The Thermal Reaction of 3-Benzoylguaiazulene and Methyl Guaiazulene-3-carboxylate

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(Received January 31, 1972)

3-Benzoylguaiazulene (I) and methyl guaiazulene-3-carboxylate (XI) were heated at 250—260°C. From 3-benzoylguaiazulene we obtained, besides S-guaiazulene (II), three new azulenoids, which were established to be 2-benzoylguaiazulene (III), 1-benzoyl-7-isopropyl-3,4-dimethylazulene (IVa) and 2-benzylguaiazulene (V). On the other hand, the products yielded from methyl guaiazulene-3-carboxylate, together with S-guaiazulene, were elucidated to be methyl 7-isopropyl-3,4-dimethylazulene-1-carboxylate (XII) and methyl guaiazulene-2-carboxylate (XIII). In addition to the loss and the migration of the acyl group, the exchange of acyl and methyl groups in the five-membered ring took place in both acylguaiazulenes, as well as in the case of 3-acetylguaiazulene reported earlier. Moreover, the reduction of the acyl group was also observed in 3-benzoylguaiazulene.

In an earlier paper[1] dealing with the thermal reaction of 3-acetylguaiazulene at 200°C, it was shown that S-guaiazulene (II) and 2-acetylguaiazulene (VI) were formed by the loss or the migration of the acetyl group. In the same reaction, 1-acetyl-7-isopropyl-3,4-dimethylazulene (XIV) was also found to be formed by the exchange of acetyl and methyl groups in the five-membered ring of the azulene nucleus.[2] The present investigation was undertaken to see if this kind of reaction could occur in another acylguaiazulene having an acyl group such as benzoyl or methoxycarbonyl.

Results and Discussion

The Thermal Reaction of 3-Benzoylguaiazulene (I). When 3-benzoylguaiazulene (I) was heated at 250—260°C for 2 hr, three new compounds were obtained in addition to the S-guaiazulene (II) formed by the loss of the benzoyl group.

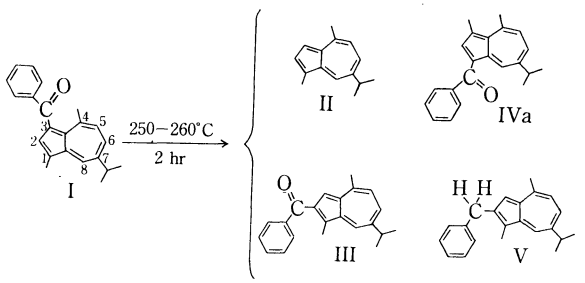

Chart 1.

a) 2-Benzoylguaiazulene (III). The green crystalline substance (mp 87.5—88.5°C) which was isolated as the major product in this reaction had the same molecular formula, $C_{22}H_{22}O$, as the I used as the starting material. The existence of a benzoyl group in this compound was known from the appearance of the $\nu_{C=O}$ band at 1633 cm^{-1} in its IR spectrum and from the presence of the notable ions at *m/e* 197 and 105 respectively, ascribed to $(M-C_6H_5CO)^+$ and $C_6H_5^+$ in the mass spectrum.

In the NMR spectrum of the compound taken in a deuterochloroform solution (*cf.* Experimental section) we observed, besides five aromatic proton signals ascribed to the benzoyl group, signals due to one isopropyl-, two aromatic methyl-, and four aromatic ring-protons corresponding to the guaiazulene moiety. These chemical shifts and coupling constants ($J_{5,6}$= 10.1 Hz, $J_{6,8}$=1.5 Hz) were quite close to those of 3-benzoylguaiazulene. Thus, the compound may be thought to be an isomer which differs from 3-benzoylguaiazulene in the position of the benzoyl group.

On the other hand, the NMR spectrum taken in a trifluoroacetic acid solution lacked the H_2 signal which was observed in the spectrum of I (7.50 ppm). This agreed well with the fact that the Me_1 and C_3-methylene signals[3] appeared as a triplet and a quartet (2.45 and 4.59 ppm, J=2.0 Hz) respectively because of the absence of the H_2 proton. The compound may, therefore, be concluded to hold the benzoyl group at the 2-position.

In order to confirm the above deductions, we attempted to synthesize 2-benzoylguaiazulene (III) starting from 2-acetylguaiazulene (VI), whose structure had previously been established.[1] As the first step, we attempted to prepare the carbinol (X) by the reaction of VI and a Grignard reagent derived from bromobenzene. The product, however, consisted of two kinds of blue oil. On the basis of the NMR data (*cf.* Experimental section), these compounds were elucidated to be 2-(1-phenylethenyl)guaiazulene (VII) and 2-(1-phenylethyl)guaiazulene (VIII), which would be formed from carbinol (X) through dehydration or hydrogenation, respectively. Successively, the olefin

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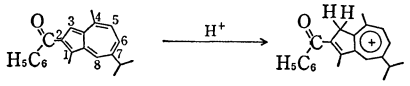
1) S. Kurokawa, This Bulletin, **43**, 509 (1970).

2) S. Kurokawa, *Tetrahedron Lett.*, **1969**, 3567.

3) For instance, the protonation occurs in 2-benzoylguaiazulene as follows. All the compounds in this paper except the 1-benzoyl compound (IVa) take this type of conjugate acid form, in which protonation occurs at the 3-position:



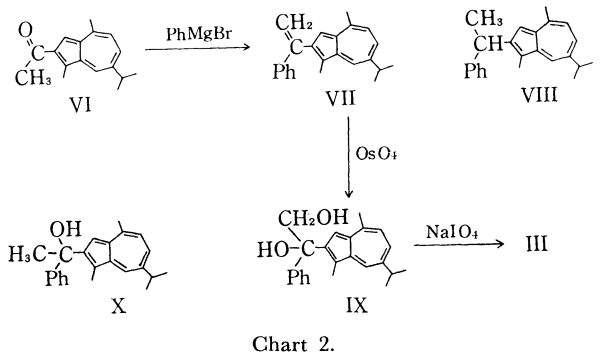


Chart 2.

(VII) was oxidized with osmium tetroxide[4] to give glycol (IX), which was then further oxidized with periodate to afford III. The green crystalline substance obtained in the thermal reaction of I was identical with the synthesized product; thus, it was concluded to be 2-benzoylguaiazulene (III).

b) 1-Benzoyl-7-isopropyl-3,4-dimethylazulene (IVa). A purple oil with a molecular formula of $C_{22}H_{22}O$ was isolated from a benzene-eluted fraction in the elution chromatography of the reaction products. This compound exhibited a $\nu_{C=O}$ band at 1606 cm^{-1} in the IR spectrum and gave 2,4-dinitrophenylhydrazone (mp 249—251°C). Moreover, the *m/e* 105 ion, the base peak in the mass spectrum, was attributed to $C_6H_5CO^+$. Thus, it is certain that the compound also contains a benzoyl group.

Furthermore, all the signals observed in the NMR spectrum (Fig. 1A) corresponded well to those in the spectra of the starting material (I) and 2-benzoylguaiazulene (III). This compound may, therefore, be thought to be an isomer which differs from I and III only in the positions of the substituents.

The two doublet signals of 9.78 (d, 1H, J=2.1 Hz) and 7.17 ppm (d, 1H, J=10.5 Hz) seen in the aromatic-proton region of the NMR spectrum can reasonably be assigned to H_8 and H_5 respectively, for their coupling constants and coupling pattern agree very closely with those of S-guaiazulene (II) and I. The H_6 proton, though unrecognizable due to the overlap of the benzene-ring protons, must exist, because no other proton can be a coupling partner of the above two protons. Consequently, the seven-membered ring of this compound has the same 4,7-disubstitution as that of the starting material.

Among these signals, the signal of the H_8 proton (9.78 ppm) moves downfield by 1.73 ppm relative to that of S-guaiazulene. Such a remarkable shift is characteristic of the acylazulenes with an acyl group at the peri position (1-position) [*cf.* 1-acetylazulene; 9.89 ppm.[5] 1-acetyl-7-isopropyl-3,4-dimethylazulene; 10.28 ppm[2]]. Thus, the compound has the benzoyl group at the 1-position.

The methyl doublet of 2.79 ppm with J=1.0 Hz (Me_3) observed in the NMR spectrum taken in a trifluoroacetic acid solution (Fig. 1B) may be attributed to the methyl protons of the five-membered ring spin-coupled with an adjacent olefinic proton

4) J. B. Brown, H. B. Henbest, and E. R. H. Jones, *J. Chem. Soc.*, **1952**, 3172.

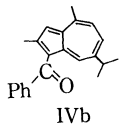


Chart 3.

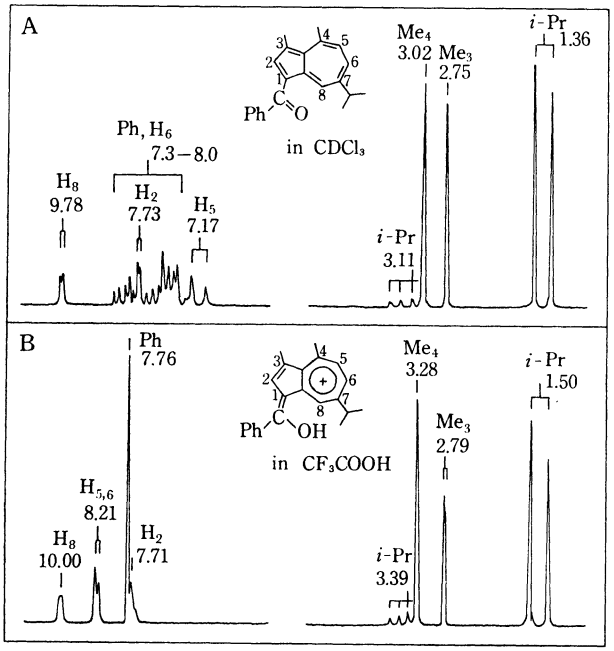


Fig. 1. NMR spectra of 1-benzoyl-7-isopropyl-3,4-dimethylazulene (A) and its conjugate acid (B).

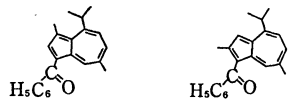
(7.71 ppm; H_2). One of the methyl groups should, therefore, be located at either the 2- or 3-position. From the above data, the two formulae of IVa and IVb become possible for this compound.[6] However, the compound represented by IVb has already been reported by Treibs *et al.* to be the benzoylation product of Se-guaiazulene,[7] and it is evidently different from the present compound. The present compound must, therefore, be 1-benzoyl-7-isopropyl-3,4-dimethylazulene (IVa).

c) 2-Benzylguaiazulene (V). A blue oily substance, which had a molecular formula of $C_{22}H_{24}$ and which gave a dark brown picrate (mp 106—108°C), was separated by the *n*-hexane-silica-gel elution chromatography of the reaction products.

In the NMR spectrum of the compound taken in a deuterochloroform solution (*cf.* Experimental section) we observed a sharp singlet (4.29 ppm, 2H) assigned to the protons of a methylene group, in addition to the

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

6) Strictly speaking, the following formulae are also possible for this compound. The examination on these formulae is, however, abbreviated in this paper for they, accompanying the changes in the seven-membered ring, have already been discussed in a preceding paper (Ref. 2):



7) W. Treibs, Ch. Vollard, and M. Reimann, *Ann.*, **648**, 164.

signals due to a benzene ring and a guaiazulene moiety. Thus, the compound may be thought to have a benzyl group formed through the reduction of the benzoyl group in the starting material (I).

When a visible absorption maximum (592 nm) of the compound is analyzed according to the Plattner rule,[8] three positions, 2, 6, and 8, are possible for the benzyl group. Of these positions, the 2-position is selected, since the signal attributable to H_2 is not observed in the NMR spectrum of the compound taken in a trifluoroacetic acid solution (*cf.* Experimental section); this is in accordance with the appearance of the C_3-methylene and Me_1 signals as a quartet and a triplet respectively (3.89 and 2.52 ppm respectively; J=1.8 Hz).

Based on the above knowledge, this compound was synthesized through the Huang-Minlon reduction of 2-benzoylguaiazulene (III), whose structure had been established before (*cf.* a); thus, it was determined to be 2-benzylguaiazulene (V).

The Thermal Reaction of Methyl Guaiazulene-3-carboxylate (XI). The heating of the methyl ester (XI) at 250°C for 1 hr produced two kinds of ester compounds besides S-guaiazulene.

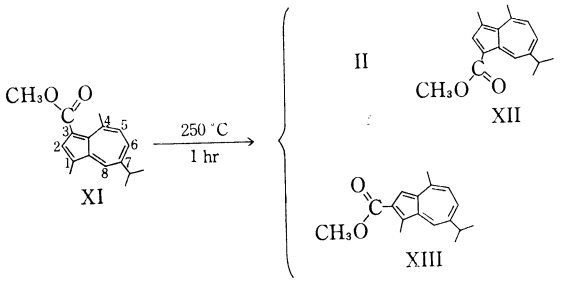


Chart 4.

a) Methyl 7-Isopropyl-3,4-dimethylazulene-1-carboxylate (XII). A purple oily substance, the major product of the reaction, had a molecular formula of $C_{17}H_{20}O_2$, the same as XI. This compound showed a $\nu_{C=O}$ band at 1688 cm^{-1} in its IR spectrum, and it exhibited a sharp methyl singlet (3.91 ppm) in its NMR spectrum (Fig. 2A) which was assigned to a methoxy group. Moreover, the *m/e* 225 peak seen in the mass spectrum was attributed to the $(M-OCH_3)^+$ ion. Thus, the compound is a methyl ester similar to the starting material. A doublet signal of an aromatic-ring proton (9.78 ppm, 1H, J=2.0 Hz), observed at the lowest field in the NMR spectrum (Fig. 2A), was ascribed to the H_8 proton by comparison with the spectra of other azulenes. The chemical shift of this proton was, however, of an extremely downfield nature, which is the characteristic of the acylazulenes having an acyl group at the peri position [*cf.* 1-benzoyl compound (IVa)]. Accordingly, the compound may be thought to hold a methoxycarbonyl group at the 1-position.

Furthermore, the NMR spectrum of a conjugate acid (Fig. 2B) showed a methyl singal (1.62 ppm, d, J=7.2 Hz; Me_3) and a methine signal (4.48 ppm, double quartet, J=7.2 and 1.8 Hz; H_3), spin-coupled to one another. On the other hand, as only the 3-position is known to be possible for the protonation in an azulene nucleus,[3] the above methyl group apparently exists at the 3-position.

8) J. F. Tilney-Basset and W. A. Waters, *J. Chem. Soc.*, **1959**, 3123. *cf.* E. Heilbronner, "Non-Benzenoid Aromatic Compounds," ed. by D. Ginsburg, Interscience, New York (1959), p. 171.

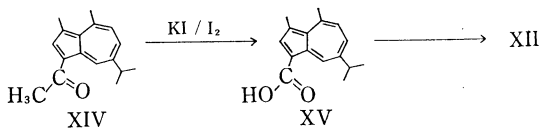
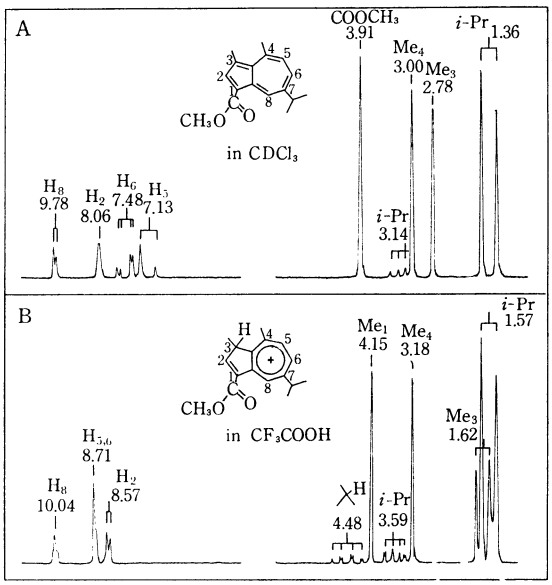


Chart 5.



δ, ppm

Fig. 2. NMR spectra of methyl 7-isopropyl-3,4-dimethylazulene-1-carboxylate (A) and its conjugate acid (B).

These data suggest that the compound has the structure of methyl 7-isopropyl-3,4-dimethylazulene-1-carboxylate (XII). On the basis of this deduction, the structure was established as follows: 1-Acetyl-7-isopropyl-3,4-dimethylazulene (XIV), elucidated earlier,[2] was oxidized with hypoiodite to give the carboxylic acid (XV), which was then treated with diazomethane to afford the same methyl ester (XII) as was obtained from XI.

b) Methyl Guaiazulene-2-carboxylate (XIII). Trace amounts of a blue oil isolated from the reaction products were found to be XIII by comparison with an authentic specimen.[1]

Sequence of the Reaction. Table 1 lists the yields (%) of the reaction products formed from the three

Table 1. The yield (%) of the thermal isomerization products

Products	Acyl groups		
	CH_3CO[1,2]	C_6H_5CO	CH_3OCO
S-Guaiazulene	1.4	1.8	0.8
2-Acylguaiazulene	16.4	11.3	0.08
1-Acyl-7-isopropyl-3,4-dimethylazulene	7.0	5.7	5.3
2-Benzylguaiazulene	—	2.5	—

3-acylguaiazulenes studied thus for.

As is obvious from Table 1, all of the 3-acylguaiazulenes gave reaction products of the common type, *viz.*, those formed through the loss of the acyl group, through the migration of the same group from the 3- to the 2-position, and through the exchange between acyl- and methyl-groups in the five-membered ring of the azulene nucleus. However, some discrepancy among the reactions due to the differences in the acyl substituents is also observed: the main reaction in ketone is the migration of the acyl group, while that in the methyl ester is the exchange of acyl- and methyl-groups in the five-membered moiety, and the reduction of acyl group is noted only in the benzoyl compound. How these differences in the reactivity occur is not apparent at present, but we are continuing to make our best efforts to solve this problem in our laboratory.

Experimental

All the melting points in this paper are uncorrected. The UV and visible absorption spectra were taken in a cyclohexane solution. The IR spectra were obtained using liquid films or KBr disks, and the mass spectra (MS), at 70 eV. The NMR spectra were measured at 60 MHz, and the chemical shifts are given by ppm, using TMS as the internal standard. The thin-layer chromatography (tlc) was conducted by the use of silica gel-G (Merck).

3-Benzoylguaiazulene (I). This compound was synthesized by the reaction of S-guaiazulene (II) and benzoyl chloride in the presence of an aluminium chloride catalyst.[9] The recrystallization of the product from *n*-hexane-ethanol (1 : 1) gave green prisms [mp 122.8—123.2°C (mp 121.5°C,[9] mp 120—121°C[10])], which showed a single brown spot (R_f, 0.20) in tlc using benzene. IR: 1606 cm^{-1} (C=O) [1637 cm^{-1} in nujol mull[10]]. UV: nm (log ε), 244.5 (4.51), 280sh (4.30), 290 (4.42), 309 (4.08), 323.5 (4.10), 401 (3.91) [249, 289, 314, and 319 nm respectively[10]]. Visible absorption spectrum: nm (ε), 586 (443), 639sh (329) [583 nm[10]]. NMR ($CDCl_3$): 2.55 (s, 3H; Me_1), 7.55 (S, 1H; H_2), 2.71 (s, 3H; Me_4), 7.12 (d, 1H, J=11.0 Hz; H_5), 1.37/3.09 (d, 6H/m, 1H, J=6.0 Hz; i-Pr), 8.20 (d, 1H, J=1.8 Hz; H_8), 7.3—8.0 (m, 6H; Ph, H_6). NMR (CF_3COOH)[3]: 2.51 (q, 3H; Me_1), 7.50 (m, 1H; H_2), 6.44 (m, 1H; H_3), 2.96 (s, 3H; Me_4), 8.78 (s, 2H; $H_{5,6}$), 1.62/3.61 (d, 6H/m, 1H, J=6.8 Hz; *i*-Pr), 8.84 (s, 1H; H_8), 7.7—8.5 (m, 5H; Ph). MS: *m/e* 302 (M, $C_{22}H_{22}O$; 1.7%), *m/e* 287 (M-CH_3; 46.5%), *m/e* 105 (C_6H_5CO; 25.8%), *m/e* 77 (C_6H_5; 90%).

Thermal Reaction of 3-Benzoylguaiazulene (I). 3-Benzoylguaiazulene (2.00 g) was heated at 250—260°C in a sealed tube for 2 hr. The reaction mixture, after being dissolved in a small amount of benzene, was eluted through a silica-gel column with benzene, and separated into the following four fractions, depending upon the color:[11]

Fr. 1 blue oil (654.9 mg)··· {S-guaiazulene (II) (35.3 mg) / 2-benzylguaiazulene (V) (50.0 mg)}

Fr. 2 green oil (338.6 mg)···2-benzoylguaiazulene (III) (225.9 mg)

Fr. 3 purple oil (340.1 mg)···1-benzoyl-7-isopropyl-3,4-dimethylazulene (IVa) (113.4 mg)

Fr. 4 brown oil (715.2 mg)···3-benzoylguaiazulene (I) (recovered)

2-Benzylguaiazulene (V). The blue oil of Fr. 1 showed two blue spots (R_f, 0.36 and 0.16) in tlc with *n*-hexane. By means of *n*-hexane-silica-gel elution chromatography, it was separated into two components, corresponding to the two spots in tlc. The oil of R_f, 0.36 was identical with the authentic specimen of II in tlc. V was obtained as a blue oil with an R_f of 0.16, and it gave a dark brown picrate upon treatment by the usual method. After being recrystallized from ethanol, it showed a mp of 106—108°C. UV: nm (log ε), 247.6 (4.38), 291 (4.75), 297 (4.80), 309 (4.23), 341 (3.65), 355 (3.76), 382 (3.26), 390sh (2.74). Visible absorption spectrum: nm (ε), 550sh (313), 592 (422), 632sh (368). NMR ($CDCl_3$): 2.53 (s, 3H; Me_1), 4.29 (s, 2H; CH_2), 7.20 (s, 5H; Ph), 2.75 (s, 3H; Me_4), 1.34/2.95 (d, 6H/m, 1H, J=6.8 Hz; *i*-Pr), 8.16 (d, 1H, J=1.8 Hz; H_8), 6.8—7.7 (m, 3H; $H_{3,5,6}$). NMR (CF_3COOH)[3]: 2.52 (t, 3H, J=1.8 Hz; Me_1), 4.20 (s, 2H; CH_2), 7.34 (s, 5H; Ph), 3.89 (q, 2H, J=1.8 Hz; $2H_3$), 2.92 (s, 3H; Me_4), 8.47 (s, 2H; $H_{5,6}$), 1.55/3.53 (d, 6H/m, 1H, J=6.8 Hz; i-Pr), 8.67 (s, 1H; H_8). MS: *m/e* 288 (M, $C_{22}H_{24}$; 14.3%), *m/e* 273 (M-CH_3; 11.4%), *m/e* 197 (M-$C_6H_5CH_2$; 11.2%), *m/e* 91 (C_7H_7; base peak).

Huang-Minlon Reduction of 2-Benzoylguaiazulene (III). By reference to the procedure of Treibs,[12] a solution of III (104.9 mg) and 100% hydrazine hydrate (0.2 m*l*) in triethylene glycol (2 m*l*) was heated under reflux for 1 hr. To this hot solution, powdered potassium hydroxide (100 mg) was slowly added; the mixture was then gradually brought to room temperature, during which time a vigorous evolution of nitrogen gas was observed and the color of the mixture changed from green to blue. A blue-colored fraction was collected by distilling, under reduced pressure, a mixture of triethylene glycol diluted with water, and the colored material was extracted repeatedly with benzene to give a blue oil (70.7 mg). By means of successive petroleum ether-silica-gel elution chromatography, 2-benzylguaiazulene (V) was separated as a blue oil (36.8 mg) which showed a single spot (R_f, 0.16) in tlc with *n*-hexane.

2-Benzoylguaiazulene (III). The green oil of Fr. 2 was purified by repeated benzene-silica-gel elution chromatography to afford green crystals which showed, after recrystallization from ethanol, a mp of 87.5—88.5°C. It exhibited a single spot (R_f, 0.42) in tlc with benzene. IR: 1633 cm^{-1} (C=O). UV: nm (log ε), 252.5 (4.45), 302 (4.73), 307.5sh (4.67), 345 (3.82), 356 (3.81). Visible absorption spectrum: nm (ε), 645 (598), 736sh (258). NMR ($CDCl_3$): 2.69 (s, 3H; Me_1), 2.74 (s, 3H; Me_4), 6.94 (d, 1H, J=10.1 Hz; H_5), 1.35/3.04 (d, 6H/m, 1H, J=6.4 Hz; *i*-Pr), 8.27 (d, 1H, J=1.5 Hz; H_8), 7.2—8.0 (m, 7H; Ph, $H_{3,6}$). NMR (CF_3COOH)[3]: 2.45 (t, 3H, J=2.0 Hz; Me_1), 4.59 (q, 2H, J=2.0 Hz; $2H_3$), 3.18 (s, 3H; Me_4), 8.91 (s, 2H; $H_{5,6}$), 1.63/3.54 (d, 6H/m, 1H, J=7.0Hz; *i*-Pr), 9.03 (s, 1H; H_8), 7.6—8.2 (m, 5H; Ph). MS: *m/e* 302 (M, $C_{22}H_{22}O$; base peak), *m/e* 287 (M-CH_3; 69.1%), *m/e* 259 (M-C_3H_7; 8.4%), *m/e* 197 (M-C_6H_5CO; 19.1%), *m/e* 105 (C_6H_5CO; 76.2%), *m/e* 77 (C_6H_5; 83.8%).

Found: C, 87.05; H, 6.82. Calcd for $C_{22}H_{22}O$: C, 87.37; H, 7.33%.

The Grignard Reaction of 2-Acetylguaiazulene (VI) with Bromobenzene. To an ethereal solution of a Grignard reagent prepared from bromobenzene (8.4 g) in the usual manner,

9) W. Treibs, *Chem. Ber.*, **90**, 761 (1957).

10) D. H. Reid, W. H. Stafford, and W. L. Staffored, *J. Chem. Soc.*, **1958**, 1118.

11) Next to the dotted lines are shown the compounds obtained from each fraction after it had been further purified by means of elution chromatography or recrystallization.

12) W. Treibs, H.-J. Neupert, and J. Hiebsch, *Chem. Ber.*, **92**. 141 (1959).

under water cooling, another solution of VI (1.9 g) in ether (20 ml) was added, drop by drop, over a 10-min period. After the mixture had then been allowed to stand at room temperature for 7 hr, the excess reagent was decomposed with methanol (25 ml) and subsequently with a dilute aqueous solution of ammonium hydroxide. From the ether layer, a green resinous material was obtained; it was separated into two components by the use of petroleum ether-silica-gel elution chromatography. The olefin (VII) was obtained from the quickly-eluted fraction as a blue oil (169.0 mg) which showed a single spot (R_f, 0.68) in tlc with petroleum ether. NMR ($CDCl_3$): 2.37 (s, 3H; Me_1), 5.74/5.35 (d, 1H/d, 1H, J=2.0 Hz; $=CH_2$), 7.16 (s, 5H; Ph), 2.72 (s, 3H; Me_4), 6.84 (d, 1H, J=10.5 Hz; H_5), 1.28/3.02 (d, 6H/m, 1H, J=7.2 Hz; *i*-Pr), 8.04 (d, 1H, J=1.8 Hz; H_8), 7.0—7.4 m, 2H; $H_{3,6}$).

From the slowly-eluted fraction, the reduced product (VIII) was obtained as a blue oil (269.3 mg), which exhibited a single spot (R_f, 0.58) in tlc with petroleum ether. NMR ($CDCl_3$): 2.40 (s, 3H; Me_1), 1.74/4.45 (d, 3H/q, 1H, J=7.5 Hz; $-CH-CH_3$), 7.05 (s, 5H; Ph), 2.76 (s, 3H; Me_4), 6.80 (d, 1H, J=10.5 Hz; H_5), 1.30/2.98 (d, 6H/m, 1H, J=6.8 Hz; *i*-Pr), 7.97 (d, 1H, J=2.0 Hz; H_8), 7.0—7.3 (m, 2H; $H_{3,6}$).

The Oxidation of 2-(1-Phenylethenyl)guaiazulene (VII) with Osmium Tetroxide. The olefin (VII) (169.0 mg) thus obtained was dissolved in a mixed solvent of pyridine (0.14 ml) and ether (5 ml), and then the solution was added, under dry ice-ethanol cooling (*ca.* −53°C), to a solution of osmium tetroxide (136 mg) in ether (15 ml). The mixture, when cooled for a further hour and then left to stand for a few hrs at room temperature, yielded green crystals; these crystals were separated by filtration and combined with those resulting from the filtrate by letting them stand a further hour at room temperature. The combined crystals were taken up into chloroform (20 ml), and the solution was shaken for 10 min with an aqueous solution (20 ml) containing mannitol (2.1 g) and potassium hydroxide (0.2 g). The subsequent removal of the solvent yielded rough glycol (IX) as a dark green oil (293.2 mg).

Periodate Oxidation of 1-Phenyl-1-(2-guaiazulenyl)ethanediol-1,2 (IX). The rough glycol (IX) dissolved, without further purification, in methanol (29 ml) was oxidized with a 0.05M aqueous solution of sodium metaperiodate by stirring the mixture at room temperature for 40 min under a nitrogen atmosphere. The reaction mixture was then poured into a saturated aqueous solution of sodium chloride, and the precipitate was extracted with ether to give a green mass (372.9 mg). This mass was chromatographed on silica gel with benzene, and then separated into blue crystals (1.9 mg, II) and green crystals (3.1 mg) of 2-benzoylguaiazulene (III).

1-Benzoyl-7-isopropyl-3,4-dimethylazulene (IVa). The purple oil of Fr 3 was further purified with benzene - silica-gel-elution chromatography to give IVa as a purple oil which showed a single spot (R_f, 0.24) in tlc with benzene. IR: 1606 cm^{-1} (C=O). UV: nm (log ε), 250 (4.43), 292 (4.34), 316 (4.38), 393 (4.01), 408sh (3.94). Visible absorption spectrum: nm (ε), 532sh (648), 565 (722), 600sh (576).

The 2,4-dinitrophenylhydrazone of this compound was obtained by using a mixed solvent of ethanol and phosphoric acid[13] as a reddish-brown powder. After being recrystallized with a mixed solvent of ethanol and ethyl acetate, it showed a mp of 249—251°C.

Found: C, 68.97; H, 5.56; N, 11.56%. Calcd for $C_{28}H_{26}N_4O_4$: C, 69.69; H, 5.43; N, 11.61%.

Methyl Guaiazulene-3-carboxylate (XI). This compound was synthesized by treating II with phosgene, followed by the treatment of acid chloride with methanol.[14] It was obtained as a purple oil which showed a single spot (R_f, 0.33) in tlc with benzene. IR: 1699 cm^{-1} (C=O). UV: nm (log ε), 228.5 (4.72), 238 (4.47), 239.5 (4.47), 243.5 (4.57), 249 (4.65), 255 (4.61), 261 (4.37), 264sh (4.00), 267.5 (4.00), 273sh (4.17), 280sh (4.40), 292sh (4.60), 298.5 (4.61), 314sh (4.39), 382 (3.86). Visible absorption spectrum: nm (ε), 544sh (462), 575 (552), 617sh (454) [572 nm[15]]. NMR ($CDCl_3$): 2.55 (s, 3H; Me_1), 7.94 (s, 1H; H_2), 3.87 (s, 3H; MeO), 2.91 (s, 3H; Me_4), 7.19 (d, 1H, J=10.8 Hz; H_5), 7.50 (dd, 1H, J=10.8 and 1.8 Hz; H_6), 1.34/3.07 (d, 6H/m, 1H, J=5.8 Hz; *i*-Pr), 8.23 (d, 1H, J=1.8 Hz; H_8). NMR CF_3COOH)[3]: 2.46 (t, 3H, J=1.8 Hz; Me_1), 7.37 (m, 1H; H_2), 3.91 (s, 3H; MeO), 5.16 (m, 1H; H_3), 3.01 (s, 3H; Me_4), 1.56/3.44 (d, 6H/m, 1H, J=6.6 Hz; *i*-Pr), 8.68 (s, 3H; $H_{5,6,8}$). MS: *m/e* 256 (M, $C_{17}H_{20}O_2$; base peak), *m/e* 241 (M-CH_3; 25.5%), *m/e* 225 (M-OCH_3; 31.8%).

Thermal Reaction of Methyl Guaiazulene-3-carboxylate (XI). XI (1.66 g) was heated in a sealed tube at 250°C for 1 hr. The reaction mixture was chromatographed on silica gel with benzene, and then separated into the following fractions:

Fr. 1 S-guaiazulene (II) (13.2 mg)
Fr. 2 methyl guaiazulene-2-carboxylate (XIII) (1.3 mg)[1]
Fr. 3 methyl 7-isopropyl-3,4-dimethylazulene-1-carboxylate (XII) (87.3 mg)
Fr. 4 methyl guaiazulene-3-carboxylate (XI) (1.22 g) (recovered)

Methyl 7-Isopropyl-3,4-dimethylazulene-1-carboxylate (XII). In order to prevent contamination by a non-azulenic component or an acidic material, the purple oil of Fr. 3 (30.2 mg) was dissolved in a mixed solvent of benzene (1 ml) and petroleum ether (100 ml), after which the solution was extracted twice with 85% phosphoric acid (50 ml). An orange-colored phosphoric acid layer was washed repeatedly with petroleum ether and diluted with ice-water, and purple oil thus isolated was taken up into petroleum ether. After the removal of the solvent, XII was obtained as a purple oil (29.9 mg) which exhibited a single spot (R_f, 0.34) in tlc with benzene. IR: 1688 cm^{-1} (C=O). UV: nm (log ε), 228.5sh (4.23), 234sh (4.34), 240.5sh (4.47), 243.5 (4.56), 249 (4.63), 254.5 (4.54), 261 (4.22), 264 (3.71), 267.5 (3.69), 299.5 (4.68), 306.5 (4.66), 312 (4.51), 350 (3.73), 367 (3.93), 385 (4.08). Visible absorption spectrum: nm (ε), 532sh (540), 571 (720), 615.5 (594). MS: *m/e* 256 (M, $C_{17}H_{20}O_2$; base peak), *m/e* 241 (M-CH_3; 70.2%), *m/e* 225 (M-OCH_3; 23.6%).

Found: C, 78.96; H, 7.72%. Calcd for $C_{17}H_{20}O_2$: C, 79.65; H, 7.86%.

Hypoiodate Oxidation of 1-Acetyl-7-isopropyl-3,4-dimethylazulene (XIV). A solution of XIV (169.0 mg) in dioxane (22 ml) was mixed with a 10% aqueous solution of sodium hydroxide (23 ml) with stirring at 80°C. To this mixture, kept at 80°C, we added, drop by drop over a 20-min period, another aqueous solution (8.2 ml) of iodine (820 mg) and potassium iodide (1.64 g). After the mixture had been stirred for a further 10 min, the excess iodine was reduced by adding a few drops of a saturated sodium hydrogen sulfite

13) G. D. Johnson, *J. Amer. Chem. Soc.*, **73**, 5888 (1951).

14) W. Treibs, H.-J. Neupert and J. Hiebsch, *Chem. Ber.*, **92**, 1216 (1959).

15) W. Treibs, *ibid.*, **92**, 2152 (1959).

solution, the mixture was cooled to room temperature, and the reddish-brown iodoform thus precipitated was filtered off. The filtrate was diluted with water (30 ml), the solution was washed repeatedly with chloroform and acidified with 2N hydrochloric acid, and a crude acidic material was taken up into ether. A rough carboxylic acid (XV) was thus obtained as a brown oil (82.7 mg).

Preparation of Methyl Ester of 7-Isopropyl-3,4-dimethylazulene-1-carboxylic Acid (XV). To a solution of crude carboxylic acid (XV) (82.7 mg) in ether, we added an ethereal solution of diazomethane prepared from nitrosomethylurethane (4 g); the solution was then kept at room temperature for 8 hr. The reaction mixture was, after being treated in the usual manner, submitted to benzene - silica-gel elution chromatography to afford methyl 7-isopropyl-3,4-dimethylazulene-1-carboxylate (XII) as a purple oil (8.1 mg).