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Autoxidation of Guaiazulene and 4,6,8-Trimethylazulene in Polar Aprotic Solvent: Structural Proof for Products[1)]

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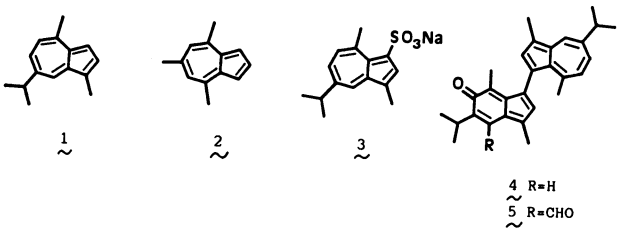
Autoxidation of guaiazulene and 4,6,8-trimethylazulene at 100—120 °C in DMF (or HMPA) respectively yielded 25 and 17 separable products, including several known compounds. Most of these new compounds were derivatives of 1,5- and 1,7-azulenequinone, 1*H*-inden-1-one, naphthoquinone, and benzenoid, or dimeric and trimeric forms; structures of these products were established on the basis of spectroscopic (NMR, UV, IR, and MS) and half-wave potential ($E_{1/2}$) data. ^{1}H NMR (200-MHz) parameters of various azulene derivatives are given for comparative study. Possible reaction pathways are suggested for the formation of such a wide variety of interesting products.

Azulene and its derivatives constitute a highly interesting class of compounds due to the fused five-seven bicyclic aromatic ring system. Thus azulenes have been regarded as one of the representative examples of nonbenzenoid aromatic hydrocarbons, which usually do not undergo Diels-Alder-type addition reactions but are easily susceptible to many electrophilic substitution reactions (most easily at the 1 and/or 3 position).[2)]

It has been long-known that some azulenes gradually suffer oxidation even on exposure to air at room temperature and this air oxidation is facilitated by light. Pailer and Lobenwein[3)] have found that, when adsorbed on the surface of silic gel and exposed to air, naturally originating guaiazulene (**1**) gave three major products: 3,3′-biguaiazulene (**1B**, see below) and two guaiazulenylindenones for which the 5*H*-inden-5-one structures (**4**, **5**) were presented. Precise studies on the facile autoxidation of azulenes (especially **1**) are exceedingly of interest in view of preparation of a number of pharmacologically important azulenes because of the fact that a clinically used anti-inflammatory sodium guaiazulene-3-sulfonate (**3**), for example, gradually decomposes on standing but is stabilized by the presence of oxygen-absorbers in the tablet package.[4)] Moreover, information on a general aspect of the reaction mechanism of oxidation of azulenes would be important in exploiting an expedient conversion of azulenes directly to many valuable compounds such as polyazulenes[5)] and azulenequinones,[6)] syntheses of which are currently drawing an increasing interest because of the potential utility of their physicochemical properties as well as biological activity. In this paper, by employing two trialkylazulenes [**1** and 4,6,8-trimethylazulene[7)] (**2**)] as model compounds, we wish to describe the first detailed study on autoxidation of azulenes, together with presumable reaction pathways for the formation of a wide variety of the products, most of which possess highly interesting structures.



Results and Discussion

Autoxidation of Guaiazulene (1). The oxidation was carried out by passing finely bubbling oxygen into a solution of the substrate **1** in DMF (or HMPA) at 100 °C. When the reaction was monitored by the use of silica-gel TLC and the reversed phase high-pressured liquid chromatography (HPLC), simultaneous formation of more than twenty kinds of products was observed over a period of 24 h (see Fig. 1). In order to examine an earlier stage of the oxidation, the reaction products were separated into each component by using chromatography, when about a half of the starting material was consumed. The products thus obtained as pure components (25 altogether besides the recovered starting material **1**) are referred to as Compounds **1A—S** according to their decreasing R_f values on silica-gel TLC (developed with 15 : 85 AcOEt-hexane); when more than two products are separated from the same fraction by using a different kind of solvent system, they are further distinguished by a subscript number (see Fig. 1).

In Chart I are summarized structures of these products which were established by UV-visible, IR, high-resolution mass (MS), and ^{1}H NMR (and ^{13}C NMR for some compounds) spectroscopy as will be explained below. The theoretical yields of these isolated products (see Experimental Section) totaled to 54%; besides these, there still remained ca. 34% (w/w) yield of unidentified resinous polar products of rather high molecular weights.

Compound $\mathbf{1A}_1$ was the unreacted starting material **1** from the spectroscopic and chromatographic data.

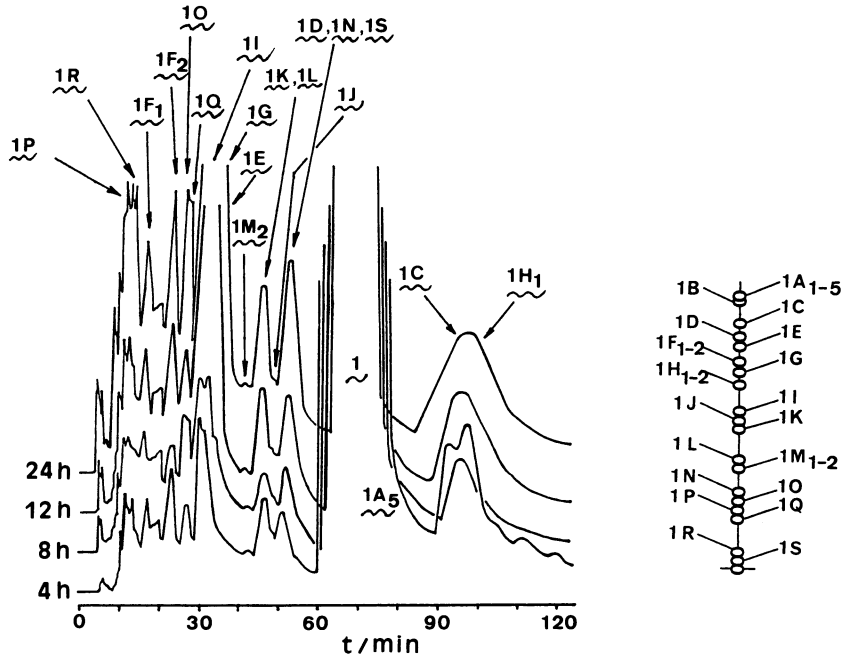


Fig. 1. Time-dependent HPLC diagram of autoxidation of **1** in DMF at 100 °C and TLC diagram of the oxidation products from **1**.

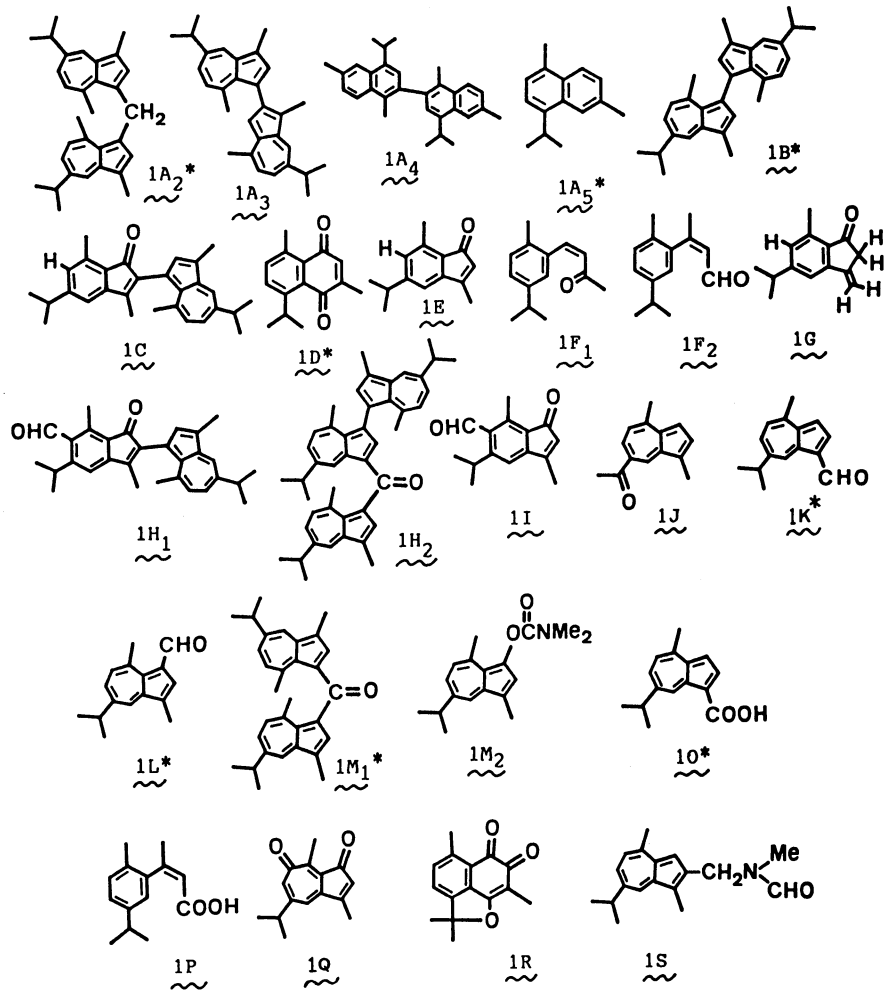


Chart 1. Structures of autoxidation products of guaiazulene (**1**); *Previously known compounds.

Table 1. ^{1}H NMR (200 MHz) Parameters for Azulene Derivatives[a)]

Compd	H-1 (H-1′)	H-2 (H-2′)	H-3 (H-3′)	Me-4 (Me-4′)	H-5 (H-5′)	H-6 (H-6′)	H-7 (H-7′)	H-8 (H-8′)	J (J)
1	2.66[b)]	7.61	7.21	2.83	7.00	7.41	1.36, 3.08[c)]	8.19	d, e, f)
1A$_2$	2.52[b)]	7.10	5.21[g)]	2.93	6.78	7.24	1.34, 3.01[c)]	8.05	e, f)
1A$_3$	2.35[b)]	—	7.35	2.81	7.04	7.36	1.38, 3.08[c)]	8.20	e, f)
	(2.70)[b)]	(7.56)	—	(2.48)	(6.89)	(7.35)	(1.38, 3.10)[c)]	(8.18)	(e, f)
1B	2.68[b)]	7.46	—	2.18	6.78	7.29	1.39, 3.07[c)]	8.18	e, f)
1J	2.74[b)]	7.66	7.50	2.87	7.04	8.18	2.74[h)]	8.98	d, e, f)
1K	10.32[i)]	8.17	7.26	2.93	7.49	7.72	1.41, 3.24[c)]	9.72	d, e, f)
1L[j)]	2.56[b)]	8.19	10.56[i)]	3.13	7.38	7.55	1.38, 3.15[c)]	8.25	e, f)
1M$_1$[j)]	2.56[b)]	7.73	—	2.92	7.29	7.56	1.39, 3.14[c)]	8.28	e, f)
1M$_2$[j)]	2.60[d)]	7.35	k)	2.82	6.70	7.21	1.32, 2.98[c)]	8.03	e, f)
1O	1.59[l)]	8.39	7.25	2.94	7.45	7.70	1.42, 3.25[c)]	9.81	d, e, f)
1Q[j)]	2.29[b)]	6.23	—	2.64	—	6.76	1.26, 2.76[c)]	6.63	f, m, n)
1S	2.55[b)]	o)	7.38	2.88	6.86	7.29	1.32, 3.02[c)]	8.05	e, f)
2	7.34	7.64	7.34	2.88	7.05	2.62[b)]	7.05	2.88[b)]	d)
2A$_2$	5.16[g)]	7.14	7.03	2.77	6.83	2.52[b)]	6.80	2.93[b)]	d, p)
2F	7.50	7.92	7.50	3.02	7.64	10.06[i)]	7.64	3.02[b)]	d)
2G	6.67[q)]	7.27	7.22	2.82	6.91	2.55[b)]	6.97	2.95[b)]	d, p)
2I	—	6.38	8.06	2.33	7.09	2.27[b)]	—	2.65[b)]	d, r)
2J	—	6.25	7.94	2.31	—	2.24[b)]	7.04	2.60[b)]	d)
2K$_1$	10.64[i)]	8.28	7.30	2.92	7.38	2.68[b)]	7.40	3.18[b)]	d, p)
2K$_3$	—	7.96	7.16	2.90	7.38	2.71[b)]	7.47	3.18[b)]	d, p)
2L	s)	7.13	7.09	2.74	6.72	2.52[b)]	6.77	2.94[b)]	d, p)
2M (a)	7.29	t)	7.45	2.84	7.00	2.60[b)]	7.00	2.96[b)]	
2M (b)	7.31	t)	7.49	2.84	7.02	2.59[b)]	7.02	2.95[b)]	

a) Chemical shifts (δ) are parts per million from Me_4Si measured in $CDCl_3$ (concn <ca. 0.5% v/v). Coupling constants (J, Hz) were confirmed by double resonance. b) Me. c) *i*-Pr; J=7.0 Hz. d) $J_{2,3}$=4.0 Hz. e) $J_{5,6}$=11.0 Hz. f) $J_{6,8}$=2.0 Hz. g) CH_2. h) Ac. i) CHO. j) For the purpose of comparison, the numbering of this compound corresponds to that of the starting material. k) δ 3.05 and 3.17 (both 3H, s, Me_2NCOO-3). l) COOH. m) $J_{2,8}$=0.5 Hz. n) $J_{Me(1),2}$=1.5 Hz. o) There exist a set of three singlets (3:2:1) due to (-CH_2NMeCHO) at (**a**) δ 2.82, 5.00 and 8.13, (**b**) δ 2.72, 5.11 and 8.13, **a** and **b** being a 3:2 mixture due to restricted rotation of the C-N bond in the amide group; a large number of similar patterns are observed for many amide, e.g., see A. Mannschreck, *Tetrahedron Lett.* **1965**, 1341. p) $J_{5,7}$= 0.5 Hz. q) OHCCH-1; also present is a doublet at δ 10.06 (1H, J=2.3 Hz, CHO). r) $J_{5,Me(6)}$=1.5 Hz. s) There singlets (3:2:1) due to (-CH_2NMeCHO) at δ 3.08, 5.25, and 8.23. t) A set of there singlets (3:2:1) due to (-CH_2NMeCHO) at (**a**) δ 2.88, 5.07, and 8.21, (**b**) 2.77, 5.16 and 8.21, **a** and **b** being a 3:2 mixture; see Ref. in o).

For the purpose of comparison in determining the structures of the oxidation products, the 200-MHz ^{1}H NMR parameters for **1** and other important azulene derivatives obtained in the present study are summarized in Table 1, although slightly different values have been reported for a few of these azulenes (mostly measured at 60-MHz in much concentrated CCl_4 or CH_2Cl_2 solutions).[3,8)] Compound **1A$_2$**, one of the major products of this oxidation, was spectroscopically (MS and ^{1}H NMR) identical with known 3,3′-methylenebisguaiazulene.[9)] While the chemical shifts of other signals of **1A$_2$** closely resembled those of **1**, an appreciable upfield shift (δ ca. 0.5) was observed for the H-2 signal (see Table 1) presumably due to an electronic as well as an anisotropic effect by a nonplanar conformation of the two azulene nuclei owing to the steric repulsion.

Compound **1A$_3$** was shown to have a composition of $C_{30}H_{34}$ by MS and the structure of 2,3′-biguaiazulene was assigned to this minor product by the careful comparison of the ^{1}H NMR spectral data (see Table 1), as well as their melting points, with those of the reported 2,2′- and 3,3′-biguaiazulenes.[10)] Compound **1B** was confirmed by spectroscopy to be identical with 3,3′-biguaiazulene;[3,10)] an appreciable upfield shift (δ ca. 0.65) for Me-4 signal in the ^{1}H NMR spectrum (see Table 1) by the same reason as described for **1A$_2$** should be noticed.

Compounds **1A$_5$** ($C_{15}H_{18}$) and **1A$_4$** ($C_{30}H_{34}$ by MS) were shown spectroscopically to be 4-isopropyl-1,6-dimethylnaphthalene (cadalene) and its 2,2′-dehydro dimer, respectively. The assignment of the oxidative coupling position of the new naphthalene dimer **1A$_4$** was based on the ^{1}H NMR data (see the Experimental Section). Compounds **1D** and **1R** were identified by MS, IR, UV, and NMR spectroscopy to be 8-isopropyl-2,5-dimethyl-1,4-naphthoquinone[11)] and the 1,2-naphthoquinone derivative,[11b)] respectively, both of which had been obtained by autoxidation of **1A$_5$** under the same conditions.[11b)]

Compound **1C** ($C_{29}H_{32}O$) and **1H$_1$** ($C_{30}H_{32}O_2$ by MS) appeared to be identical (by ^{1}H NMR) with the autoxidation products which had been obtained[3)] from **1** by autoxidation on the surface of silica gel and respectively assigned to be the 3-guaiazulenyl-5*H*-inden-5-one derivatives **4** and **5**. The 1*H*-inden-1-one structures **1C** and **1H$_1$**, however, were apparently more compatible with the observed spectral data, taking into account the spectral parameters for the related 1*H*-inden-1-one derivatives **1E** and **1I**, as well as consider-

ing the mode of formation of these products from **1** (see later); the corrected assignments of the 200-MHz ^{1}H NMR data of **1C** and **1H$_1$** are shown in the Experimental Section.

Compounds **1E** and **1G** (both $C_{14}H_{16}O$ by MS) turned out to be non-azulenic compounds (by UV) but contained a conjugated carbonyl group (IR). Structures of 1*H*-inden-1-one (**1E**) and the prototropic isomer 2,3-dihydro-3-methylene-1*H*-inden-1-one (**1G**) were assigned to these products by taking into consideration the reported ^{1}H NMR data of structurally related parent 1*H*-inden-1-one[12] and 2,3-dihydro-3-alkylidene-1*H*-inden-1-ones.[13] It has been noted that 1*H*-inden-1-one (**1E**) was converted to **1G** gradually on standing (or more quickly when dissolved in $CDCl_3$) at 25 °C, and then slowly gave four kinds (by TLC and GC-MS) of colorless dimers.[14] The lability of these indenones **1E** and **1G** are in analogy with the case of the parent 1*H*-inden-1-one which has been recorded to dimerize quickly at room temperature.[12] Compound **1I** ($C_{15}H_{16}O_2$ by MS) were assigned to the 6-formyl derivative of **1E** on the basis of IR and ^{1}H NMR spectra. Interestingly, this monoformyl compound has been found, on standing at 25 °C, to rearrange to the diformyl compound **1N** (see below). The assignments of the NMR data, which are in good agreement with the proposed structures **1E**, **1G**, and **1I**, are recorded in the Experimental Section.

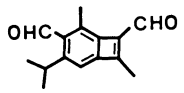
Compounds **1F$_1$** and **1F$_2$** (both $C_{14}H_{18}O$ by MS) were found spectroscopically to be both benzenoid derivatives, namely (*Z*)-4-(5-isopropyl-2-methylphenyl)-3-buten-2-one and (*Z*)-3-(5-isopropyl-2-methylphenyl)-2-butenal, respectively. Compound **1P** was the corresponding carboxylic acid of **1F$_2$** on the evidences of the MS, UV, IR, and NMR spectra (Experimental Section). The (*Z*) configuration of **1F$_1$** was derived from the magnitude of the medium $J_{3,4}$ value (11.0 Hz), while the same (*Z*) configuration of **1F$_2$** and **1P** were decided on the basis of the close similarity in the UV absorption maximums (and the δ values of H-2 and H-6′) between **1F$_1$** and **1F$_2$**/**1P**.

Compound **1H$_2$** was an extremely minor product which possessed a trimeric composition of $C_{45}H_{48}O$ (by MS) and a carbonyl group (1720 cm^{-1}) attached to C-1 of a guaiazulene nucleus (UV λ_{max} 538 nm). Although its NMR data were not available because of the limited amount of the material, the structure of **1H$_2$** shown in Chart 1 is proposed for this compound from the above spectral data and also by considering the most favorable mode of oxidative trimerization of guaiazulene.

Compound **1J** possessed an acetyl group (instead of an isopropyl) conjugated to the azulene nucleus (by UV, IR, and ^{1}H NMR). Structure of 7-acetyl-1,4-dimethylazulene was therefore assigned to this extremely minor product; see Table 1 for the NMR parameters for **1J**. Compounds **1K** and **1O** were indentified spectroscopically as 7-isopropyl-4-methyl-1-azulenecarbaldehyde and the corresponding carboxylic acid derivative, respectively.[15] Compound **1L** was found to be also the known 3-formyl derivative[15,16] of **1** on the basis of spectral data. The 200-MHz ^{1}H NMR parameters for these compounds are given in Table 1.

Compound **1M$_1$** was spectroscopically identical with bis(3,3′-guaiazulenyl) ketone;[17] although Fry et al.[18] have reported 60-MHz ^{1}H NMR data, more precise 200-MHz parameters for this compound are given in Table 1. Compound **1M$_2$** ($C_{18}H_{23}NO_2$ by MS) contained a dimethylcarbamoyloxy group attaching to guaiazulene nucleus on the evidence of the UV, IR, and ^{1}H NMR data (Table 1). The position (C-3) of the carbamoyl group on the guaiazulene nucleus was derived from the close resemblance of the visible absorption maximums (634 and 654 nm) with those of structurally similar 1-azulenyl benzoate (610 and 644 nm),[19] as well as by judging from the appearance of H-2 signal at relatively low field (7.35) in the NMR spectrum.

Compound **1N**, which is a structural isomer (by MS) of **1I** (see above), contained two formyl groups (1715 and 1700 cm^{-1}; δ 10.56 and 10.68, both singlets) and only one aromatic proton (δ 7.02, singlet), in addition to two methyl (δ 2.68 and 2.90, singlets) and an isopropyl (δ 1.28 and 3.65) groups. The UV spectra (λ_{max} 269, 317, 344, and 418 nm) suggested no azulenyl structure in the molecule. This compound was stable even in air when kept as solid at below 5 °C, but in a $CHCl_3$ solution at 25 °C **1N** gradually gave four kinds (by TLC and GC) of colorless dimers.[14],*



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Compound **1Q** ($C_{15}H_{16}O_2$ by MS) was assigned to 5-isopropyl-3,8-dimethyl-1,7-azulenequinone on the evidences of UV, IR, NMR spectral data which were in conformity with the reported values of parent 1,7-azulenequinone;[6d] the assignments of the ^{1}H and ^{13}C NMR data are shown in Table 1 and Experimental Section, respectively. This compound is stable on standing at room temperature as in the case of the parent 1,7-azulenequinone.[6d] The quinone structure was confirmed by rather low values of the two half-wave potentials (E_1=−1.13 and E_2=−1.52 V) of **1Q** obtained by cyclic voltammetry.[20]

Compound **1S** was found to be a condensation product of **1** with a molecule of DMF; the position of the substitution at C-2 was derived by comparison of the ^{1}H NMR data (Table 1) with those of **2L** and **2M** (see later).

*For a possible structure of **1N** we tentatively suggested[1] 4-isopropyl-2,6-dimethylbenzocyclobutene-1,5-dicarbaldehyde (**6**). However, the precise structure for **1N** is currently under investigation in relation to those of the dimeric products.[14]

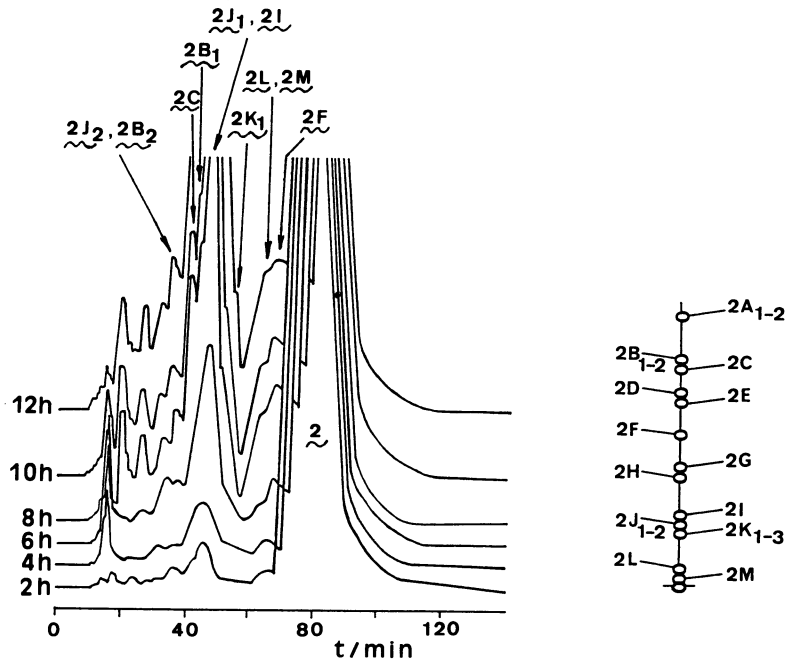


Fig. 2. Time-dependent HPLC diagram of autoxidation of **2** in DMF at 120°C and TLC diagram of the oxidation products from **2**.

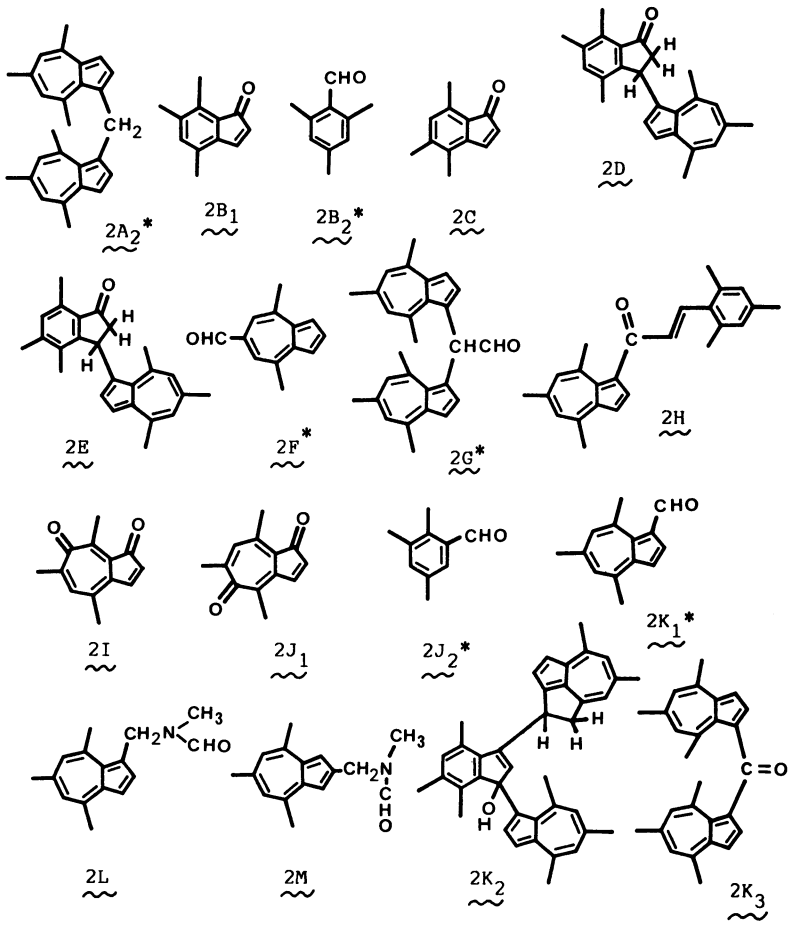


Chart 2. Structures of autoxidation products of 4,6,8-trimethylazulene (**2**); *Previously known compounds.

Autoxidation of 4,6,8-Trimethylazulene (2). The oxidation was carried out in DMF or HMPA at 120 °C for 12 h in a manner similar to that described for **1** and a complex HPLC diagram (Fig. 2) was also obtained, when the reaction was monitored by HPLC; in contrast to that of **1**, the oxidation of **2** took place very slow by at 100 °C. The resulting mixture (see TLC in Fig. 2) was carefully separated by using chromatography, and 17 products (**2A—M**) were obtained as pure components besides the recovered starting material **2** (**2A**$_1$). Structures of these products which have been established as follows are shown in Chart 2. The total theoretical yields of these isolated products were 28%, although there still remained a large amount (59% w/w) of unidentified polar products of relatively high molecular weights as well as a certain amount of inseparable **2**.

Compounds **2A**$_2$ ($C_{27}H_{28}$) and **2K**$_3$ ($C_{27}H_{26}O$ by MS) were readily found to possess structures 1,1′-methylenebis(4,6,8-trimethylazulene) and bis(4,6,8-trimethyl-1-azulenyl) ketone on the basis of their ^{1}H NMR data which closely resembled those of **1A**$_2$ and **1M**$_1$, respectively. The NMR parameters for these new compounds are summarized in Table 1.

Compounds **2B**$_1$ and **2C** (both $C_{12}H_{12}O$ by MS) were spectroscopically assignable to two isomers of 1*H*-inden-1-one having three methyl substituents on the six-membered ring: The structures were presumed to be 4,6,7-trimethyl- and 4,5,7-trimethyl-1*H*-inden-1-one, respectively, when the chemical shifts of the concomitant methyl and ring proton signals (δ 2.22 and 6.88 for **2B**$_1$ vs. δ 2.15 and 6.76 for **2C**) were compared in view of an electronic and anisotropic shift exerted by the carbonyl group on the five-membered ring. Assignments of the NMR data are given in the Experimental Section. Indenones **2B**$_1$ and **2C** both yielded three kinds of dimers[14] on standing at 20 °C.

Compounds **2B**$_2$ and **2J**$_2$ were identified as 2,4,6-[21] and 2,3,5-trimethylbenzaldehyde,[22] respectively, by spectroscopy (MS and NMR).

Compounds **2D** and **2E** (both $C_{25}H_{26}O$ by MS) consisted of a 4,6,8-trimethyl-1-azulenyl group and a 2,3-dihydro-1*H*-inden-1-one moiety having three methyl groups on the six-membered ring. The presence of ABX proton signals (at δ 2.7, 3.3, and 5.4—5.5) as well as a considerable upfield shift (δ ca. 1.0) of the Me-4 signal of the 1-azulenyl moiety indicated that the azulenyl group was linked to C-3 of the indenone moiety for both **2D** and **2E**. The chemical shifts of the singlets at δ 7.14 and 7.00 due to the aromatic six-membered ring proton of **2D** and **2E** suggested the structures of 4,6,7-trimethyl- and 4,5,7-trimethylindenone, respectively, for these products. The assignments of the NMR signals are recorded in the Experimental Section.

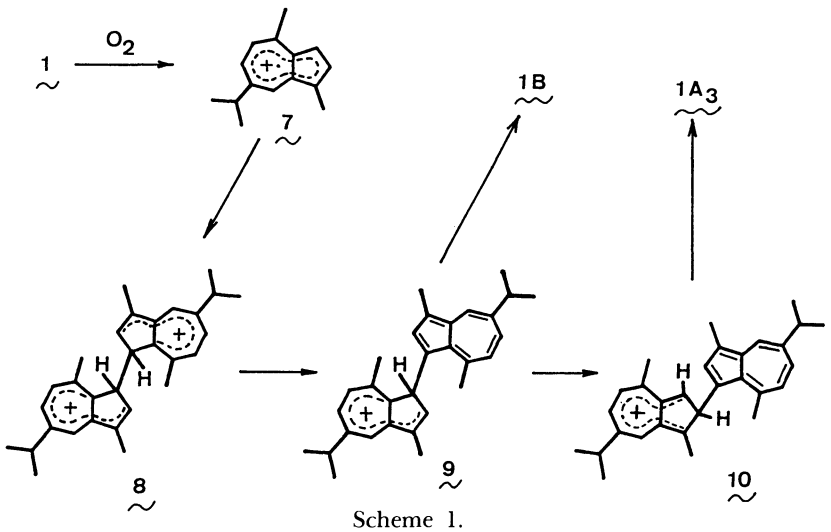
Compounds **2F**, **2G**, and **2K**$_1$ were identified by spectroscopy to be all known compounds, namely 4,8-dimethyl-6-azulenecarbaldehyde,[23] bis(4,6,8-trimethyl-1-azulenyl)acetaldehyde,[24] and 4,6,8-trimethyl-1-azulenecarbaldehyde,[16a] respectively; the 200-MHz ^{1}H NMR parameters for these products are summarized in Table 1. Compound **2H** ($C_{25}H_{26}$ by MS) contained a carbonyl group (1710 cm^{-1}) attached to C-1 of the 4,6,8-trimethylazulene moiety (from UV and ^{1}H NMR data). In addition, **2H** possessed a unique (*E*)-(2,4,6-trimethyl)styryl group linked to the carbonyl group on the ground of the NMR data; the (*E*) configuration was derived from the large *J* value (16 Hz) of the vinyl proton coupling; see Experimental Section for assignments of the NMR data.

Compounds **2I** and **2J**$_1$ (both $C_{13}H_{12}O_2$ by MS) were shown by the analysis of their spectroscopic data to be 4,6,8-trimethyl-1,7-azulenequinone and the corresponding 1,5-quinone, respectively. All data were in accord with those of the reported parent 1,7- and 1,5-azulenequinone[6d] as well as that of the trialkyl derivative **1Q**; see Table 1 and Experimental Section for the assignments of ^{1}H and ^{13}C NMR data. These trimethylazulenequinones are stable on standing at room temperature as in the case of **1Q**. The two half-wave potential values[20] (E_1/E_2) obtained for **2I** and **2J**$_1$ were −1.05/−1.5 and −1.05/−1.46 V, respectively, which are slightly higher than those of **1Q** (see above).

Compound **2K**$_2$ ($C_{39}H_{38}O$ by MS) contained a hydroxyl group (3750—3150 cm^{-1}) and a 4,6,8-trimethyl-1-azulenyl group (UV and ^{1}H NMR). Furthermore, the careful analysis of the NMR data obtained by a decoupling technique indicated the presence of 1,3-disubstituted 1*H*-inden-1-ol having three methyl groups on the six-membered ring. The rest of the molecule constituted of 1,8-disubstituted 4,6-dimethylazulene that exhibited ABX proton signals at δ 4.10, 4.39, and 5.40 (J_{AB}=4.0, J_{AX}=7.5, and J_{BX}=0.5 Hz). Combination of these spectral data led to 3-(1,2-dihydro-5,7-dimethylcyclopenta[*c*,*d*]azulen-2-yl)-4,6,7-trimethyl-1-(4,6,8-trimethyl-1-azulenyl)-1*H*-inden-1-ol as the most probable structure for **2K**$_2$.

Compounds **2L** and **2M** (both $C_{16}H_{19}NO$ by MS) were shown by UV, IR, and ^{1}H NMR data to be 4,6,8-trimethylazulene having an *N*-formyl-*N*-methylaminomethyl group at C-1 and C-2, respectively; see Table 1 for assignments of the NMR data of these compounds.

Possible Reaction Pathways for the Formation of Autoxidation Products of 1 and 2. The findings that the present autoxidation of the trialkylazulenes **1** and **2** has resulted in the simultaneous formation of many kinds of products even at an early stage are strongly indicative of the presence of a large number of highly competitive processes during the oxidation obviously initiated by attack of oxygen diradical[25] (or various other free radical species) on several sites of the azulene nucleus. Although electrophilic substitution reactions of azulenes are well-known to take place most easily at the 1 position,[2] no detailed study on radical reactions of azulenes has been made thus far, except for a few, brief descriptions on radical methylation,[26] benzyla-



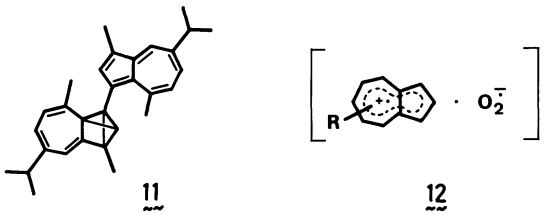
Scheme 1.

tion,[27] and bezoyloxylation,[19] all of which yield the corresponding substitution products preferentially at C-1. Nevertheless, since an unprecedented large number of products have been isolated in a high total, reproducible yield by noncatalyzed autoxidation of the two trialkylazulenes and most of their structures have been established in the present study, an attempt will now be made to suggest presumable reaction pathways for the formation of such a variety of products for the purpose of further detailed investigations of oxidation reactions of azulenes. For convenience, mechanistic considerations on the products from both **1** and **2** are concurrently made after having been divided into several groups according to the site of the oxidation on the azulene nucleus and the type of the products, as illustrated in the following Schemes 1—7.

Oxidative Dimerization. Because of the relatively high reduction potential (E_{pa} 0.71 V vs. SCE),[5] guaiazulene **1** is expected to be very easily oxidized by molecular oxygen, giving the radical cation **7** (see Scheme 1). This in turn undergoes a radical dimerization with a second molecule of **7** to give **8**. Subsequent proton loss from this dimeric cation would lead to the intermediate **9**, which then yields a major product 3,3′-biguaiazulene (**1B**) and a smaller proportion of the 2,3′-isomer (**1A**$_3$) (most likely through the isomerized intermediate **10**). It is assumed that the linkage of the coupling takes place between the sites (C-3) of the highest spin density in the cation radical **7** in the above radical dimerization. At present stage, we consider that such a pathway as described here is the most favorable for this dimerization on the grounds of (a) a preliminary theoretical calculation of the π-electron density in **1** and **7** in connection with the problem of the linkage[28a] and (b) isolation of a high yield of a 2 : 1 mixture of **1B** and **1A**$_3$ by the anodic oxidation of **1** which apparently proceeds through condensation of the radical cation **7**.[28b]

Both dimers **1B** and **1A**$_3$ have remained virtually unchanged on heating in DMF at 100 °C for 24 h in the absence of oxygen. Therefore, once these products are formed, no radical-catalyzed, thermal interconversion would exist between these two products through an equilibrium intermediate **11** analogous to the one proposed for the thermal conversion of 1-phenylazulene to the 2-phenyl isomer.[29]

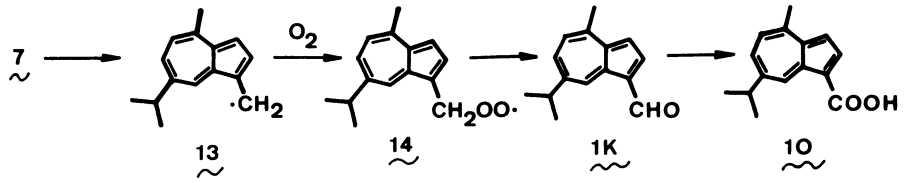
No such 1,1′- or 1,2′-dimer was isolated among the products from 4,6,8-trimethylazulene **2** under these autoxidation conditions apparently due to further polymerization at 1,3-positions, whereas an appreciable amount of a 2 : 1 mixture of such 1,1′-dimer and a trimer containing 1,2′-linkage were obtained by the anodic oxidation of **2**.[28b]



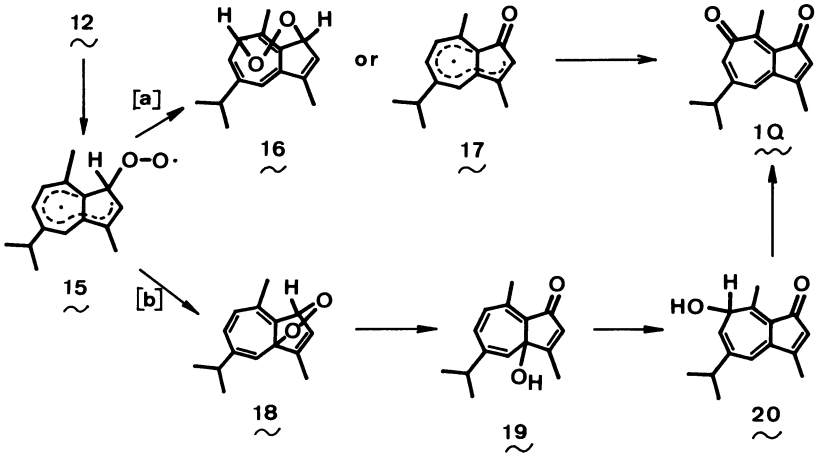
11 **12**

Although such oxidative dimerization described above takes place as one of the major pathways, other products are derived by oxidation of the starting azulenes with oxygen molecule ($^3O_2$), apparently proceeding through a complex shown as formula **12** by an electron transfer.[30] This complex is then expected to lead to a covalent linkage between the azulene nucleus and active radical species such as $^{\bullet}OO^-$, $^{\bullet}OOH$, and $^{\bullet}OH$ (or even $^1O_2$ produced during the oxidation) at various positions according to the ease of their affinity and steric requirement, thus providing several kinds of key intermediates for the formation of a wide variety of other products as outlined in Schemes 2—7.

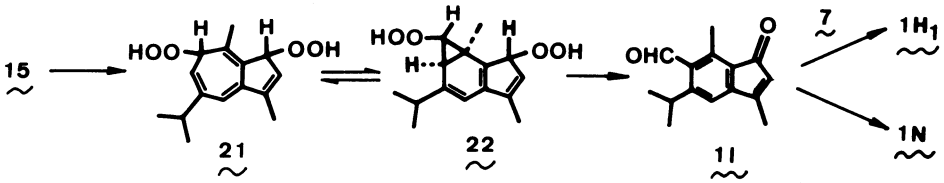
Oxidation of Side Chain. Scheme 2 illustrates the proposed reaction pathways for the products formed by oxidation of the side chains. One of the major product **1K** is considered to be derived by the attack of



Scheme 2.



Scheme 3.



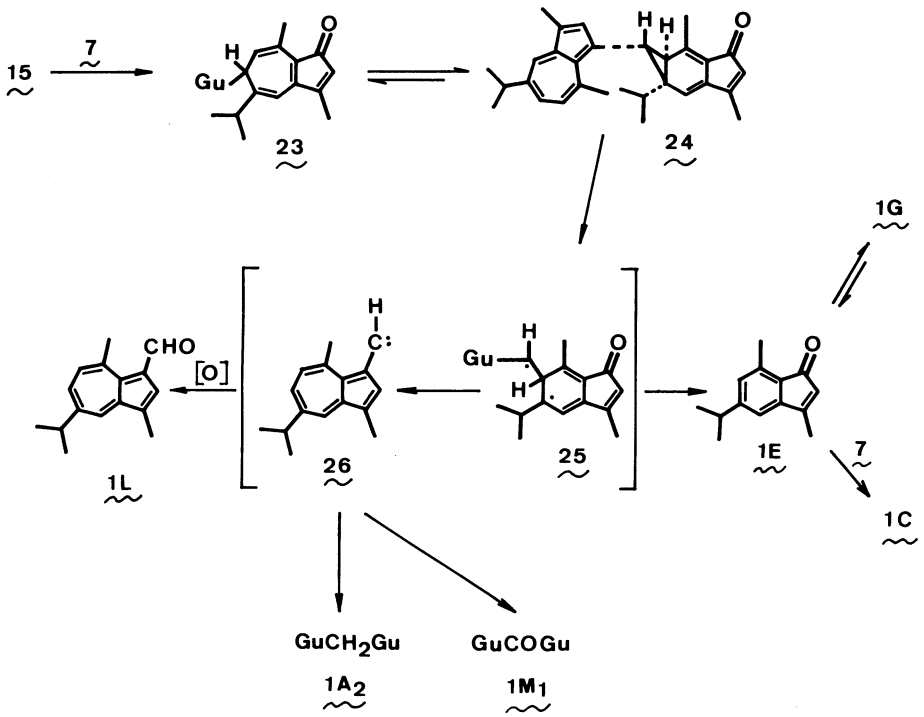
Scheme 4.

an oxygen molecule upon the alkyl side chain of the radical intermediate **13** (derived from **7**) to form the primary peroxyl radical **14** in a manner similar to the well-accepted mechanism for the autoxidation of side chains of alkylbenzenes and naphtalenes.[31] Further autoxidation of the aldehyde **1K** in the usual way gives the carboxylic acid **1O**. The oxidation of the side chain on the 1 position constitutes one of the major pathways in the autoxidation of **1** under the present conditions. The 7-acetylazulene **1J** is available only in an extremely samll amount by oxidation of the isopropyl group of **1**. These facts contrast with the efficient preparation of acetophenone derivatives from isopropylbenzenes by the same autoxidation in DMF.[32] Only an extremely small extent of the side chain oxidation is observed for **2**, affording 6-formyl derivative **2F**. Both **1J** and **2F** are obviously formed via pathways through the radical intermediates similar to those for **1K** outlined in Scheme 2.

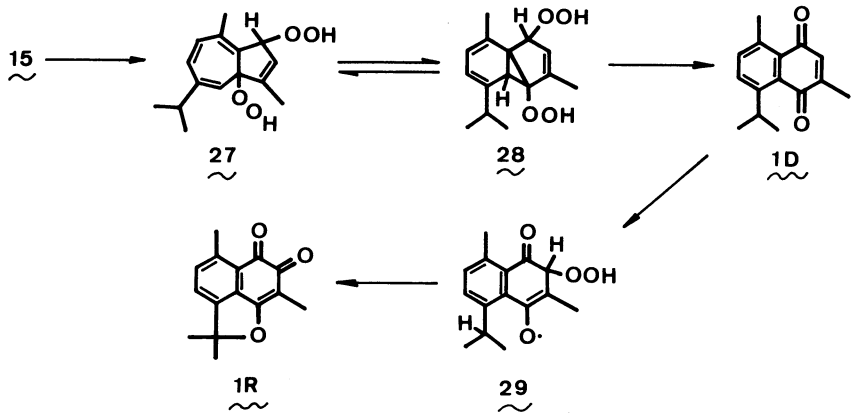
Azulenequinones. Scheme 3 illustrates a major reaction pathway when the azulene-oxygen complex **12** from **1** is transformed into the 3-guaiazulenylperoxyl diradical **15**.[33] As in the case of oxidation with singlet oxygen in protic solvent, a stepwise transformation of **15** into a precursor **20** via endo-peroxide **18** and hydroxy ketone **19** by a thermal [1,5] shift of the OH group on the seven-membered ring (path-b) may not be excluded for the formation of **1Q**. However, the fact that 1,7-guaiazulenequinone **1Q** has also been obtained on standing **1** in the dark even at 25 °C for a prolonged period (in as high as 15% yield)[34] suggests to us the transient formation of a highly strained, cross-linked endo-peroxide like **16** (or of a radical ketone **17**) (path-a), as a more likely pathway.

The same type of oxidative pathways for **2** would account for the formation of two azulenequinones $\mathbf{2J_1}$ and **2I**.

6-Formyl-1*H*-inden-1-ones and Related Compounds. Possible reaction pathways for the formation of these compounds are illustrated in Scheme 4. Addition of hydroperoxyl radical to the 5 position of **15** is considered to give an intermediate such as hydroperoxide **21** that would be converted into the 6-formylindenone **1I** most likely through the equilibrated norcaradiene form[35] (e.g. **22**). The formation of no such 6-formylindenone from **2** is obviously due to the presence of the three methyl groups at such positions as to suppress the transformation of the corresponding norcaradiene



Scheme 5.



Scheme 6.

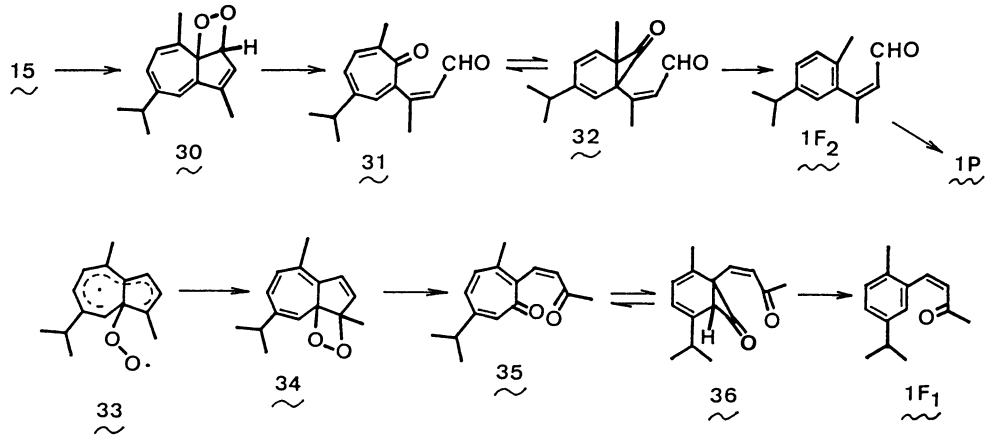
form (cf. **22**) into the formyl-substituted six-membered ring.

From indenones **1I** and **1E** (which has liberated one carbon by the rearrangement, see Scheme 5) several secondary products are derived: (i) oxidative coupling of **1I** and **1E** with the 2 position of the unreacted starting material **1** (or more probably **7**) to afford 2-(3-guaiazulenyl)indenones $\mathbf{1H_1}$ and **1C**, respectively, (ii) isomerization to **1N**, and (iii) transformation of **1E** into the thermodynamically more stable prototropic isomer **1G**.

Compounds Formed by Intermolecular One-Carbon Transfer. It should be particularly noticed in the present autoxidation of the trialkylazulenes **1** and **2** that compounds having extra-carbon(s) such as 3-formylguaiazulene (**1L**), 3,3′-methylenebisguaiazulene ($\mathbf{1A_2}$), and related compounds ($\mathbf{1M_1}$, $\mathbf{2A_2}$, $\mathbf{2G_1}$, **2K**) have always been obtained in relatively high yields.

The facts that compound **24**[36] has recently been proved to degrade to **1E** and **1L** on standing in air and the reaction of **24** with an equivalent of guaiazulene **1** under nitrogen in DMF at 100 °C has given $\mathbf{1A_2}$ as one of the major products strongly suggest that this dimeric norcaradiene **24** (formed through **23**) is the most likely key intermediate (Scheme 5). Compound **24**, which is expected to be thermodynamically more stable than **23** due to the absence of a cyclpentadienone form, would then undergo fragmentation (through diradical **25**) to give 1*H*-inden-1-one **1E** and a certain intermediate having a reactive extra-carbon side chain (such as a carbene species **26**). Then, a condensation reaction of the latter with the starting material **1** would afford $\mathbf{1A_2}$, whereas oxidation with $^3O_2$ is considered to give 3-formylguaiazulene **1L**.

Similar pathways for **2** involving intermediates illustrated for **1** would account for the formation of the



Scheme 7.

bis-trimethylazulenyl derivative **2A**$_2$ and indenones **2B**$_1$ and **2C**, as well as the 1-formyltrimethylazulene **2K**$_1$.

Naphthalenoid Compounds. Proposed pathways for these products are outlined in Scheme 6. Among these products, the formation of the naphthoquinones **1D** and **1R** constitute one of the major reaction pathways from **1**. Taking into account the results of an independent model study,[11b] this transformation may be explained in terms of the process through the intermediates **15** (Scheme 3) and then **27** formed by the addition of the second molecule of oxygen to C-8a of guaiazulene nucleus, followed by the rearrangement involving the norcaradiene intermediate **28** and loss of two hydroxyl radicals. An addition of hydroperoxyl radical at C-2 of **1D** to give an intermediate **29**, and subsequent loss of hydroxyl and H radicals would afford **1R**.

Benzenoid Compounds. The formation of a number of further degraded benzenoid derivatives (**1F**$_2$, **1P**, and **1F**$_1$) from **1** is most likely explained by the intramolecular radical cyclization of **15** at C-3a and of **33** at C-1 to give the dioxetane intermediates **30** and **34** which subsequently yield the benzenoid products through the ring-opened tropone-norcaradiene dicarbonyl compounds **31**, **32** and **35**, **36**, respectively, followed by facile decarbonylation, as illustrated in Scheme 7. The benzenoid compounds (**2B**$_2$, **2H**, and **2J**$_2$) from **2** are derived via essentially similar ring-opening schemes as those described for the benzenoid products from **1**.

The detailed mechanistic consideration for the formation of other minor compounds, however, is not made here because of the limited evidences at this stage with regard to the reaction pathways. Besides these isolated compounds described so far, considerable amounts (34 and 57%) of intractable resinous substances are accompanied by the autoxidation (of **1** and **2**, respectively). Of particular, it is noted that the latter substrate (**2**) bearing no substituents at the most reactive sites C-1 and C-3 tends to give a larger proportion of the polymerized products.

It has now become apparent that the autoxidation of the trialkylazulenes is extraordinarily complex and highly competitive involving oxidation of the nucleus (at various positions), substitutions, ring contraction, and other reactions such as the rearrangement to naphthalenes, although the exact mechanism is under further investigation in detail by employing azulene itself and various other alkylazulenes under various reaction conditions. Nevertheless, the present findings are believed to provide valuable information on exploitation of a convenient preparative route for some useful azulenoid compounds.[37] It is further of interest in relation to the recent isolation, from the polyps of a deep sea gorgonian (at −350 m), of a number of azulene derivatives, including 3,3′-methylenebisguaiazulene[38a] (**1A**$_2$) and 1,7-guaiazulenequinone[38b] (**1Q**) which coincide with the autoxidation products described in this paper.

Experimental

Melting points were determined with a Yanagimoto MP-S3 instrument and are uncorrected. Column chromatography was performed with Wako C-300 silica gel. TLC was conducted on plates precoated with silica gel 60F (0.25 mm, Merck) by using 15 : 85 AcOEt–hexane as eluant. HPLC was carried out with Hitachi gel #3011 with methanol as solvent.

UV (in MeOH) and IR (as KBr disk, unless otherwise stated) spectra were taken on Hitachi 323 and a Nihonbunko IR-A-202 Grating spectrometer, respectively. NMR spectra were recorded in $CDCl_3$ with a JEOL-FX200 cryospectrometer (200-MHz for ^1H and 50 MHz for ^{13}C) at 27 °C. Chemical shifts are reported as δ values in parts per million relative to tetramethylsilane (δ 0.0) as the internal standard. The assignments of all signals were made by employing a first-order analysis with the aid of decoupling technique and the parameters were confirmed by a computer-assisted simulation analysis; those values for simple azulene derivatives are summarized in Table 1. Mass spectra were taken on a Shimadzu LKB-9000 (with a Shimadzu PAC 90 mass data system) low resolution or a JEOL JMS-HX100 (with a JEOL JMA-DA5000 mass data system) high-resolution instrument (for chemical ionization with isobutane), and are given in terms of m/z (rel. intensity) compared with the base peak.

Oxidation of Guaiazulene (1) in DMF. A solution of **1**[39]

(1.00 g) in freshly distilled DMF (20 cm^3) was placed in a Pyrex flask (ϕ 1.8 cm, 60 cm height) and subjected to autoxidation by allowing finely bubbling oxygen to pass through the solution (from the bottom of the flask) for 24 h at 100±5 °C. After cooling, the mixture was diluted with water (200 cm^3) and extracted with AcOEt (4×50 cm^3). The combined organic layers were washed with water, dried (Na_2SO_4), and evaporated in vacuo, giving a brown oil (0.98 g); the HPLC and TLC diagrams of this crude mixture are given in Fig. 1. This residue was preliminarily separated into five fractions by means of preparative HPLC with Hitachi gel #3019 (100 g) using methanol as eluant. Then each fraction was carefully separated by silica-gel column or thin layer with AcOEt-hexane; when necessary, this chromatographic procedure was repeated. Thus, the following 25 products were obtained as pure substances, besides the recovered starting material **1** (**1A**$_1$: 0.41 g; R_f=0.95; ^{1}H NMR, see Table 1) and polar resinous substances [0.20 g, 34% (w/w); R_f=0.0]. The yield of each product is based on the consumed starting material (0.59 g).

3,3′-Methylenebisguaiazulene[9] **(1A$_2$):** Dark blue prisms; 50 mg (8.2% yield); mp 188 °C (Ref. 9a, 187—189 °C); R_f=0.95; ^{1}H NMR, see Table 1. (Found: *m/z* 408.2883).

2,3′-Biguaiazulene (1A$_3$): Dark green prisms; 5 mg (0.9%); mp 149 °C; R_f=0.95; UV ($CHCl_3$) 250, 299, 311, 353, 368,^{sh} 446, and 610 nm (log ε 4.42, 4.46, 4.47, 4.20, 4.07, 3.94, and 2.91); ^{1}H NMR, see Table 1; EI MS, *m/z* 394 (M^+; 56), 379 (100), 336 (19), 321 (20), and 198 (17).

Found: *m/z* 349.2654. Calcd for $C_{30}H_{34}$: M, 394.2660.

4,4′-Diisopropyl-1,1′,6,6′-tetramethyl-2,2′-binaphthalene (1A$_4$): Pale yellow-green oil; 2 mg (0.4%); R_f=0.95; UV 231, 291, 326, and 441 nm (log ε 4.82, 3.82, 2.45, and 2.50); ^{1}H NMR 1.38 (12H, d, *J*=7.0 Hz, 2 *i*-Pr-4), 2.55 (6H, s, 2Me-6), 2.64 (6H, s, 2Me-1), 3.72 (2H, sept, 2CH-4), 7.22 (2H, s, 2H-3), 7.34 (2H, dd, $J_{7,8}$=9.0, $J_{5,7}$=1.7 Hz, 2H-7), 7.90 (2H, d, 2H-5), and 7.91 (2H, d, 2H-8); EI MS, *m/z* 394 (M^+; 100), 379 (30), 351 (35), and 197 (30).

Found: *m/z* 394.2666. Calcd for $C_{30}H_{34}$: M, 394.2661.

4-Isopropyl-1,6-dimethylnaphthalene (Cadalene)[40] **(1A$_5$):** Colorless oil; 5 mg (0.9%); R_f=0.95; ^{1}H NMR 1.32 (6H, d, *J*=7.0 Hz, *i*-Pr-4), 2.49 (3H, s, Me-6), 2.58 (3H, s, Me-1), 3.68 (1H, sept, CH-4), 7.13 (1H, d, *J*=7.0 Hz, H-2), 7.22 (1H, d, H-3), 7.26 (1H, dd, *J*=8.0, 1.0 Hz, H-7), 7.85 (1H, d, H-8), and 7.89 (1H, d, H-5); EI MS, *m/z* 198 (M^+; 100).

3,3′-Biguaiazulene[3,10] **(1B):** Greenish blue prisms; 40 mg (6.8%); mp 144 °C (Ref. 15, 142 °C); R_f=0.93; ^{1}H NMR, see Table 1; EI MS, *m/z* 394 (M^+; 100).

2-(3-Guaiazulenyl)-5-isopropyl-3,7-dimethyl-1*H*-inden-1-one (1C): Dark red prisms; 13 mg (2.2%); R_f=0.86; UV 252, 293, 305,^{sh} 352, 370,^{sh} and 500 nm (log ε 4.59, 4.66, 4.60 4.06, 4.00, and 3.51); IR (CCl_4) 1690 (C=O) cm^{-1}; ^{1}H NMR 1.28 (6H, d, *J*=7.0 Hz, *i*-Pr-5), 1.34 (6H, d, *J*=7.0 Hz, *i*-Pr-7′), 2.08 (3H, s, Me-3), 2.52 (3H, s, Me-7), 2.62 (3H, s, Me-4′), 2.64 (3H, s, Me-1′), 2.89 (1H, sept, CH-5), 3.04 (1H, sept, CH-7′), 6.83 (2H, bs, H-4,6), 6.90 (1H, d, $J_{5',6'}$=11.0 Hz, H-5′), 7.32 (1H, dd, $J_{6',8'}$=2.0 Hz, H-6′), 7.36 (1H, s, H-2′), and 8.12 (1H, d, H-8′); CI MS, *m/z* 397 (M+1; 100).

Found; *m/z* 396.2438. Calcd for $C_{29}H_{32}O$: M, 396.2453.

8-Isopropyl-2,5-dimethyl-1,4-naphthoquinone[11] **(1D):** Yellow oil; 35 mg (5.1%); R_f=0.81; CI MS, *m/z* 229 (M+1; 100).

5-Isoproply-3,7-dimethyl-1*H*-inden-1-one (1E): Pale yellow oil; 10 mg (1.7%); R_f=0.78; UV ($CHCl_3$) 250, 331, 341,^{sh} and 370^{sh} nm (log ε 4.33, 3.73, 3.69, and 3.05); IR (neat) 1680 (C=O) cm^{-1}; ^{1}H NMR 1.23 (6H, d, *J*=7.0 Hz, *i*-Pr-5), 2.20 (3H, d, $J_{2,Me}$=1.5 Hz, Me-3), 2.44 (3H, s, Me-7), 2.88 (1H, sept, CH-5), 5.61 (1H, q, H-2), 6.79 (1H, bs, H-4*), and 6.83 (1H, bs, H-6*), *the assignments may have to be interchanged; ^{13}C NMR 198.79 (C-1), 160.24, 154.11, 146.75, 136.65, 129.64, 124.45, 115.92, 34.45, 23.59, 17.11, and 13.72; CI MS, *m/z* 201 (M+1; 100).

Found: *m/z* 200.1140. Calcd for $C_{14}H_{16}O$: M, 200.1201.

(*Z*)-4-(5-Isopropyl-2-methylphenyl)-3-buten-2-one (1F$_1$): Colorless oil; 10 mg (1.7%); R_f=0.72; UV 279 nm (log ε 4.36); IR (neat) 1680 (C=O) cm^{-1}; ^{1}H NMR 1.21 (6H, d, *J*=7.0 Hz, *i*-Pr-5′), 1.92 (3H, s, H_3-1), 2.26 (3H, s, Me-2′), 2.85 (1H, sept, CH-5′), 6.16 (1H, d, *J*=11.0 Hz, H-3), 7.03 (1H, bs, H-6′), 7.09 (1H, bd, $J_{3',4'}$=8.0 Hz, H-4′), 7.13 (1H, d, H-3′), and 7.15 (1H, d, H-4); EI MS, *m/z* 202 (M^+; 100).

Found: *m/z* 202.1264. Calcd for $C_{14}H_{18}O$: M, 202.1357.

(*Z*)-3-(5-Isopropyl-2-methylphenyl)-2-butenal (1F$_2$): Colorless oil; 10 mg (1.7%); R_f=0.72; ^{1}H NMR 1.24 (6H, d, *J*=7.0 Hz, *i*-Pr-5′), 2.22 (3H, s, Me-2′), 2.24 (3H, d, $J_{2,4}$=1.5 Hz, H_3-4), 2.88 (1H, sept, CH-5′), 6.14 (1H, dq, $J_{1,2}$=8.0 Hz, H-2), 6.92 (1H, bd, $J_{4',6'}$=1.0 Hz, H-6′), 7.10 (1H, dd, $J_{3',4'}$=8.0 Hz, H-4′), 7.16 (1H, d, H-3′), and 9.20 (1H, d, H-1); EI MS, *m/z* 202 (M^+; 100).

Found: *m/z* 202.1295. Calcd for $C_{14}H_{18}O$: M, 202.1357.

2,3-Dihydro-5-isopropyl-7-methyl-3-methylene-1*H*-inden-1-one (1G): Colorless needles; 5 mg (0.8%); mp 84 °C; R_f=0.69; UV 245, 265,^{sh} and 330 nm (log ε 4.32, 4.17, and 3.79); IR (CCl_4) 1720 (C=O) cm^{-1}; ^{1}H NMR 1.29 (6H, d, *J*=7.0 Hz, *i*-Pr-5), 2.62 (3H, s, Me-7), 2.96 (1H, sept, CH-5), 3.25 (2H, dd, 2H-2), 5.24 [1H, t, $J_{2,HC(3)}$=1.8 Hz, (*E*)-H-C-3], 5.78 [1H, t, $J_{2,HC(3)}$=2.0 Hz, (*Z*)-H-C-3), 7.02 (1H, d, $J_{4,6}$=1.0 Hz, H-6], and 7.43 (1H, d, H-6).

Found: *m/z* 200.1205. Calcd for $C_{14}H_{16}O$: M, 200.1202.

2-(3-Guaiazulenyl)-5-isopropyl-3,7-dimethyl-1-oxo-1*H*-indene-6-carbaldehyde (1H$_1$): Reddish brown prisms; 13 mg (2.1%); mp 147 °C (decomp); R_f=0.64; UV 225,^{sh} 256, 293, 307,^{sh} 353, 369, and 537 nm (log ε 4.43, 4.53, 4.60, 4.53, 4.00, 3.93, and 3.50); IR (CCl_4) 1690 and 1680 (C=O) cm^{-1}; ^{1}H NMR 1.33 (6H, d, *J*=7.0 Hz, *i*-Pr-7′), 1.37 (6H, d, *J*=7.0 Hz, *i*-Pr-5), 2.14 (3H, s, Me-3), 2.64 (6H, s, Me-1′, 4′), 2.80 (3H, s, Me-7), 3.01 (1H, sept, CH-7′), 3.79 (1H, sept, CH-5), 6.95 (1H, d, $J_{5',6'}$=11.0 Hz, H-5′), 7.08 (1H, s, H-4), 7.36 (1H, dd, $J_{6',8'}$=2.0 Hz, H-6′), 7.39 (1H, s, H-2′), 8.16 (1H, d, H-8′), and 10.60 (1H, s, OHC-6); CI MS, *m/z* 425 (M+1; 100).

Found: *m/z* 424.2444. Calcd for $C_{30}H_{32}O_2$: M, 424,2404.

3-Guaiazulenyl 3-(3-Guaiazulenyl)-7-isopropyl-4-methyl-1-azulenyl Ketone (1H$_2$): Reddish brown paste; 1 mg (0.2%); R_f=0.64; UV ($CHCl_3$) 248, 290, 394, and 538 nm (log ε 4.70, 4.70, 3.24, and 3.34); IR 1720 (C=O) cm^{-1}; EI MS, *m/z* 604 (M^+; 100), 589 (7), 561 (4), 408 (17), 393 (5), 198 (20), and 183 (19).

Found: *m/z* 604.3670. Calcd for $C_{45}H_{48}O$: M, 604.3704.

5-Isopropyl-3,7-dimethyl-1-oxo-1*H*-indene-6-carbaldehyde (1I): Yellow needles; 20 mg (2.9%); mp 87 °C; R_f=0.55; UV ($CHCl_3$) 268, 342, and 374^{sh} nm (log ε 4.27, 3.96, and 3.66); IR 1700 and 1695 (C=O) cm^{-1}; ^{1}H NMR 1.32 (6H, d, *J*=6.9 Hz, *i*-Pr-5), 2.26 (3H, d, $J_{2,Me}$=1.4 Hz, Me-3), 2.76 (3 H, s, Me-7), 3.72 (1H, sept, HC-5), 5.80 (1H, q, H-2), 7.04 (1H, s, H-4), and 10.58 (1H, s, CHO); ^{13}C NMR 197.56, 193.41, 159.19, 157.44, 149.91, 138.40, 134.26, 129.70, 127.13, 115.28, 29.02, 23.59, 13.67, and 13.37; EI MS, *m/z* 228 (M^+; 100), 213 (47), 199 (23), and 185 (32).

Found: m/z 228.1132. Calcd for $C_{15}H_{16}O_2$: M, 228.1150.

7-Acetyl-1,4-dimethylazulene (1J): Violet bule prisms; 2 mg (0.3%); mp 55 °C; R_f=0.52; UV 245, 304, 396, and 575 nm (log ε 4.47, 4.68, 3.76, and 2.72); IR 1670 (C=O) cm^{-1}; ^1H NMR, see Table 1; EI MS, m/z 198 (M^+; 100), 183 (75), and 155 (52).

Found: m/z 198.1014. Calcd for $C_{14}H_{14}O$: M, 198,1045.

7-Isopropyl-4-methyl-1-azulenecarbaldehyde[15] (1K): Red prisms; 50 mg (7.9%); mp 61 °C (Ref. 15, 61 °C); R_f=0.49; ^1H NMR, see Table 1; EI MS, m/z 212 (M^+; 100).

3-Guaiazulenecarbaldehyde[16] (1L): Brownish red needles; 10 mg (1.5%); mp 86 °C (Ref. 16, 85—86 °C); R_f=0.38; ^1H NMR, see Table 1; EI MS, m/z 226 (M^+; 100).

Bis(3,3′-guaiazulenyl) Ketone[17] ($1M_1$): Dark green prisms; 10 mg (1.6%); mp 191 °C (Ref. 17, 189—190 °C); R_f=0.35; ^1H NMR, see Table 1; EI MS, m/z 422 (M^+; 17), 407 (69), 331 (20), 198 (16), 169 (81), 109 (50), and 43 (100).

3-Guaiazulenyl Dimethylcarbamate ($1M_2$): Dark blue paste; 5 mg (0.6%); R_f=0.35; UV ($CHCl_3$) 249, 290, 352, 368, 634, and 654^{sh} nm (log ε 4.20, 4.26, 3.78, 3.75, 2.67, and 2.63); IR (CCl_4) 1705 (C=O) cm^{-1}; ^1H NMR, see Table 1; EI MS, m/z 285 (M^+; 10), 213 (58), 72 (100), and 42 (12).

Found: m/z 285.1733. Calcd for $C_{18}H_{23}NO_2$: M, 285.1728.

Compound 1N: Pale yellow crystals; 2 mg (0.3%); R_f=0.26; UV 229,^{sh} 242,^{sh} 254,^{sh} 269, 317, 344, and 418 nm; IR (CCl_4) 1715 and 1700 (C=O) cm^{-1}; ^1H NMR* 1.28 (6H, d, J=7.0 Hz, i-Pr-4), 2.68 (3H, s, Me-7), 2.90 (3H, s, Me-2), 3.65 (1H, sept, HC-4), 7.02 (1H, s, H-5), 10.56 (1H, s, OHC-8), and 10.68 (1H, s, OHC-3), *the assignments were made for the tentative structure **6** (see the footnote on p. 1418); CI MS, m/z 229 (M+1; 100).

7-Isopropyl-4-methyl-1-azulenecarboxylic Acid[15] (1O): Red-violet needles; 10 mg (1.5%); mp 169 °C (Ref. 15, 169 °C); R_f=0.23; ^1H NMR see Table 1; EI MS, m/z 228 (M^+; 100).

(*Z*)-3-(5-Isopropyl-2-methylphenyl)-2-butenoic Acid (1P): Colorless needles; 15 mg (2.3%); mp 128 °C; R_f=0.20; UV 269 and 278 nm (log ε 4.31 and 4.23); IR 3200—2300, 1680—1660 (COOH) cm^{-1}; ^1H NMR 1.21 (6H, d, J=7.0 Hz, i-Pr-5′), 2.12 (3H, d, $J_{2,4}$=1.5 Hz, H_3-4), 2.14 (3H, s, Me-2′), 2.84 (1H, sept, HC-5′), 4.16 (1H, m, COOH; D_2O exchangeable), 5.92 (1H, q, H-2), 6.78 (1H, dd, $J_{4',6'}$=2.0, $J_{3',6'}$=0.5 Hz, H-6′), 7.05 (1H, $J_{3',4'}$=8.0 Hz, H-4′), and 7.08 (1H, dd, H-3′); ^{13}C NMR 169.47 (C-1), 159.02, 146.11, 140.27, 130.58, 129.82, 125.38, 124.15, 118.02, 33.64, 27.45, 24.00, and 18.57.

Found: m/z 218.1308. Calcd for $C_{14}H_{18}O_2$: M, 218.1307.

5-Isopropyl-3,8-dimethyl-1,7-azulenequinone (1Q): Yellow needles; 10 mg (1.5%); mp 94 °C; R_f=0.18; $E_{1/2}$ −1.13 and −1.52 V (vs. SCE); UV ($CHCl_3$) 232, 252, 288,^{sh} 310,^{sh} 386, 394,^{sh} and 420^{sh} nm (log ε 4.14, 4.14, 3.95, 3.92, 3.74, 3.73, and 3.53); IR 1680 and 1590 (C=O) cm^{-1}; ^1H NMR, see Table 1; ^{13}C NMR 196.57 (C-1), 189.38 (C-7), 164.16 (C-3), 154.99 (C-5), 148.91 (C-8), 144.53 (C-3a), 133.09 (C-6), 133.04 (C-8a), 131.45 (C-4), 124.10 (C-2), 37.84 (Me-8), 29.67 (Me_2CH-5), 22.54 (Me_2CH-5), and 14.25 (Me-3); EI MS, m/z 228 (M^+; 100), 213 (80), 199 (16), 195 (12), 185 (26), and 171 (16).

Found: m/z 228.1138. Calcd for $C_{15}H_{16}O_2$: M, 228.1150

2,2,5,8-Tetramethyl-2*H*-naphtho[1,8-*bc*]furan-6,7-dione[11b] (1R): Orange needles; 5 mg (0.7%); mp 220 °C (Ref. 11b, mp 220 °C); R_f=0.05; EI MS, m/z 242 (M^+; 54) and 171 (100).

***N*-(2-Guaiazulenylmethyl)-*N*-methylformamide (1S):** Blue paste; 5 mg (0.6%); R_f=0.02; UV 245, 285, 349, and 608 nm (log ε 4.38, 4.60, 3.68, and 2.64); IR (CCl_4) 1665 (C=O) cm^{-1}, ^1H NMR, see Table 1; EI MS, m/z 269 (M^+; 27), 254 (25), 226 (26), 213 (100), and 198 (23).

Oxdation of 1 in HMPA. The same oxidation procedure was employed, and virtually the same products were obtained except for certain compounds in which fragments from the solvent are incorporated (e.g., $1M_2$ and **1S**).

Oxidation of 4,6,8-Trimethylazulene (2) in DMF. Autoxidation **2**[39] (1.00 g) in DMF (20 cm^3) was carried out for 12 h at 120±5 °C in a manner similar to that described for **1**, thus affording, after the careful chromatographic separation, 17 products as pure compounds (**2A—M**; see Fig. 2 for HPLC and TLC), besides the recovered starting material **2** ($2A_1$, 0.45 g, R_f=0.94; ^1H NMR, see Table 1) and polar resinous substances [0.324 g, 59% (w/w); R_f=0.0]. They yield of each product is based on the consumed starting material (0.55 g).

1,1′-Methylenebis(4,6,8-trimethylazulene) ($2A_2$): Dark violet prisms; 10 mg (1.8%); mp 205 °C; R_f=0.94; UV ($CHCl_3$) 249, 306, 356, and 570 nm (log ε 4.80, 4.89, 4.27, and 2.97); ^1H NMR, see Table 1; EI MS m/z 352 (M^+; 68), 182 (100), and 170 (84).

Found: m/z 352.2176. Calcd for $C_{27}H_{28}$: M, 352.2190.

4,6,7-Trimethyl-1*H*-inden-1-one ($2B_1$): Yellow needles; 30 mg (5.4%); mp 38 °C; R_f=0.79; UV 249, 313, and 400 nm (log ε 3.87, 3.50, and 3.02); IR 1700 (C=O) cm^{-1}; ^1H NMR 2.20 (3H, s, Me-4), 2.22 (3H, s, Me-6), 2.43 (3H, s, Me-7), 5.74 (1H, d, $J_{2,3}$=6.0 Hz, H-2), 6.88 (1H, s, H-5), and 7.58 (1H, d, H-3); EI MS, m/z 172 (M^+; 100) and 129 (20).

Found: m/z 172.0888. Calcd for $C_{12}H_{12}O$: M, 172.0888.

2,4,6-Trimethylbenzaldehyde[21] ($2B_2$): Colorless oil; 2 mg (0.4%); R_f=0.79; ^1H NMR 2.31 (3H, s, Me-4), 2.56 (6H, s, Me-2,6), 6.90 (2H, s, H-3,5), and 10.56 (1H, s, CHO): EI MS, m/z 148 (M^+; 100).

4,5,7-Trimethyl-1*H*-inden-1-one (2C): Yellow needles; 30 mg (5.4%); mp 64 °C; R_f=0.78; UV 247, 349, and 400^{sh} nm (log ε 3.88, 3.52, and 3.25); IR 1695 (C=O) cm^{-1}; ^1H NMR 2.15 (3H, s, Me-5), 2.20 (3H, s, Me-4), 2.42 (3H, s, Me-7), 5.78 (1H, d, $J_{2,3}$=6.0 Hz, H-2), 6.76 (1H, s, H-6), and 7.62 (1H, d, H-3); ^{13}C NMR 200.01, 146.81, 143.31, 143.13, 135.19, 132.91, 131.75, 128.59, 127.13, 19.97, 16.76, and 13.78; EI MS, m/z 172 (M^+; 100) and 129 (22).

Found: m/z 172.0880. Calcd for $C_{12}H_{12}O$: M, 172.0888.

2,3-Dihydro-4,6,7-trimethyl-3-(4,6,8-trimethyl-1-azulenyl)-1*H*-inden-1-one (2D): Violet prisms; 10 mg (1.8%); mp 145 °C; R_f=0.69; UV 266, 297, 359, 563, and 600^{sh} nm (log ε 3.66, 4.30, 3.49, 2.67, and 2.61); IR 1695 (C=O) cm^{-1}; ^1H NMR 1.82 (3H, s, Me-4), 2.32 (2H, s, Me-6), 2.58 (2H, s, Me-6′), 2.64 (3H, s, Me-4′), 2.67 (1H, dd, $J_{2,2}$=18.0, $J_{2,3}$=3.0 Hz, H-2), 2.78 (3H, s, Me-8′), 3.14 (3H, s, Me-7), 3.26 (1H, dd, $J_{2,3}$=8.0 Hz, H-2), 5.42 (1H, dd, H-3), 6.75 (1H, d, $J_{2',3'}$=4.0 Hz, H-2′), 6.94 (1H, s, H-5′), 6.96 (1H, s, H-7′), 7.12 (1H, d, H-3′), and 7.14 (1H, s, H-5); EI MS, m/z 342 (M^+; 10) and 170 (100).

Found: m/z 342.1969. Calcd for $C_{25}H_{26}O$: M, 342.1984.

2,3-Dihydro-4,5,7-trimethyl-3-(4,6,8-trimethyl-1-azulenyl)-1*H*-inden-1-one (2E): Violet prisms; 10 mg (1.8%); mp 145 °C; R_f=0.63; UV 266, 297, 359, 563, and 600^{sh} nm (log ε 3.59, 4.30 3.44, 2.62, and 2.56); IR 1695 (C=O) cm^{-1}; ^1H NMR 1.80 (3H, s, Me-4), 2.28, (3H, s, Me-5), 2.60 (3H, s, Me-6′), 2.64 (3H, s, Me-4′), 2.65 (1H, dd, $J_{2,2}$=18, $J_{2,3}$=3.0 Hz, H-2), 2.78 (3H, s, Me-8′), 3.16 (3H, s, Me-7), 3.26 (1H, dd, $J_{2,3}$=8.0 Hz, H-2), 5.49 (1H, dd, H-3), 6.71 (1H, d, $J_{2',3'}$=4.0 Hz, H-2′), 6.95 (1H, s, H-5′), 6.97 (1H, s, H-7′), 7.00 (1H, s, H-6), and 7.11 (1H, d, H-3′); EI MS, m/z 342 (M^+; 22) and 170 (100).

Found: m/z 342.1979. Calcd for $C_{25}H_{26}O$: M, 342.1984.

4,8-Dimethyl-6-azulenecarbaldehyde[23] (2F): Dark green

prisms; 3 mg (0.5%); mp 98 °C (Ref. 23, 98 °C); R_f=0.57; ^{1}H NMR, see Table 1; EI MS, *m/z* 184 (M^+; 100).

Bis(4,6,8-trimethyl-1-azulenyl)acetaldehyde[24] (2G): Dark violet prisms; 3 mg (0.5%); mp 167 °C (Ref. 24, mp 177 °C); R_f=0.41; UV ($CHCl_3$) 249, 298,^{sh} 308, 355, 560, and 640^{sh} nm (log ε 4.63, 4.63, 4.63, 4.45, 2.79, and 2.61): IR 2810 and 1720 (CHO) cm^{-1}; ^{1}H NMR, see Table 1; EI MS, *m/z* 380 (M^+; 8), 351 (100), 321 (35), 183 (25), and 170 (32).

Found: *m/z* 380.2108. Calcd for $C_{28}H_{28}O$: M, 380.2140.

4,6,8-Trimethyl-1-azulenyl-(*E*)-2,4,6-Trimethylstyryl Ketone (2H): Dark orange prisms; 3 mg (0.5%); mp 132 °C; R_f=0.37; UV ($CHCl_3$) 244, 298, 340, 428, and 530^{sh} nm (log ε 4.52, 4.40 4.22, 4.21, and 2.99); IR (CCl_4) 1710 (C=O) cm^{-1}; ^{1}H NMR 2.22 (6H, s, Me-2′, 6′), 2.30, (3H, s, Me-4′), 2.56 (3H, s, Me-6), 2.69 (3H, s, Me-4), 2.82 (3H, s, Me-8), 6.79 (1H, d, *J*=16 Hz, CH-CO), 6.84 (2H, s, H-3′,5′), 7.01 (1H, d, $J_{5',7'}$=1.0 Hz, H-5), 7.08 (1H, d, H-7), 7.29 (1H, d, $J_{2',3'}$=4.0 Hz, H-3), 7.94 (1H, d, H-2), and 8.14 (1H, d, CH=C-CO); EI MS, *m/z* 342 (M^+; 25), 327 (100), 196 (25), 181 (73), 165, (43), 147 (85), 119 (38), and 91 (24).

Found: *m/z* 342.1946. Calcd for $C_{25}H_{26}O$: M, 342.1984.

4,6,8-Trimethyl-1,7-azulenequinone (2I): Yellow needles; 15 mg (2.3%); mp 118 °C decomp; $E_{1/2}$ −1.05 and −1.5 V (vs. SCE); R_f=0.25; UV 260, 307, 370, 386, and 404^{sh} nm (log ε 4.35, 4.19, 3.95, 3.95, and 3.87); IR 1695 and 1580 (C=O) cm^{-1}; ^{1}H NMR, see Table 1; ^{13}C NMR 197.21 (C-1), 187.28 (C-7), 150.84 (C-3), 148.16 (C-6), 143.95 (C-8), 143.54 (C-3a), 140.56 (C-5), 138.17 (C-8a), 137.70 (C-4), 133.61 (C-2), 23.94 (Me-8), 21.67 (Me-4), and 16.12 (Me-6); EI MS, *m/z* 200 (M^+; 100), 172 (8), 149 (10), 128 (8), 80 (12), 57 (10), and 43 (10).

Found: *m/z* 200.0833. Calcd for $C_{13}H_{12}O_2$: M, 200.0837.

4,6,8-Trimethyl-1,5-azulenequinone ($2J_1$): Yellow needles; 15 mg (2.3%); mp 120 °C (decomp); R_f=0.23; $E_{1/2}$ −1.05 and −1.46 V (vs. SCE); UV 245, 318, 380,^{sh} and 400^{sh} nm (log ε 4.17, 3.83, 3.75, and 3.65); IR 1695 and 1575 (C=O) cm^{-1}; ^{1}H NMR, see Table 1; ^{13}C NMR 198.67 (C-1), 189.97 (C-5), 151.25 (C-3), 145.99 (C-6), 144.30 (C-4), 139.10 (C-8), 138.99 (C-7), 138.87 (C-3a), 133.67 (C-8a), 130.81 (C-2), 23.53 (Me-8), 21.55 (Me-4), and 14.72 (Me-6); EI MS, *m/z* 200 (M^+; 100), 172 (57), 157 (16), 144 (16), 129 (68), 115 (20), 91 (10), 77 (16), and 51 (20).

Found: *m/z* 200.0829. Calcd for $C_{13}H_{12}O_2$: M, 200.0837.

2,3,5-Trimethylbenzaldehyde[22] ($2J_2$): Colorless needles; 2 mg (0.4%): R_f=0.23; ^{1}H NMR 2.29 (3H, s, Me-5), 2.32 (3H, s, Me-4), 2.47 (3H, s, Me-2), 6.72 (1H, s, H-3), 7.08 (1H, s, H-6), and 9.98 (1H, s, CHO); EI MS, *m/z* 148 (M^+; 100).

4,6,8-Trimethyl-1-azulenecarbaldehyde[16a] ($2K_1$): Red prisms; 5 mg (0.8%); mp 107 °C (Ref. 16a, 107 °C): R_f=0.18; ^{1}H NMR, see Table 1; EI MS, *m/z* 198 (M^+; 100).

3-[1,2-Dihydro-5,7-dimethyl-cyclopenta[*c,d*]azulen-2-yl]-4,6,7-trimethyl-1-(4,6,8-trimethyl-1-azulenyl)-1*H*-inden-1-ol ($2K_2$): Dark violet prisms; 1 mg (0.2%); mp 202 °C (decomp); R_f=0.18; UV ($CHCl_3$) 247, 306, 340, 566, and 652^{sh} nm (log ε 4.46, 4.45, 4.13, 2.80, and 2.46); IR (CCl_4) 3750—3150 (OH) cm^{-1}; ^{1}H NMR 1.56 (1H, m, OH), 2.14 (3H, s, Me-7), 2.22 (3H, s, Me-6), 2.48 (3H, s, Me-6″), 2.53 (3H, s, Me-7′), 2.69 (3H, s, Me-8″), 2.73 (3 H, s, Me-4″), 2.80 (3H, s, Me-5′), 2.97 (3H, s, Me-4), 4.10 (1H, $J_{1',2'}$=7.5, $J_{1',1'}$=4.0 Hz, H-1′), 4.39 (1H, $J_{1',2'}$=0.5 Hz, H-1′), 5.40 (1H, H-2′), 6.36 (1H, s, H-2), 6.59 (1H, d, $J_{6',8'}$=0.5 Hz, H-8′), 6.64 (1H, d, $J_{5'',7''}$=0.5 Hz, H-7″), 6.82 (1H, d, H-5″), 6.86 (1H, d, H-6′), 6.86 (1H, s, H-5), 7.11 (1H, d, $J_{2'',3''}$=4.0 Hz, H-3″), 7.32 (1H, d, $J_{3',4'}$=4.0 Hz, H-4′), 7.43 (1H, d, H-2″), and 7.85 (1H, d, H-3′); EI MS, *m/z* 522 (M^+; 9), 364 (53), 350 (43), 335 (100), 180 (36), 170 (85), and 155 (38).

Found: *m/z* 522.2932. Calcd for $C_{39}H_{38}O$: M, 522.2922.

Bis(4,6,8-trimethyl-1-azulenyl) Ketone ($2K_3$): Orange prisms; 1 mg (0.2%); mp 171 °C; R_f=0.18; UV ($CHCl_3$) 249, 329, 404, and 480^{sh} nm (log ε 4.55, 4.53, 4.25 and 3.59); IR 1635 (C=O) cm^{-1}; ^{1}H NMR, see Table 1; EI MS, *m/z* 366 (M^+; 0.8), 351 (3), 331 (3), 197 (100), 169 (14), 153 (11), and 43 (25).

***N*-Methyl-*N*-[(4,6,8-trimethyl-1-azulenyl)methyl]formamide (2L):** Blue paste; 6 mg (0.8%); R_f=0.06; UV 247, 294, 358, 600, 625,^{sh} and 650^{sh} nm; IR (CCl_4) 1690 (C=O) cm^{-1}; ^{1}H NMR, see Table 1; EI MS, *m/z* 241 (M^+; 66), 226 (27), 198 (22), 183 (100), 167 (38), 153 (34), 141 (20), 128 (24), and 42 (62).

***N*-Methyl-*N*-[(4,6,8-trimethyl-2-azulenyl)methyl]formamide (2M):** Violet needles 20 mg (2.6%); mp 90 °C; R_f=0.02; UV 251, 292, 354, and 550 nm (log ε 4.60, 4.66, 4.17, and 2.78); IR 1655 (C=O) cm^{-1}: ^{1}H NMR, see Table 1; EI MS, *m/z* 241 (M^+; 100), 226 (41), 198 (24), 183 (83), 167 (29), and 153 (19).

Found: *m/z* 241.1471. Calcd for $C_{16}H_{19}NO$: M, 241,1467.

Oxidation of 2 in HMPA. The same procedures as those for **2** were employed, and virtually the same products were obtained except for certain compounds in which fragments from the solvent are incorporated (e.g., **2L** and **2M**).

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