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On the Oxidation of Guaiazulene*1,*2

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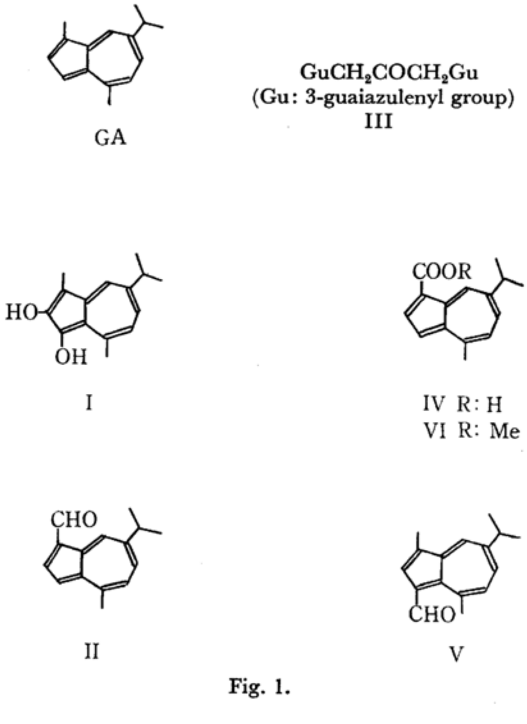
Guaiazulene was oxidized with potassium permanganate and with selenium dioxide according to the Treibs procedure. An acidic and a neutral crystalline compounds obtained from the permanganate oxidation in acetone were identified by means of UV, IR, and NMR spectrum measurements as 4-methyl-7-isopropylazulene-1-carboxylic acid and 1-formyl-4-methyl-7-isopropylazulene respectively. It was also confirmed that the selenium dioxide oxidation of guaiazulene in acetone gave 3-formylguaiazulene and 3,3′-diguaiazulenylacetone, the chemical structure of which had already been established by Treibs.

In 1957, Treibs[1] reported that guaiazulene (GA) was oxidized in acetone with pulverized potassium permanganate to yield small amounts of an acidic compound, A, and also that the oxidation with selenium dioxide gave compounds B and C. According to the results of the elemental analyses and the visible absorption spectrum measurements, he proposed the structural formula; 2,3-dihydroxyguaiazulene (I), 1-formyl-4-methyl-7-isopropylazulene (II), and 3,3′-diguaiazulenylacetone (III)[2] for the compounds A, B, and C respectively.

In the present work the oxidation of GA was carried out by Treibs procedure in order to prepare these three compounds as reference substances for the thin-layer chromatographic study of the photooxidation of GA.[3] By the selenium dioxide oxidation of GA, compounds B and C were obtained as has been described by Treibs;[1,2] in the case of permanganate oxidation, another neutral compound, D, was obtained together with an acidic compound,


GA

$GuCH_2COCH_2Gu$
(Gu: 3-guaiazulenyl group)
III

I

IV R: H
VI R: Me

II

V

Fig. 1.

[*1] Studies of the Azulenes. Part II. Part I: N. Sakota and K. Kohara, *Nippon Kagaku Zasshi (J. Chem. Soc. Japan, Pure Chem. Sect.)*, **86**, 747 (1965).

[*2] Presented at 10th Symposium on the Chemistry of Terpenes, Essential Oils and Aromatics, Tokyo, 1966.

1) W. Treibs, *Ber.*, **90**, 761 (1957).

2) W. Treibs and R. Vogt, *ibid.*, **94**, 1739 (1961).

3) K. Kohara, Y. Otani and N. Sakota, Preprints for the 9th Symposium on the Chemistry of Terpenes, Essential Oils and Aromatics (Sendai, 1965), p. 147.

A. The present results of the IR and NMR spectra measurements of these compounds revealed that compounds A, B, and D should correspond to the structures 4-methyl-7-isopropylazulene-1-carboxylic acid (IV), 3-formylguaiazulene (V) and 1-formyl-4-methyl-7-isopropylazulene (II) respectively, and that compound C is III, as was determined by Treibs and Vogt.

Experimental

Measurements. The NMR data were obtained on a Japan Optics Lab. JNM-3H-60 spectrometer using tetramethylsilane as an internal standard. The infrared absorption spectra were recorded on a Shimadzu model IR-27 infrared spectrophotometer. The ultraviolet and visible absorption measurements were carried on a Jasco model ORD/UV-5 recording spectrophotometer. The plates for thin-layer chromatography were prepared with silica gel G (Merck) and developed with ethyl acetate - *n*-hexane (15 : 85).

Oxidation of GA with Potassium Permanganate. To a solution of 10.0 g of GA in 1000 m*l* of acetone containing 60 m*l* of water, 25 g of powdered potassium permanganate were added in small portions at room temperature. The reaction mixture was then filtered to separate manganese dioxide. By evaporating off the acetone from the filtrate under reduced pressure, a blue, oily product was obtained.

Purification of 4-Methyl-7-isopropylazulene-1-carboxylic Acid (IV). The ether solution of the blue, oily product was extracted with a 2% sodium hydroxide solution, and the alkaline layer was then acidified with hydrochloric acid and extracted again with ether. The deep-red-colored ether extract was washed with a dilute sodium bicarbonate solution and then with water, and dried. The evaporation of ether gave 0.3 g of the acidic compound, A, as red needle crystals, mp 169°C. It was recrystallized from petroleum ether, mp 171°C, and was identified as IV, as will be shown later. Found: C, 78.03; H, 7.18%. Calcd for $C_{15}H_{16}O_2$: C, 78.92; H, 7.07%. Visible: λ_{max} 532, 565, 620 mμ. IR: 1628 cm^{-1} for C=O, 2550 cm^{-1} for O–H (Nujol). Tlc: R_f=0.15 (red).

Methyl 4-Methyl-7-isopropylazulene-1-carboxylate (VI). A tenth of a gram of IV was dissolved in 2 m*l* of anhydrous methanol containing a small amount of sodium. To this solution 0.4 g of methyl sulfate was added, drop by drop, under cooling with ice. The mixture was then poured into water and extracted with ether. The ether solution was dried on sodium sulfate and evaporated to give a red oil. The red oil was purified by chromatography through a silica gel column (Wako gel C-200) with ethyl acetate - *n*-hexane (15 : 85). Found: C, 78.99; H, 7.61%. Calcd for $C_{16}H_{18}O_2$: C, 79.31; H, 7.49%. Visible: λ_{max} 536, 574, 627 mμ. IR: 1692 cm^{-1} for C=O (CCl$_4$). Tlc: R_f=0.46 (red).

Isolation of 1-Formyl-4-methyl-7-isopropylazulene (II). A neutral oil obtained by the permanganate oxidation was chromatographed on silica gel. About 5.5 g of unreacted GA was eluted with petroleum ether, while several kinds of colored compounds (red, yellowish-green, blue, *etc.*) remained on the column. They could be eluted separately with ethyl acetate - *n*-hexane (15 : 85). A tenth of a gram of the red compound, D, which spotted at R_f=0.52 on a thin-layer was purified by repeated elution chromatography with ethyl acetate - *n*-hexane (15 : 85) on a silica-gel column. Thus, 0.05 g of dark red crystals, mp 60—61°C, was obtained. Found: C, 84.44 H, 7.67%. Calcd for $C_{15}H_{16}O$: C, 84.87; H, 7.60%. Visible: λ_{max} 535, 580 (shoulder), 630 mμ. IR: 1645 cm^{-1} for C=O, 2790, 2700 cm^{-1} for aldehydic C–H (CCl$_4$). Tlc: R_f=0.52 (red). 2,4-DNP, mp 265—266°C. Found: C, 64.49; H, 5.03; N, 14.20%. Calcd for $C_{21}H_{20}O_4N_4$: C, 64.27; H, 5.14; N, 14.28%.

Oxidation of GA with Selenium Dioxide. A solution of 7 g of SeO$_2$ in 50 m*l* of water was added, drop by drop, to a solution of 15 g of GA in 1000 m*l* of acetone under ice cooling; the mixture was allowed to stand for 24 hr at room temperature. Meanwhile, the solution changed green from blue. After the neutralization of the mixture with solid sodium carbonate, the solvent was distilled off and the residue was extracted with cyclohexane. A carbonyl compound, C, and a small quantity of an aldehyde, B, were obtained by repeated chromatography with benzene on a silica gel column. Only a small amount of GA was recovered at that time.

3-Formylguaiazulene (V). Compound B (0.1 g) was recrystallized from ethanol as brownish-red crystals, mp 84—86°C. Found: C, 85.14; H, 7.94%. Calcd for $C_{16}H_{18}O$: C, 84.92; H, 8.02%. Visible: λ_{max} 568 mμ IR: 1630 cm^{-1} for C=O, 2680 cm^{-1} for aldehydic C–H (CCl$_4$). Tlc: R_f=0.28 (brownish-red). 2,4-DNP, mp 181°C. Found: C, 64.82; H, 5.32; N, 13.88%. Calcd for $C_{22}H_{22}O_4N_4$: C, 65.01; H, 5.46; N, 13.79%.

3,3-Diguaiazulenylacetone (III). Compound C (3.8 g) was recrystallized from *n*-hexane as blue needle crystals, mp 196°C. Found: C, 88.13; H, 8.32%. Calcd for $C_{33}H_{38}O$: C, 87.95; H, 8.50%. Visible: λ_{max} 622, 675 mμ. IR: 1705 cm^{-1} for C=O (Nujol). Tlc: R_f=0.59 (blue).

Results and Discussion

Structure of Acidic Compound A. Treibs[1] proposed the structure I for an acidic compound, A, in view of the position of the visible absorption maximum of compound A and the formation of guaiazulene dimethyl ether-2,3 (compound E) by treating compound A with methyl sulfate.

In the present work, however, a broad absorption of ν_{O-H} near 2550 cm^{-1} (Nujol) and an intense absorption of a hydrogen-bonded carbonyl at 1628 cm^{-1} were found in the infrared spectrum of compound A. Furthermore, the treatment of compound A with methyl sulfate led to the disappearance of the ν_{O-H} absorption and the shift of the $\nu_{C=O}$ absorption to a higher frequency in CCl$_4$. Moreover, compounds A and E were found to have the visible absorption maximum at 532 and 536 mμ in *n*-hexane respectively (Fig. 2). Hence, it was deduced that the acidic compound, A, should be a carboxylic acid and that compound E should be the methyl ester of compound A.

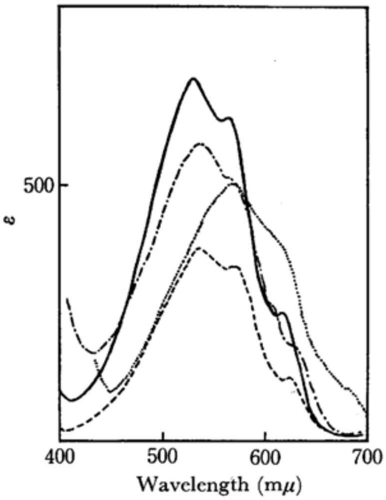


Fig. 2. The visible absorption spectra of compound A(IV)(——), B(V)(·········), D(II)(·–·–) and E(VI)(------) in *n*-hexane.

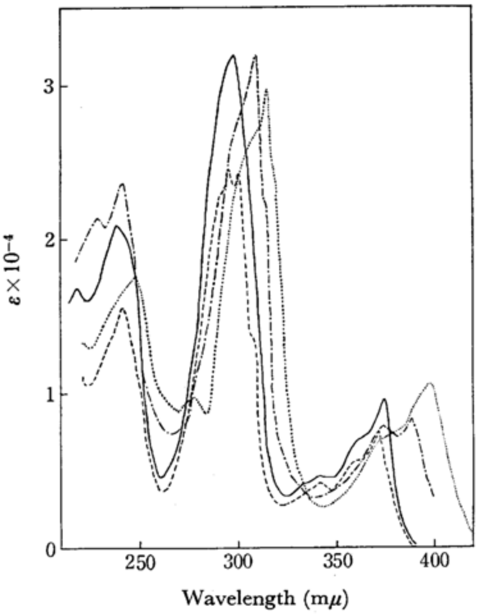


Fig. 3. The ultraviolet absorption spectra of compound A(IV)(——), B(V)(·········), D(II)(·–·–) and E(VI)(------) in *n*-hexane.

The NMR spectra of compounds A and E are shown in Fig. 4. In comparison with the assignment of the NMR spectrum of GA, which had already been reported,[4] it was found that the signal corresponding to one of the two methyl groups of GA disappeared in the spectrum of compound A and that the two signals due to ring protons, H_2 and H_8, shifted considerably to a lower magnetic field compared with those of GA. Those results have lead the present author to conclude that the methyl group in the 1-position was oxidized to a carboxyl group. The signals of ring protons can be assigned as is shown in Fig. 4-a. As the signal at 7.14 ppm, which was not assigned to the ring proton, remains unchanged upon deuterium exchange, it may be assigned to the peak of a proton of $CHCl_3$ in the solvent $CDCl_3$. The signal to be assigned to an acidic proton was not found in Fig. 4-a; this is presumably because of the disappearance of the signal by shifting to a lower magnetic field or by a spectral broadening of the peak. The NMR spectrum of compound E indicated the

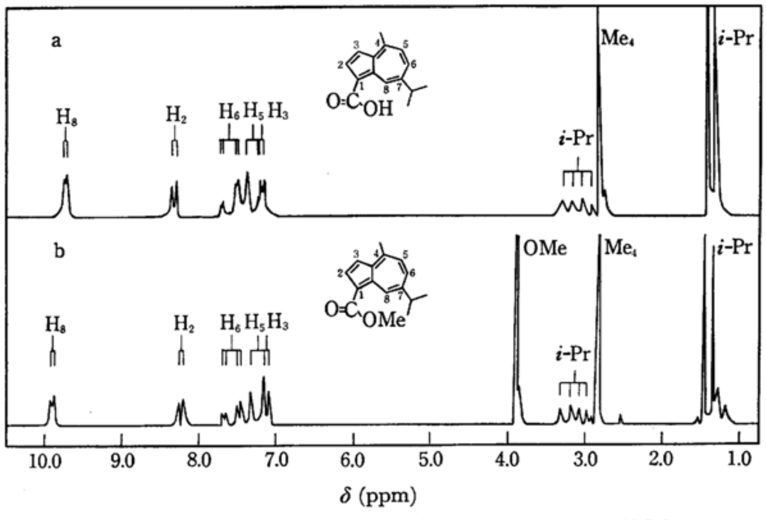


Fig. 4. The NMR spectra of two compounds at 60 Mc.
a, compound A in $CDCl_3$. b, compound E in CCl_4.

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[4] D. Meuche, B. B. Molloy, D. H. Reid and E. Heilbronner, *Helv. Chim. Acta*, **46**, 2483 (1963).

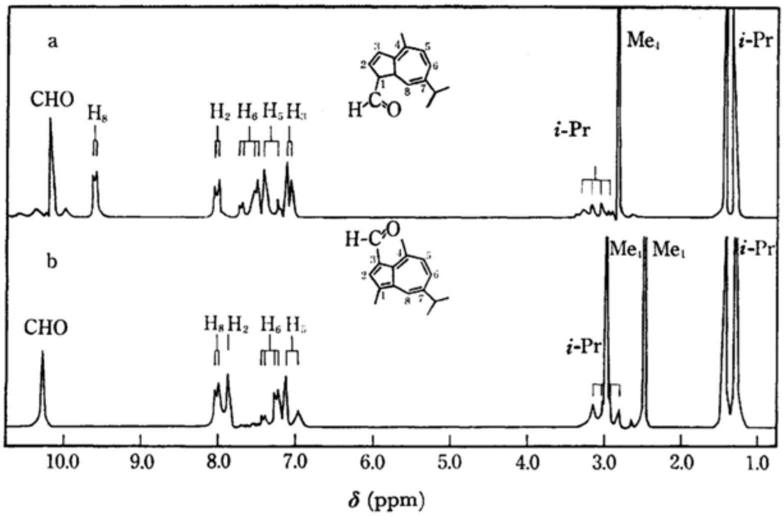

Fig. 5. The NMR spectra of azulene aldehydes at 60 Mc.
a, compound D in CCl_4. b, compound B in CCl_4.

presence of an ester methyl (3.89 ppm), a ring methyl (2.84 ppm), and five ring protons which are in just the same positions as those of the carboxylic acid, A. Besides, the chemical shifts of the ester methyl and ring protons (H_2 and H_3) in compound E are in good agreement with those of the methyl 4-methylazulene-1-carboxylate isolated by Meuche *et al.*[5] from natural Moose. From the results above mentioned, it may be deduced that the structures of compounds A and E should correspond to 4-methyl-7-isopropylazulene-1-carboxylic acid (IV) and methyl 4-methyl-7-isopropylazulene-1-carboxylate (VI) respectively. The absorption maxima in the visible region of these compounds satisfy the Plattner rule.[6]

Structure of Compound D. The dark red crystal (mp 60—61°C) obtained from a neutral portion of the reaction mixture in the permanganate oxidation is a new substance which had not been isolated by Treibs or by others. The visible absorption spectrum of compound D showed a maximum at 535 mμ, which shifted by 70 mμ to a shorter wavelength as compared with that of GA at 605 mμ. The UV spectrum of compound D (Fig. 3) showed a maximum at 390 mμ corresponding to carbonyl. The infrared spectrum of compound D also indicates a strong $\nu_{C=O}$ absorption at 1645 cm^{-1} and ν_{C-H} (aldehydic) absorptions at 2790 and 2700 cm^{-1} (CCl_4). In the NMR spectrum of compound D (Fig. 5-a), a methyl proton signal in the 1-position of GA vanished and an aldehydic proton[7,8] appeared at 10.12 ppm. The ring protons are assigned as indicated in the figure from the coupling constants. From these results, it may be concluded that compound D is 1-formyl-4-methyl-7-isopropylazulene (II). It has also been clarified by thin-layer chromatography that this aldehyde is gradually oxidized in CCl_4 to give a carboxylic acid (IV). This structure is also supported by the fact that the absorption maxima of the compound D at 535, 580, and 630 mμ are closely similar to those of lactaroviolin[9—12] at 538, 577, and 633 mμ.

Structure of Compound B. Treibs has reported that an aldehyde, mp 88.5—89.5°C, obtained by the selenium dioxide oxidation of GA corresponds to formula II. As is shown in Fig. 5-b, however, the NMR spectrum of this aldehyde, mp 84—86°C, obtained by the present author showed that two methyl groups and one isopropyl group remained as they were in GA. An aldehydic proton signal[7,8] was found at 10.34 ppm. The formyl group should be situated in the 3-position of the azulene ring, since four ring protons were assigned to H_2, H_5, H_6, and H_8, as is indicated in Fig. 5-b. The R_f value of tlc and the UV, visible, IR, and NMR spectra of compound B were in good agreement with those of 3-formylguaiazulene obtained by means of the formylation of GA,[13] and

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[5] D. Meuche and S. Huneck, *Ber.*, **99**, 2669 (1966).

[6] E. Heilbronner, "Non-Benzenoid Aromatic Compounds," ed. by D. Ginsburg, Interscience, New York (1959), p. 171.

[7] D. Meuche, D. Dreyer, K. Hafner and E. Heilbronner, *Helv. Chim. Acta*, **50**, 1178 (1967).

[8] A. J. Fry, B. W. Bowen and P. A. Leermakers, *J. Org. Chem.*, **32**, 1970 (1967).

[9] H. Willstaedt, *Ber.*, **68**, 333 (1935).

[10] P. Karrer, H. Ruckstuhl and E. Zbinden, *Helv. Chim. Acta*, **28**, 1177 (1945).

[11] E. Heilbronner and R. W. Schmidt, *ibid.*, **37**, 2018 (1954).

[12] K. Hafner and C. Bernhard, *Angew. Chem.*, **69**, 533 (1957).

[13] K. Hafner and C. Bernhard, *Ann.*, **625**, 108 (1959).

the melting point of compound B was not depressed when it was mixed with the latter. From these results, it may be concluded that the aldehyde B is not II but 3-formylguaiazulene (V).

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