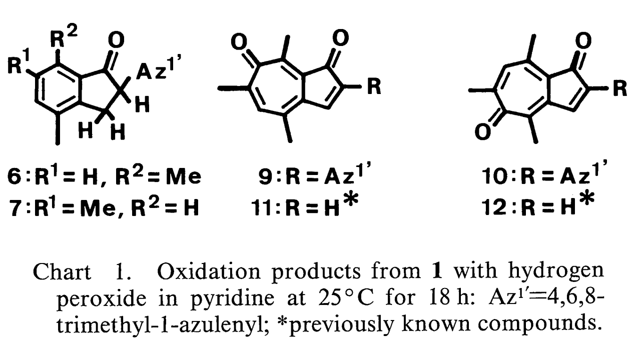
Gu3'= 3-guaiazulenyl

Oxidation of 4,6,8-Trimethylazulene (1). Oxidation of **1** with hydrogen peroxide in pyridine was carried out at 25 °C for 18 h, during which the reaction was monitored by the use of the reversed-phase high-pressure liquid chromatography (HPLC) and silica-gel TLC. As in the case of our previous studies no oxidation of azulenes, the reaction products were carefully separated into each component by using chromatography, when about 33% of the starting material **1** was consumed. Thus, we obtained seven products (**6**—**12**); the sequence of the compound numbers corresponds to the decreasing R_f values on silica-gel TLC (15:85 AcOEt–hexane). In Chart 1 are summarized these products, whose structures were established by UV-visible, IR ^{1}H NMR, and EI MS spectroscopy as will be explained below. Yields of the isolated products, which are based on the consumed starting material **1**, totaled to 36%. Besides these, there still remained 63% (w/w) yield of unidentified polar resinous products.

Compound **6** (5% yield) (M^+: *m*/*z* 328 by EI MS) contained a carbonyl group (1695 cm^{-1}) and a 4,6,8-trimethyl-1-azulenyl moiety (^{1}H NMR). A careful analysis of the ^{1}H NMR spectra with the aid of decoupling techniques and by comparison of the parameters (δ and J values) with those of related compounds[2)] established the structure of 2,3-dihydro-4,7-dimethyl-2-(4,6,8-trimethyl-1-azulenyl)-1*H*-inden-1-one for **6**. The assignments of the ^{1}H NMR signals are recorded in the Experimental section. Compound **7** (5% yield) turned out to be the 4,6-dimethyl isomer of **6** by the similar analysis of the IR, ^{1}H NMR, and EI MS spectral data.

Compound **8** (1% yield) possesed a dimeric composition ($C_{26}H_{24}O_3$ by HR MS) and contained three carbonyl groups (1705, 1675, and 1570 cm^{-1}). The ^{1}H NMR data indicated the presence of a 2-substituted 4,6,8-trimethyl-1,5-azulenequinone[2b)] moiety and a certain nucleus ($C_{13}H_{13}O$) that exhibited three methyl groups (at δ=2.18, 2.86, and 3.18, all singlet), an olefinic proton (at δ=6.53, singlet), and three aromatic protons [at δ=6.93(2H) and 6.96, both singlet]. However, structure of **8**[6)] is not yet determined.

Compounds **9** and **10** (9% yield), a inseparable mixture, were found to be a mixture of 2-(4,6,8-trimethyl-1-azulenyl)-4,6,8-trimethyl-1,7- and -1,5-azulenequinones in a ratio of ca. 1:1, respectively. The assignment of the coupling positions (C_2–$C_{1'}$) of the two moieties in these compounds were based on an NOE



6:R^1 = H, R^2 = Me **9**:R = Az$^{1'}$ **10**:R = Az$^{1'}$
7:R^1 = Me, R^2 = H **11**:R = H* **12**:R = H*

Chart 1. Oxidation products from **1** with hydrogen peroxide in pyridine at 25 °C for 18 h: Az$^{1'}$=4,6,8-trimethyl-1-azulenyl; *previously known compounds.

experiment on the Me-4 and H-3 signals of the 4,6,8-trimethyl-1,7- and -1,5-azulenequinone moieties. Compounds **11** and **12** (8% yield each) were identified by UV, IR, ^{1}H NMR, and EI MS spectroscopy as 4,6,8-trimethyl-1,7- and -1,5-azulenequinones,[2b] respectively. It is noteworthy that azulenequinones (**11** and **12** as well as **9** and **10**) were produced in significantly higher yields under the present conditions than the previous autoxidation of **1** in DMF at 120 °C (1% yield each for **11** and **12**).[2b]

No oxidation was found to take place, when **1** was treated with pyridine 1-oxide[7–8] in pyridine at 25 °C for 18 h. Therefore, the above results are most likely due to the lower reaction temperature and the neutral conditions that would prevent those products decomposition during the oxidation.

Oxidation of Guaiazulene (2). Compound **2** was treated with hydrogen peroxide in pyridine at 25 °C for 8 h in a manner similar to that described for **1**. After separation, sixteen products (**13**—**28**) were obtained as pure compounds besides the recovered starting material **2** (60%). Structures of these products are shown in Chart 2, among which thirteen compounds (**13**, **15**, **17**, and **19**—**28**) were spectroscopically identical with those obtained previously by autoxidation of **2**.[2]

Compound **14** was found to be the 3,5′-isomer by spectroscopy. Compound **16** (M^+: *m*/*z* 394 by EI MS) contained a 3-guaiazulenyl moiety attached to a methyl group of the 7-isopropyl substituent of **2** (UV and ^{1}H NMR). Compound **18** (M^+: *m*/*z* 354 by EI MS) possessed a 3-guaiazulenyl moiety attached to C-2 of 3,7-dimethyl-1*H*-inden-1-one (UV and ^{1}H NMR).

The total yields of the isolated products from **2** were 72%, but there still remained a 20% (w/w) yield of unidentified polar resinous products. 5-Isopropyl-3,8-dimethyl-1,7-azulenequinone (**28**) was obtained in the highest yield (10%) among the isolated products. The newly isolated compounds **14** and **16** are apparently formed by two new types of bimolecular coupling reactions: Namely, coupling of the most reactive site (C-3) of guaiazulene with a seemingly far less reactive site of the seven-membered nucleus C-7 (to give **14**) and of a side-chain isopropyl group of **2** (to give **16**).

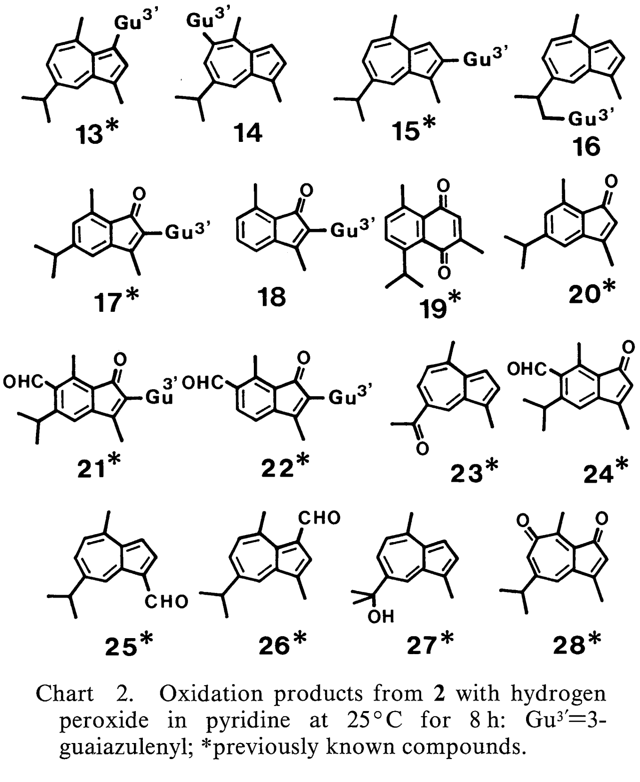


Chart 2. Oxidation products from **2** with hydrogen peroxide in pyridine at 25 °C for 8 h: Gu3′=3-guaiazulenyl; *previously known compounds.

Although the exact reaction mechanism has still remained to be clarified, the present work is believed to provide notable information on potential synthetic application to the preparation of some azulenequinones.

Experimental

Melting points were determined with a Yanagimoto MP-S3 instrument and are uncorrected. Chromatographic saparation and the spectral measurement were carried out according to the procedures described before,[2a] except that ^{1}H NMR spectra were recorded with a JEOL GSX-270 (270 MHz for ^{1}H).

Oxidation of 4,6,8-Trimethylazulene (1). Compound **1**[9] (0.33 g) was added to a stirred solution of hydrogen peroxide (30% aq, 10 ml) in pyridine (20 ml). The mixture was stirred at 25 °C for 18 h. The reactant was treated with cold 10% aq HCl (500 ml), carefully neutralized with aq Na_2CO_3, and extracted with hexane (3×100 ml). The extract was washed with water, dried (Na_2SO_4), and evaporated in vacuo. The residue (0.34 g) was purified by silica-gel column chromatography first with hexane (to recover the unreacted **1**), then with hexane-ethyl acetate (to separate several products), and finally with methanol (to eluate the polar substance) as the eluants. Then, each fraction of the products was further purified by preparative HPLC; when necessary, this chromatographic procedure was repeated. Thus, the following seven products were obtained as pure substances (**6**—**12**), besides the recovered starting material **1** [0.22 g (conversion: 33%); R_f=0.94] and polar resinous substances [76 mg, 63% (w/w); R_f=0.0]. The yield of each product is based on the consumed starting material (0.11 g).

2,3-Dihydro-4,7-dimethyl-2-(4,6,8-trimethyl-1-azulenyl)-1*H*-inden-1-one (6): Violet needles; 6 mg (5%); mp 154 °C; R_f=0.56; IR ($CHCl_3$) 1695 cm^{-1} (C=O); ^{1}H NMR δ=2.32 (3H, brs, Me-4), 2.59 (3H, s, Me-6′), 2.64 (3H, brs, Me-7), 2.82 (3H, s, Me-4′), 3.14 (3H, brs, Me-8′), 3.17 (1H, dd, J=17.5, 4.0 Hz, H-3), 3.63 (1H, dd, J=17.5, 8.5 Hz, H-3), 4.92 (1H, brdd, J=8.5, 4.0 Hz, H-2), 6.97 (1H, s, H-5′), 6.99 (1H, s, H-7′), 7.08 (1H, brd, J=7.5 Hz, H-6), 7.26 (1H, brd, J=4.0 Hz, H-3′), 7.28 (1H, d, J=4.0 Hz, H-2′), and 7.30 (1H, brd, J=7.5 Hz, H-5); EI MS *m*/*z* 328 (M^+; 100%), 313 (39), 285 (50), 270 (54), 253 (24), 239 (20), 170 (62), 152 (15), 128 (13), 115 (21), 91 (9), 77 (4), 65 (4), and 51 (3).

2,3-Dihydro-4,6-dimethyl-2-(4,6,8-trimethyl-1-azulenyl)-1*H*-inden-1-one (7): Violet needles; 6 mg (5%); mp 182 °C; R_f=0.49; IR ($CHCl_3$) 1695 cm^{-1} (C=O); ^{1}H NMR δ=2.33 (3H, brs, Me-4), 2.41 (3H, brs, Me-6), 2.59 (3H, s, Me-6′), 2.82 (3H, s, Me-4′), 3.13 (3H, brs, Me-8′), 3.14 (1H, dd, J=17.0, 4.0 Hz, H-3), 3.65 (1H. dd. J=17.0, 8.0 Hz, H-3), 4.94 (1H, brdd, J=8.0, 4.0 Hz, H-2), 6.98 (1H, s, H-5′), 6.99 (1H, s, H-7′), 7.26 (1H, brd, J=4.0 Hz, H-3′), 7.28 (1H, d, J=4.0 Hz, H-2′), 7.30 (1H, s, H-5), and 7.51 (1H, s, H-7); EI MS *m*/*z* 328 (M^+; 100%), 313 (60), 285 (38), 270 (56), 253 (26), 239 (21), 170 (45), 152 (17), 128 (14), 115 (20), 91 (11), 77 (9), 65 (4), 51 (4), and 41 (5).

4,6,8-Trimethyl-2-(4,6,8-trimethyl-1-azulenyl)-1,7- and -1,5-azulenequinone (9 and 10): (As a ca. 1:1 mixture, respectively); dark reddish violet needles; 11 mg (9%); mp 185—192 °C; R_f=0.38; IR ($CHCl_3$) 1735, 1690, and 1575 cm^{-1} (C=O); ^{1}H NMR for **9** δ=2.27 (3H, brd, $J\approx1$ Hz, Me-6), 2.36 (3H, s, Me-4), 2.615 (3H, s, Me-8), 2.69 (3H, s, Me-6′), 2.72 (3H, s, Me-4′), 2.883 (3H, s, Me-8′), 7.06 (1H, s, H-5′), 7.10 (1H, s, H-7′), 7.11 (1H, brq, $J\approx1$ Hz, H-5), 7.34 (1H, d, J=4.0 Hz, H-3′), 7.62 (1H, d, J=4.0 Hz, H-2′), and 7.69 (1H, s, H-3) and for **10** $\delta=2.30$ (3H, brd, $J\approx1$ Hz, Me-6), 2.37 (3H, s, Me-4), 2.62 (3H, s, Me-8), 2.70 (3H, s, Me-6′), 2.73 (3H, s, Me-4′), 2.877 (3H, s, Me-8′), 7.085 (1H, s, H-5′), 7.09 (1H, brq, $J\approx1$ Hz, H-7), 7.12 (1H, s, H-7′), 7.40 (1H, d, $J=4.0$ Hz, H-3′), 7.66 (1H, d, $J=4.0$ Hz, H-2′), and 7.77 (1H, s, H-3); NOE experiment [obsd NOEs(%) by irradiation of Me-4 for **9**] H-3=29, (for **10**) H-3=38; EI MS m/z 368 (M$^+$; 74%), 340 (100), 325 (35), 310 (22), 297 (28), 281 (26), 267 (37), 252 (15), 239 (17), 170 (11), 152 (20), 128 (17), 115 (24), 91 (11), 77 (13), and 41 (15).

4,6,8-Trimethyl-1,7-azulenequinone[2b] (11): Yellow needles; 10 mg (8%); mp 118 °C decomp (lit,[2b] mp 118 °C decomp); $R_f=0.25$; UV, IR, ^{1}H NMR, and EI MS, identical with the spectra of the authentic sample.

4,6,8-Trimethyl-1,5-azulenequinone[2b] (12): Yellow needles; 10 mg (8%); mp 120 °C decomp (lit.[2b] mp 120 °C decomp); $R_f=0.23$; UV, IR, ^{1}H NMR, and EI MS, identical with the spectra of the authentic sample.

Oxidation of Guaiazulene (2). Oxidation of **2**[9] (0.10 g) with hydrogen peroxide (30% aq, 3 ml) in pyridine (5 ml) was carried out at 25 °C for 8 h in a manner similar to that described for **1**, thus affording, after the careful chromatographic separation, sixteen products (**13**—**28**), besides the recovered starting material **2** (60 mg, 40% conversion, $R_f=0.95$) and polar resinous substances [8 mg, 20% (w/w); $R_f=0.0$]. The yield of each product is based on the consumed starting material (40 mg).

Previously Known Compounds: Comounds **13** (4 mg, 10%), **15** (3 mg, 8%), **17** (1 mg, 3%), **19** (1 mg, 3%), **20** (2 mg, 5%), **21** (1 mg, 3%), **22** (1 mg, 3%), **23** (1 mg, 3%), **24** (2 mg, 5%), **25** (1 mg, 3%), **26** (1 mg, 3%), **27** (2 mg, 5%), and **28** (4 mg, 10%) were obtained, which had also been produced by autoxidation of **2**.[2]

3,5′-Biguaiazulene (14): (As a ca. 37:63 mixture of **14** and **13**, respectively); dark greenish blue paste; $R_f=0.71$; ^{1}H NMR $\delta=1.31$, 1.32 (3H each, d, $J=7.0$ Hz, *i*-Pr-7′), 1.40 (6H, d, $J=7.0$ Hz, *i*-Pr-7), 2.26 (3H, s, Me-4′), 2.50 (3H, s, Me-4), 2.70 (3H, s, Me-1), 2.71 (3H, s, Me-1′), 3.02 (1H, sept, $J=7.0$ Hz, Me$_2$CH-7′), 3.08 (1H, sept, $J=7.0$ Hz, Me$_2$CH-7), 6.82 (1H, d, $J=10.0$ Hz, H-5), 7.29 (1H, d, $J=3.5$ Hz, H-3′), 7.33 (1H, dd, $J=10.0$, 2.0 Hz, H-6), 7.46 (1H, s, H-2), 7.62 (1H, d, $J=2.0$ Hz, H-6′), 7.65 (1H, d, $J=3.5$ Hz, H-2′), 8.22 (1H, d, $J=2.0$ Hz, H-8), and 8.23 (1H, d, $J=2.0$ Hz, H-8′).

7-[2-(3-Guaiazulenyl)-1-methylethyl]-1,4-dimethylazulene (16): Blue prisms; 1 mg (3%); mp 117 °C; $R_f=0.71$; UV λ_{max} (MeOH) 246, 285, 307,^{sh} 352, 369, and 613 nm (log ε 4.60, 4.65, 4.52, 3.76, 3.74, and 3.03); ^{1}H NMR $\delta=1.35$ (6H, d, $J=7.0$ Hz, *i*-Pr-7′), 1.37 (3H, d, $J=7.0$ Hz, CH_3CH-7), 2.55 (3H, s, Me-1), 2.61 (3H, s, Me-1′), 2.84 (3H, s, Me-4), 2.99 (3H, s, Me-4′), 3.01 (1H, sept, $J=7.0$ Hz, Me$_2$CH-7′), 3.24 (1H, dqd, $J=8.5$, 7.0, 6.0 Hz, CH-7), 3.46 (1H, dd, $J=14.5$, 8.5 Hz, CH–C-7), 3.66 (1H, dd, $J=14.5$, 6.0 Hz, CH–C-7), 6.82 (1H, d, $J=10.5$ Hz, H-5′), 6.99 (1H, d, $J=10.5$ Hz, H-5), 7.23 (1H, d, $J=4.0$ Hz, H-3), 7.25 (1H, dd, $J=10.5$, 2.0 Hz, H-6), 7.36 (1H, s, H-2′), 7.40 (1H, dd, $J=10.5$, 2.0 Hz, H-6′), 7.62 (1H, d, $J=4.0$ Hz, H-2), 8.03 (1H, d, $J=2.0$ Hz, H-8), and 8.16 (1H, d, $J=2.0$ Hz, H-8′); EI MS m/z 394 (M$^+$; 6%), 211 (100), 195 (4), 183 (9), 165 (4), 153 (4), and 44 (4).

2-(3-Guaiazulenyl)-3,7-dimethyl-1*H*-inden-1-one (18): Dark red paste; 2 mg (5%); $R_f=0.64$; UV λ_{max} (MeOH) 248, 283, 307,^{sh} 352, 368,^{sh} 458, and 490 nm (log ε 4.53, 4.50, 4.45, 3.65, 3.66, 3.39, and 3.38); IR (CHCl$_3$) 1695 cm^{-1} (C=O); ^{1}H NMR $\delta=1.33$ (6H, d, $J=7.0$ Hz, *i*-Pr-7′), 2.08 (3H, s, Me-3), 2.56 (3H, s, Me-7), 2.64 (3H, s, Me-4′), 2.66 (3H, s, Me-1′), 3.06 (1H, sept, $J=7.0$ Hz, Me$_2$CH-7′), 6.93 (1H, d, $J=11.0$ Hz, H-5′), 6.98 (1H, brd, $J=7.5$ Hz, H-6), 7.01 (1H, brd, $J=7.5$ Hz, H-4), 7.27 (1H, t, $J=7.5$ Hz, H-5), 7.35 (1H, dd, $J=11.0$, 2.0 Hz, H-6′), 7.40 (1H, s, H-2′), and 8.14 (1H, d, $J=2.0$ Hz, H-8′); EI MS m/z 354 (M$^+$; 100%), 339 (19), 321 (4), 309 (6), 296 (5), 279 (5), 265 (5), 253 (6), 239 (4), 177 (3), and 165 (4).

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6) Compound **8**: Dark green prisms; 1 mg (1%); mp 205 °C; $R_f=0.43$; IR (CHCl$_3$) 1705, 1675, and 1570 cm^{-1} (C=O); ^{1}H NMR $\delta=2.18$ (6H, s), 2.35 (3H, s), 2.61 (3H, s), 2.86 (3H, s), 3.18 (3H, s), 6.53 (1H, s), 6.93 (2H, s), 6.96 (1H, brs), 6.99 (1H, brs), and 7.78 (1H, s); EI MS m/z 384 (M$^+$; 85%), 356 (3), 341 (4), 313 (6), 209 (7), 185 (6), 165 (13), 147 (100), 119 (23), and 91 (4). Found: m/z 384.1704. Calcd for $C_{26}H_{24}O_3$: M, 384.1725.

7) H. S. Mosher, L. Turner, and A. Carlsmith, *Org. Synth.*, Coll. Vol. IV, 828 (1963).

8) Hydrogen peroxide alone does not normally react with nitrogen-containg heteroaromatic compounds such as pyridine: see e.g., A. R. Katritzky and J. M. Lagowski, "Chemistry of the Heterocyclic N-Oxides," Academic Press, New York (1971), p. 56.

9) We are grateful to Konan Kako Co. (Osaka) for a generous gift of 4,6,8-trimethylazulene and guaiazulene.