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Structure for the "Biguaiazulene-3,3′-dione" and Efficient Preparation of 5-Isopropyl-3,8-dimethyl-1,7-azulenedione[1)]

Yoshiharu MATSUBARA,* Masanori MORITA,† Shuichi MATSUI, Shin-ichi TAKEKUMA,
Hiroshi YAMAMOTO,*,†† Shunji ITO,††† Noboru MORITA,†††
Toyonobu ASAO,††† and Tetsuo NOZOE††††
Department of Applied Chemistry, Faculty of Science and Engineering,
Kinki University, Kowakae, Higashi-Osaka 577
†Research Institute for Science and Technology, Kinki University, Kowakae, Higashi-Osaka 577
††Department of Chemistry, Okayama University, Okayama 700
†††Department of Chemistry, College of General Education, Tohoku University, Kawauchi, Sendai 980
††††Tokyo Research Laboratories, Takasago Corporation, Kamata, Ohta-ku, Tokyo 144

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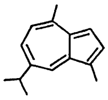
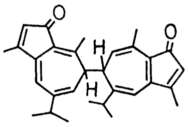
Synopsis. The dimeric compound formed from 3-guaiazulenol has been found to be identical with the main product (Q_2) of the peracid oxidation of guaiazulene, thus the previous structure of Q_2 being revised to be a ca. 1 : 1 mixture of meso (5*R*,5′*S*) and two enantiomeric (5*R*,5′*R* and 5*S*,5′*S*) forms of [5,5′-biguaiazulene]-3,3′(5*H*,5′*H*)-dione. Autoxidation of Q_2 in pyridine at 25 °C for 1 d mainly gives the title 1,7-azulenedione.

It was reported[2)] that the oxidation of guaiazulene (**1**) with peracetic acid in hexane at 25 °C for 1 h exclusively gave a dimeric 3-guaiazulenone (Q_2; 80%) together with minor products (2.4%) such as 1,7-guaiazulenedione[3)] (**3**; 0.1%) and quinonemethide **4**[2,4)] (0.1%). Structure of [5,6′-biguaiazulene]-3,3′(5*H*,6′*H*)-dione (**2**) was assigned to the major product on the basis of the UV, IR, MS, and ^{1}H NMR (270 MHz) spectra.[2)] Meanwhile, during the course of a systematic study on hydroxyazulenes and azulenethiols, one of us (T. A.) and his co-workers[5)] have recently prepared 3-guaiazulenol (**5**)[6)] by the reduction of 3-guaiazulenyl acetate with $LiAlH_4$. They noticed that **5** was unstable and changed to a mixture of 3(3a*H*)-guaiazulenone and a dimer on standing in ether. Based on the NMR data, they suggested their specimen of the dimer to be a mixture of meso and enantiomeric forms **6a** and **6b**.[5)] As we found then that the ^{1}H NMR and IR spectra of the dimer turned out to be almost superimposable with those of Q_2, we wish to describe herein detailed structural determination of the dimer, together with revision of the previous structure **2**. Also reported are some additional reactions of Q_2 to further prove the importance of this unstable, key intermediate for the oxidation of **1**.[2,3,7)]

The 2D ^{1}H NMR spectrum (in $CDCl_3$ of Q_2 ($C_{30}H_{34}O_2$ by FAB-MS)[2)] has now clearly disclosed the exact coupling interrelation of all signals, thus indicating the presence of two independent, different 3-oxo-3,5-dihydroguaiazulen-5-yl moieties in a ratio of almost 1 : 1. In particular, the absence of $J_{5,5'}$ value, which had been erroneously assigned to be 0.8 Hz (as $J_{5,6'}$ in formula **2**) owing to the insufficient separation of H-5 and H-5′ signals at 270 MHz,[2)] eliminated the previously proposed structure **2**. A careful study of the set of *J* values of H-5, H-6, and H-8 signals has led us to a ca. 2 : 1 : 1 mixture of meso and two enantiomeric forms of [5,5′-biguaiazulene]-3,3′(5*H*,5′*H*)-diones[5)] (**6a** and **6b**; Chart 1) for the structure of Q_2.



1



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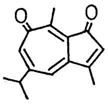

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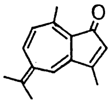

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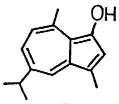

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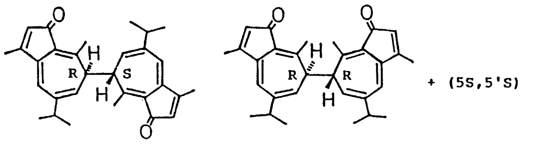
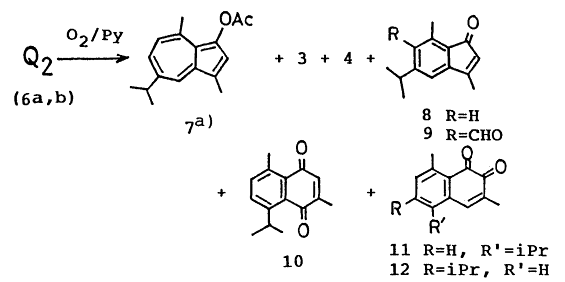


6a (meso) 6b (enantiomers)

Chart 1. Revised structures for Q_2.

An inspection of the molecular models of the most favorable conformations suggested that in the meso form **6a** an anisotropic effect exerted by the O=C(3)–C(3a)=C(4) plane region of the other moiety is likely to cause a slight upfield shift of the 7-isopropyl signals, whereas in the enantiomers **6b** the same effect would cause a slight upfield shift of the 4-methyl signal. This enabled us to make the most plausible assignment of all signals of these two compounds (see the Exptl section).

The ^{1}H NMR spectrum of Q_2 in pyridine-d_5 (measured within 1 h after having been dissolved) closely resembles that in $CDCl_3$, except for a slight downfield shift (0.2—0.3 ppm) for Me-4, H-5, and H-8 signals and a better separation of some signals in the former solvent, thus confirming Q_2 as a ca. 1 : 1 mixture of **6a** and **6b**; for the assignment of all signals, see the Exptl section. However, it has been observed during the NMR measurement in pyridine-d_5 that Q_2 gradually begins to decompose to give an appreciable amount (ca. 25% after 2 h at 27 °C) of a 3-guaiazulenyl derivative besides many other minor products (mostly benzenoids). The signals of this major product distinctly observable at δ 1.26 (d, J=7.0 Hz, Me_2C-7), 2.61 (s, Me-1), 2.82 (sept, J=7.0 Hz, HC-7), 3.21 (s, Me-4), 6.42 (d, $J_{5,6}$=10.5 Hz, H-5), 7.05 (dd, $J_{6,8}$=1.3 Hz, H-6), 7.44 (br s, H-2), and 7.93 (d, H-8) were best interpreted as the



Scheme 1. Autoxidation of Q_2 in pyridine. a) Obtained after treatment with Ac_2O/Py.

formation of unstable **5** by the comparison of its spectrum in acetone-d_6 (at −50 °C).[5]

Therefore, we have undertaken a study of autoxidation of Q_2 in pyridine. When the reaction was interrupted at an earlier stage (after 15 min at 25 °C) and then the reactant was treated with acetic anhydride, the following products were isolated besides resinous tar (ca. 50% w/w) after chromatographic separation: 3-guaiazulenyl acetate **7**[5] (12%), **3** (5%), and **4** (5%) (Scheme 1). In contrast, autoxidation of Q_2 in pyridine at 25 °C for 24 h gave **3** in 46% yield besides other minor products such as **4** (0.8%), indenones **8**[3] (6%) and **9**[3] (1%), and naphthoquinones **10**[2] (5%), **11**[3] (4%), and **12**[3] (6%). It should be noted that the same oxidation of Q_2 in $CHCl_3$ afforded[2] **4**, **8**, and 3(5*H*)-guaiazulenone as the major products but **3** only in 0.4%. Although autoxidation of another important compound **4** (readily available from Q_2)[2,4] was also studied in pyridine, the kinds and yields of the isolated products were essentially similar to those obtained in $CHCl_3$,[2] the major product being **9** (55%).

As the 3-guaiazulenone dimer Q_2 and quinonemethide **4** are considered[2] to be highly important key intermediates for the major reaction pathways for autoxidation of **1** to give a wide variety of interesting products, the present findings are believed to provide further valuable information on the reaction mechanism of oxidation of azulenic hydrocarbons. Moreover, the efficient preparative method of **3** in pyridine enables us to investigate more properties of azulenediones in detail, which draw interest in recent years in view of potential utility of their properties even with conductivity and biological activity.[8]

Experimental

The preparative procedures described in our previous papers[2,3] were followed in general. ^{1}H NMR spectra were recorded in $CDCl_3$ or pyridine-d_5 with a JEOL-GX500 cryospectrometer (500 MHz) at 27 °C.

(5*R*,5′*S*)-[5.5′-Biguaiazulene]-3,3′(5*H*,5′*H*)-dione (6a). This compound was obtained as a ca. 1 : 1, chromatographically inseparable mixture (Q_2) with **6b** (see below) by the peracid oxidation of **1**:[2] a pale yellow powder, mp 138—142 °C decomp (lit.[2] 138—142 °C); ^{1}H NMR[9] ($CDCl_3$) δ=1.02, 1.075 (6 H each, d, J=7.0 Hz, Me_2C-7,7′), 2.24 (6 H, d, $J_{Me,2}$=1.2 Hz, Me-1,1′), 2.275 (6 H, s, Me-4,4′), 2.43 (2 H, sept, J=7.0 Hz, HC-7,7′), 3.34 (2 H, dd, $J_{5,6}$=6.0 Hz, $J_{5,6'}$=2.5 Hz, H-5,5′), 5.28 (2 H, dd, $J_{6,8}$=0.8 Hz, H-6,6′), 5.98 (2 H, br s, H-2,2′), and 6.375 (2 H, br d, H-8,8′), (C_5D_5N) δ=1.035, 1.055 (6 H each, d, J=7.0 Hz, Me_2C-7,7′), 2.205 (6 H, d, $J_{Me,2}$=1.2 Hz, Me-1,1′), 2.42 (2 H, sept, J=7.0 Hz, HC-7,7′), 2.54 (6 H, s, Me-4,4′), 3.50 (2 H, dd, $J_{5,6}$= 6.0 Hz, $J_{5,6'}$=2.5 Hz, H-5,5′), 5.36 (2 H, dd, $J_{6,8}$=0.8 Hz, H-6,6′), 6.13 (2 H, br s, H-2,2′), and 6.60 (2 H, br d, H-8,8′). Other spectra of Q_2 are identical with those reported in the previous papers.[2]

(5*R*,5′*R*)- and (5*S*,5′*S*)-[5,5′-Biguaiazulene]-3,3′(5*H*,5′*H*)-dione (6b). This compound was a 1 : 1 enantiomeric mixture; ^{1}H NMR[9] ($CDCl_3$) δ=1.09, 1.115 (6 H each, d, J=7.0 Hz, Me_2C-7,7′), 2.13 (6 H, s, Me-4,4′), 2.25 (6 H, d, $J_{Me,2}$=1.2 Hz, Me-1,1′), 2.48 (2 H, sept, J=7.0 Hz, HC-7,7′), 3.30 (2 H, dd, $J_{5,6}$=6.0 Hz, $J_{5,6'}$=2.5 Hz, H-5,5′), 5.26 (2 H, dd, $J_{6,8}$=0.8 Hz, H-6,6′), 5.985 (2 H, br s, H-2,2′), and 6.385 (2 H, br d, H-8,8′), (C_5D_5N) δ=1.16, 1.165 (6 H each, d, J=7.0 Hz, Me_2C-7,7′), 2.21 (6 H, d, $J_{Me,2}$=1.2 Hz, Me-1,1′), 2.40 (6 H, s, Me-4,4′), 2.52 (2 H, sept, J=7.0 Hz, HC-7,7′), 3.54 (2 H, dd, $J_{5,6}$=6.0 Hz, $J_{5,6'}$=2.5 Hz, H-5,5′), 5.39 (2 H, dd, $J_{6,8}$=0.8 Hz, H-6,6′), 6.165 (2 H, br s, H-2,2′), and 6.61 (2 H, br d, H-8,8′).

Oxidation of the 3-Guaiazulenone Dimer Q_2. A. A solution of Q_2 (20 mg) in pyridine (2 ml) was stirred for 15 min at 25 °C under aerobic conditions. Acetic anhydride (3 ml) was slowly added and the stirring was continued for 30 min. The reactant was treated with 10% aq $CuSO_4$ (50 ml), carefully neutralized with aq Na_2CO_3, and extracted with hexane (50 ml). The extract was washed with water, dried (Na_2SO_4), and evaporated in vacuo. The residue was purified by chromatography, giving the following products, whose structures were confirmed by comparison of the EI-MS with those of the authentic samples: **7** (12%), **3** (5%), and **4** (5%).

B. When the solution of Q_2 was allowed to stand for 24 h and the reactant was similarly worked up, the following products were isolated: **3** (46%), **4** (0.8%), **8** (6%), **9** (0.8%), **10** (5%), **11** (4%), and **12** (6%).

References

1) A part of the results were presented at the 58th Meeting of the Chemical Society of Japan, Kyoto, April 1989, Abstr., No. 3IIIA30 and 3IIIA31.

2) Y. Matsubara, S. Matsui, S. Takekuma, H. Yamamoto, and T. Nozoe, *Nippon Kagaku Kaishi*, **1988**, 1704; Y. Matsubara, S. Matsui, S. Takekuma, Y. P. Quo, H. Yamamoto, and T. Nozoe, *Bull. Chem. Soc. Jpn.*, **62**, 2040 (1989).

3) Y. Matsubara, S. Takekuma, K. Yokoi, H. Yamamoto, and T. Nozoe, *Bull. Chem. Soc. Jpn.*, **60**, 1415 (1987) and references cited therein.

4) Compound **4** is quantitatively obtained from Q_2 on heating in $CHCl_3$ at 60 °C under nitrogen (Ref. 2).

5) T. Asao, S. Ito, and N. Morita, *Tetrahedron Lett.*, **30**, 6693 (1989); details of preparation and reactions of **5** will be reported elsewhere together with those of other azulenols.

6) G. Chiurdoglu and R. Fuks, *Tetrahedron Lett.*, **1963**, 1715; R. Fuks and G. Chiurdoglu, *Bull. Soc. Chim. Belqes*, **76**, 244 (1967); they reported that Dakin reaction on 3-formylguaiazulene gave, via **5**, 3(3a*H*)-guaiazulenone, which existed with its tautomer 3(2*H*)-guaiazulenone in solution. We found, however, that the compound was identical with a mixture of dimers **6a** and **6b** (Ref. 5).

7) S. Takekuma, Y. Matsubara, H. Yamamoto, and T. Nozoe, *Bull. Chem. Soc. Jpn.*, **61**, 475 (1988).

8) L. T. Scott, M. D. Rozeboom, K. N. Houk, T. Fukunaga, H. J. Lindner, and K. Hafner, *J. Am. Chem. Soc.*, **102**, 5169 (1980), and references cited therein.

9) The assignments of all signals were made by employing a first-order analysis with the aid of decoupling technique and two-dimensional COSY measurements. However, the assinments of a few of the respective ring-proton and methyl signals of **6a** and **6b** may have to be interchanged between them.