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OXIDATION OF AZULENE DERIVATIVES. AUTOXIDATION OF 4,6,8-TRIMETHYLAZULENE IN A POLAR APROTIC SOLVENT[1)]

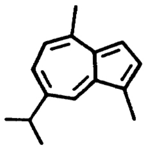
Yoshiharu MATSUBARA,* Shin-ichi TAKEKUMA, Katsumi YOKOI,
Hiroshi YAMAMOTO,*† and Tetsuo NOZOE*††

Department of Applied Chemistry, Faculty of Science and
Technology, Kinki University, Kowakae, Higashi-Osaka 577
†Department of Chemistry, Okayama University, Okayama 700
††Tokyo Research Laboratories, Takasago Corporation,
5-36-31 Kamata, Ohta-ku, Tokyo 144

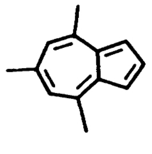
Autoxidation of 4,6,8-trimethylazulene at 120 °C in *N*,*N*-dimethylformamide yielded twelve separable products (including four known compounds), which were assigned to be azulenoquinone, inden-1-one, and azulenyl-1-indanone derivatives. A comparison of the present results with those of guaiazulene was made to obtain a mechanistic aspect of the oxidation reaction.

In the preceding paper we reported[2)] that the autoxidation of guaiazulene (1) in *N*,*N*-dimethylformamide (DMF) gave twenty-three isolable products, which were characterized to possess azulenoquinone, inden-1-one, benzocyclobutadiene, naphthoquinone, and various dimeric structures. In order to compare with this unexpectedly complex reaction of 1 and also to obtain a general aspect of the reaction mechanism of the oxidation of azulenes, we studied the autoxidation using symmetrically substituted 4,6,8-trimethylazulene (2) in the same aprotic solvent DMF, and now wish to report the results in this paper.

Thus, in a manner similar to that[2)] described for 1, a solution of 2 (1.00 g) in 20 ml of DMF was oxygenated in a pyrex flask at 120 °C; in contrast to that of 1, the oxidation of 2 was rather slow at 100 °C. The time-dependent HPLC diagram (Fig. 1) of this reaction revealed the formation of considerably fewer products ($\approx$15 peaks), compared with that of 1 (see TLC in Fig. 1).



1



2

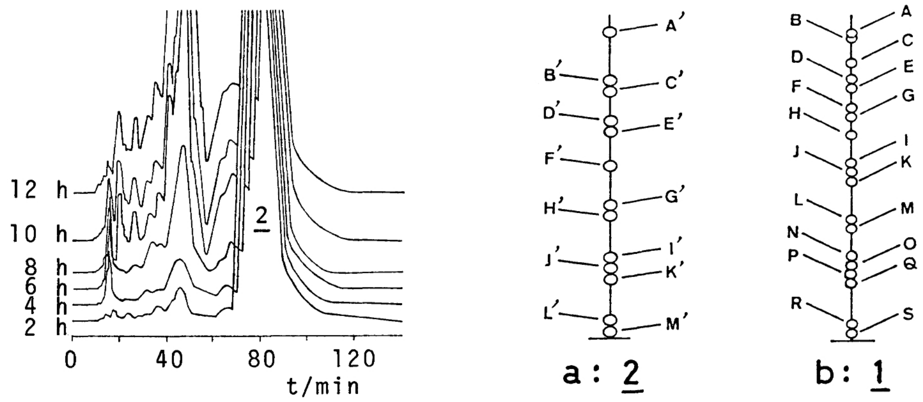
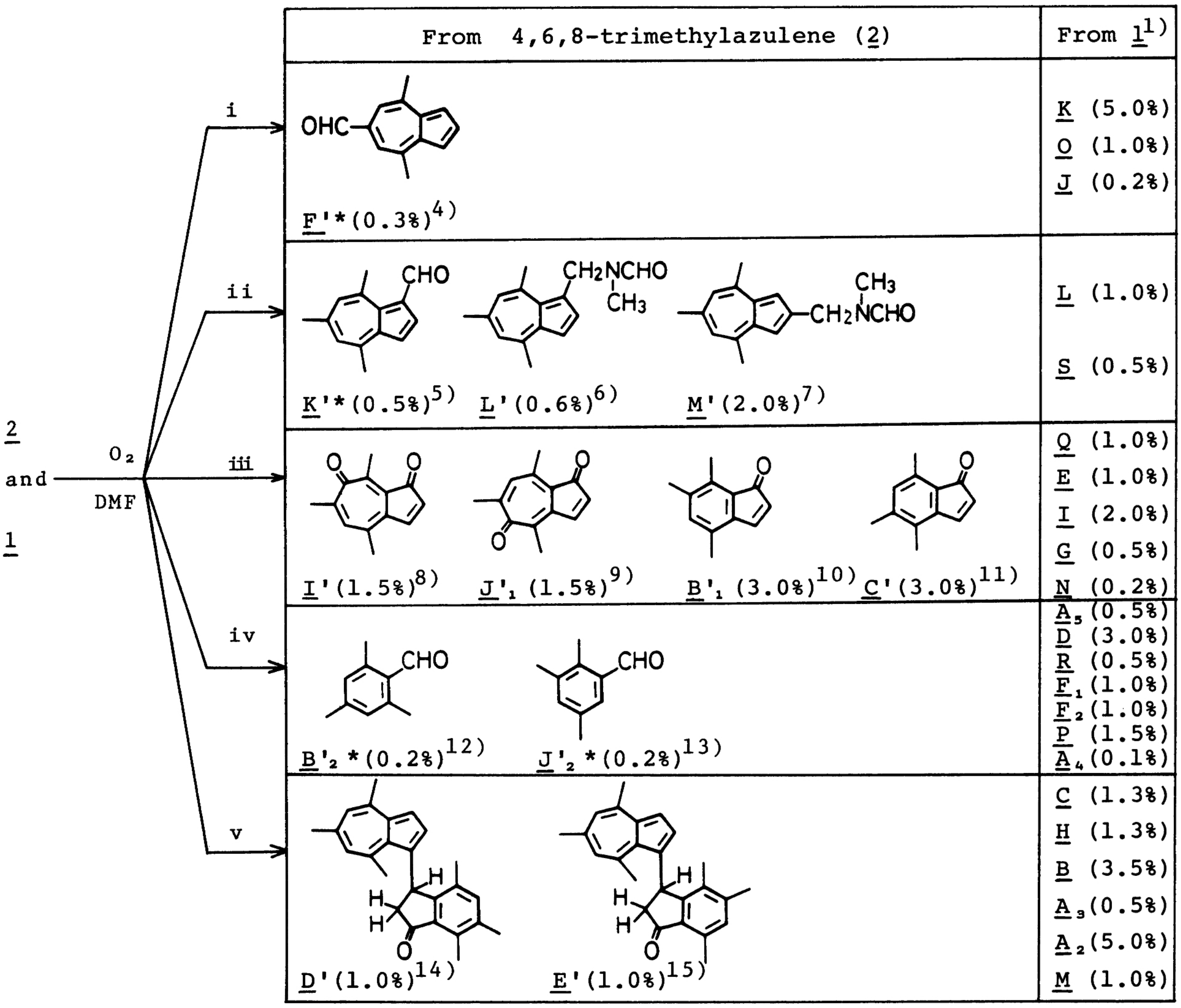


Fig. 1. Time-dependent HPLC diagram of autoxidation of 2, and TLC of the products from 2 (a) and 1 (b).

After 12 h the resulting mixture was carefully separated by using silica-gel column chromatography, TLC (with hexane/AcOEt, 85:15) and the reversed-phase HPLC (PSG-100 with methanol), thus affording twelve products as pure compounds, which will be referred to as Substances A'–M' according to their decreasing R_f values (TLC); ca. 50% of the starting material (2: A') was recovered. Separation of small amounts of Substances G' (violet-colored) and H' (orange) has not been achieved yet becuase of their intability and close overlapping on silica-gel TLC.

Structures of the pure products were established by UV-visible, IR, high-resolution mass, and NMR (^1H and ^{13}C) spectroscopy,3) and are summarized in Scheme 1, which also illustrates the most likely reaction pathways for the formation of such a variety of products by the highly competitive autoxidation of alkylazulenes 1 and 2.



Scheme 1. Structures (and yields) of the oxidation products, and the probable type of reactions: i, side-chain oxidation; ii, substitution with "CHO" or solvent; iii, nucleus oxidation with or without rearrangement; iv, isomerization to naphthalenoids and oxidative degradation to benzenoids; v, coupling with (or addition to) inden-1-ones or with 1. *Known compounds.

In general, the highly competitive intermediate processes (see Fig. 1) and the formation of a wide variety of the reaction products strongly suggest that the autoxidation of these azulenes in DMF would essentially be a radical reaction initiated by the attack of biradical oxygen.16) Since most of the structures of the oxidation products from the two alkylazulenes 1 and 2 were established, a careful examination of those experimental facts, as outlined in Scheme 1, leads to the following several remarks that would closely relate to the aspects of the reaction mechanism of these intricate oxidations:

(i) The ease of the oxidation of the side-chains depends upon their position on the nucleus; the methyl group at C-1 of 1 is apparently most sensitive towards the oxygenation, giving rise to the highest yield of the 1-formyl and 1-carboxylic acid derivatives (K, O) of 1. Then a less extent of the oxidation of the substituents at C-6 and 7 seems to take place, to afford F' and J.

(ii) The formylated compounds K' and L (at C-3 of 1) are obviously formed by the intermolecular transfer of one nucleus-carbon atom (presumably as a formyl radical) liberated during the oxidative rearrangement. A substitution reaction of the azulenes with the solvent DMF takes place at C-2 (and C-1 to a smaller extent) under these reaction conditions, giving rise to products M', L', and S.

(iii) It is significant that the trimethylazulene 2 directly gave a higher yield of both 1,5- and 1,7-azulenoquinone (J'_1 and I') compared with 1 (which gave only the corresponding 1,7-azulenoquinone Q), since synthesis of azulenoquinones are of current interest.17) An appreciable amount of 1 and 2 underwent rearrangement to give rather unstable inden-1-one derivatives B', C', E, I, and G, although the exact reaction pathways remain to be clarified.

(iv) Cadalene (A_5) and its derivatives (naphthoquinones D and R as well as 2,2'-bicadalene A_4) were formed from 1 but no such naphthalenoids have been isolated from 2. Moreover, only small amounts of benzenoids B'_2 and J'_2 were isolated, whereas such benzenoids (F_1, F_2, and P) were obtained from 1 to a considerable extent.

(v) A part of the inden-1-one derivatives (see above) subsequently condense either with their starting material to give D', E', H, and C, or with themselves to afford dimers on standing,2) as had been observed for simpler inden-1-ones.18) 3,3'- And 2,3'-biguaiazulene (B, A_3) and 3,3'-diguaiazulenylmethane and ketones (A_2, M) were formed from 1 by the autoxidation, whereas no such compounds were isolated from 2.19)

More precise studies (including theoretical calculations on 1 and 2)20) with regard to the complex reaction mechanism of the autoxidation of these alkylazulenes as well as of azulene itself and various other derivatives are currently in progress.

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7) M': Violet crystals, mp 90 °C; UV λmax 550 nm (log ε 2.67); MS m/e 241 (M^+); IR (KBr) 1655 cm^{-1}; ^{1}H NMR (a) δ 2.60 (3H, s, Me-6), 2.84 (3H, s, Me-4 or 8), 2.88 (3H, s, Me-N), 2.96 (3H, s, Me-8 or 4), 5.07 (2H, s, NCH_2-2), 7.00 (2H, s, H-5 and 7), 7.29 (1H, d, J=4.0 Hz, H-1 or 3), 7.45 (1H, d, J=4.0 Hz, H-3 or 1), and 8.21 (1H, s, N-CHO), (b) δ 2.59 (3H, s, Me-6), 2.77 (1H, s, Me-N), 2.84 (3H, s, Me-4 or 8), 2.95 (3H, s, Me-8 or 4), 5.16 (2H, s, NCH_2-2), 7.02 (2H, s, H-5 and 7), 7.31 (1H, d, J=4.0 Hz, H-1 or 3), 7.49 (1H, d, J=4.0 Hz, H-3 or 1), and 8.21 (1H, s, N-CHO), a and b being a 3:2 mixture due to restricted rotation of the C-N bond in amide group, cf. A. Mannschreck, Tetrahedron Lett., 1965, 1341.
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9) J'_1: Yellow crystals, mp 120 °C (decomp); UV λmax 400 nm (log ε 3.65); MS m/e 200 (M^+); IR (KBr) 1695 and 1575 cm^{-1}; ^{1}H NMR δ 2.24 (3H, s, Me-6), 2.31 (3H, s, Me-4), 2.60 (3H, s, Me-8), 6.25 (1H, d, J=6.0 Hz, H-2), 7.04 (1H, s, H-7), and 7.94 (1H, d, J=6.0 Hz, H-3).
10) B'_1: Yellow crystals, mp 38 °C; UV λmax 400 nm (log ε 3.33); IR (KBr) 1695 cm^{-1}; MS m/e 172 (M^+); ^{1}H NMR δ 2.20 (3H, s, Me-4), 2.22 (3H, s, Me-6), 2.43 (3H, s, Me-7), 5.74 (1H, d, J=6.0 Hz, H-2), 6.88 (1H, s, H-5), and 7.58 (1H, d, J=6.0 Hz, H-3).
11) C'_1: Yellow crystals, mp 64 °C; UV λmax 400 nm (log ε 3.42); IR (KBr) 1695 cm^{-1}; MS m/e 172 (M^+); ^{1}H NMR δ 2.15 (3H, s, Me-5), 2.20 (3H, s, Me-4), 2.42 (3H, s, Me-7), 5.78 (1H, d, J=6.0 Hz, H-2), 6.76 (1H, s, H-6), and 7.62 (1H, d, J=6.0 Hz, H-3).
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15) E': Violet crystals, mp 145 °C; UV λmax 563 nm (log ε 3.53); IR (KBr) 1695 cm^{-1}; MS m/e 342 (M^+); ^{1}H NMR δ 1.80, 2.28, 2.60, 2.64, 2.78, and 3.16 (3H each, all s, M-4, 5, 6', 4', 8', and 7), 2.65 (1H, dd, J=18.0 and 3.0 Hz, H-2), 3.26 (1H, dd, J=18.0 and 8.0 Hz, H-2), 5.49 (1H, dd, J=8.0 and 3.0 Hz, H-3), 6.71 (1H, d, J=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, J=4.0 Hz, H-3').
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