The Thermal Reaction of 3-Formylguaiazulene

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When 3-formxlguaiazulene was heated at 200 °C for 1 hr, three new compounds were isolated in addition to *S*-guaiazulene (formed by loss of the formyl group). They were shown to be 2-formylguaiazulene, produced by migration of the formyl group, and dimers produced from two molecules of the starting material through dehydration between the formyl and the aromatic methyl groups. The observed elimination or migration of the formyl group was analogous to the behavior of 3-acylguaiazulenes which had been studied earlier. On the other hand, the extent of the loss of the acyl group and the formation of the dimers was peculiar to this substance. Moreover, migration of the formyl group was not reversible at 200 °C, but was at 250 °C.

In the previous papers[1–3] dealing with the thermal reaction of 3-acylguaiazulene at 200—260 °C, it was shown that *S*-guaiazulene, 2-acylguaiazulene and 1-acyl-7-isopropyl-3,4-dimethylazulene were formed by the loss of the acyl group, migration of the acyl group, or by the interchange of the acyl and methyl groups in the five-membered ring of the azulene nucleus, respectively. On the other hand, a discrepancy among the reactions due to differences of the carbonyl components was also noted:[3] the main reaction in such a ketone as acetylguaiazulene or benzoylguaiazulene is migration of the acyl group, while that in a methyl ester is interchange of the ester and the methyl groups in the five-membered ring, and reduction of an acyl group is observed only in the benzoyl compound.

In an effort to determine the effect of a formyl substituent on the thermal reaction of 3-acylguaiazulene, the behavior of 3-formylguaiazulene was studied.

Results and Discussion

3-Formylguaiazulene (I) was heated at 200 °C for 1 hr or 2 hr, and compounds III—V were isolated in addition to *S*-guaiazulene (II), the main product, formed by loss of the formyl group.

a) 2-Formylguaiazulene (III): A dark red crystalline product (mp 80—81 °C) isolated in the next highest yield had the same molecular formula, $C_{16}H_{18}O$, as I. The existence of a formyl group was indicated by the appearance of a $\nu_{C=O}$ band at 1666 cm^{-1} and ν_{C-H} bands at 2710 and 2795 cm^{-1} in the IR spectrum, and by presence of a singlet at 10.58 ppm attributable to the formyl proton in the NMR spectrum.

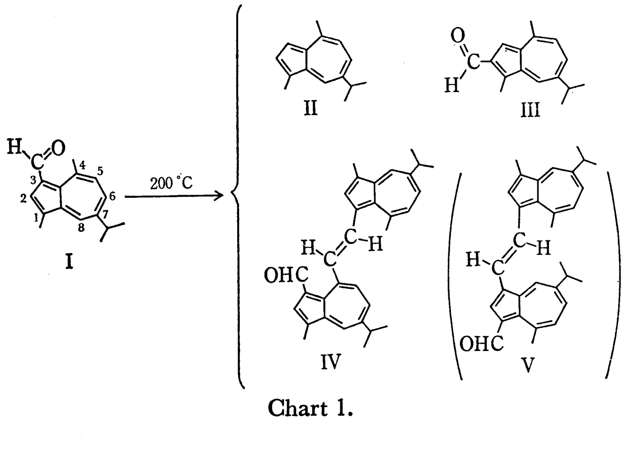


Chart 1.

Moreover, the NMR spectrum (*cf.* Experimental section) showed, besides the formyl-proton signal, signals due to one isopropyl-, two aromatic methyl-, and four aromatic ring hydrogens, a pattern of which is quite similar to that of I. The compound is, therefore, thought to be a positional isomer of I.

The visible absorption spectrum of this compound had two maxima of nearly equal intensities at 660 and 705 nm, and bore a marked resemblance to that of 2-acetylguaiazulene (VI).[1]

These facts lead us to conclude the present compound to be 2-formylguaiazulene (III). In agreement with this deduction, this compound gave VI when treated with diazomethane.[4,5]

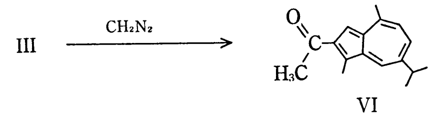


Chart 2.

b) trans-*1,2-(1,4-Diazulyl)ethene Derivative (IV).* A purple crystalline substance (mp 160—161 °C), the third reaction product, was also an aldehyde, since it exhibited a $\nu_{C=O}$ band at 1620 cm^{-1} in its IR spectrum and a formyl signal at 10.68 ppm in its NMR spectrum. It also gave semicarbazone (mp 192—194 °C). The visible absorption maximum of the compound (513 nm) exhibited, however, an ε value larger than that of I or III by a factor of about twenty, and this is not consistent with the structure of an ordinary formylguaiazulene.

Based on the molecular ion of the mass spectrum, this compound is thought to have a composition, $C_{32}H_{34}O$ (MW, 434), made up through dehydration from two molecules of I ($C_{16}H_{18}O$, 226). This deduction was supported by the observation in the NMR spectrum (*cf.* Experimental section) that the signals ascribed to 34H were recognized.

In the methyl region of the NMR spectrum there were three aromatic methyl signals in addition to two isopropyl ones. Among them, two aromatic methyl signals (2.58 and 2.62 ppm) adjacent to one another corresponded to Me$_1$ of I, and a down-field signal (3.08 ppm), to Me$_4$ of I (*cf.* Experimental section). The appearance of only one signal (3H) corresponding to Me$_4$ indicates that the formyl group of one molecule of I was condensed with methyl group at 4-position of a second molecule. Consequently, the present compound was postulated to be a diazulylethene derivative (IV).

On the other hand, this compound could possibly be a condensation product of I and III or of III and III, since III was also found in the reaction mixture. This possibility was, however, excluded because IV was isolated as a by-product in preparing I through formylation of II, where no III was obtained.

As to geometrical isomerism, IV was determined to have a *trans* configuration on the basis of the following three reasons: i) According to the NMR spectrum, the coupling constant for the olefinic protons was found to be 15.5 Hz, the value of which fits with a *trans* configuration.[6] ii) From a model examination, a fully conjugated system of two azulene rings and an olefinic bond may hardly be attainable in the *cis* form of IV. Thus, the configuration cannot explain the extremely large ε value in the visible spectrum of IV. iii) IV is expected to take a thermally stable configuration, since it is a thermal reaction product.

c) 1,2-(1,3-Diazulyl)ethene Derivative (V). This substance was isolated as a purple oil, but was not well characterized because of its poor yield and instability. On the basis of the observation in the NMR spectrum that the signals from two isopropyl and three aromatic methyl groups existed and that the pattern of an aromatic proton region was close to that for IV, this compound is thought to be another dimer V formed from two molecules of I through dehydration of the formyl group and the methyl group at 1-position.

Sequence of the Reaction. As is obvious from the above arguments, the heating of 3-formylguaiazulene (I) yielded two monomers, which were formed by elimination or migration of a formyl group, and two dimers, generated by condensation of two molecules of I.

In Table 1 are listed the yields (%) of the products obtained by a reaction time of 1 hr. The yield of IV was found to increase almost linearly with increasing reaction time, while no change in the yield of II and a decrease in that of III were observed. This kind of dehydration is well known in the presence of an appropriate dehydrating reagent,[7] and is apparently characteristic of formyl compounds.

With regard to the acyl migration 2-formylguaiazulene (III) afforded no appreciable product when heated at 200 °C for 1 hr but gave II and I by heating at 250 °C for 1 hr. Thus the acyl migration is concluded to be reversible at the higher temperature, the same as alkyl- and phenyl-migration[8,9] which were investigated at a temperature above 250 °C.

Table 1 also includes the yields (%) of the reaction products formed from the three 3-acylguaiazulenes studied before.[1-3] As is obvious from the Table 1, the thermal exchange between the acyl and the methyl groups was not observed in the case of 3-formylguaiazulene, while it was common to the other acylguaiazulenes. Another feature of the thermal reaction of the 3-formyl compound is that elimination of the acyl group, less important in the other acylguaiazulene, is a major reaction.

In order to clarify the reasons for the observed differences in the reactions, further work is in progress in our laboratory on the reactions of phenyl esters having a variety of electron releasing- or withdrawing-groups at the *p*-position.

Experimental

All melting points are uncorrected. The UV and the visible absorption spectra (VS) were taken in a cyclohexane solution. The IR spectra were obtained as KBr disks, and the mass spectra (MS), at 70 eV. Unless otherwise stated, the NMR spectra were measured at 60 MHz using deuteriochloroform as the solvent: the chemical shifts are given in ppm using TMS as an internal standard, and the coupling constants in Hz. The thin-layer chromatography (tlc) was conducted by the use of silica gel-G (Merck), and the gas chromatography (vpc), using a column (1 m in length) of Chromosorb W impregnated with Silicone SE-30 (1.5%) under a 20 ml/min flow of helium.

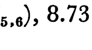
3-Formylguaiazulene (I). This compound was synthesized by a Vilsmeier-Haack formylation of *S*-guaiazulene (II).[10] The recrystallization of the product from *n*-hexane gave dark reddish-brown needles [mp 86.0—86.1 °C (mp 85—86 °C[10])], which showed a single brown spot (R_f, 0.16) in tlc (benzene). VS: nm (ε), 573 (539), 600 sh (453), 618 sh (404), 678 (297) [571 (501), 680 (118)[10]]. UV: nm (log ε), 247.5 (4.35), 277.5 (4.05), 310.5 (4.50), 316.5 (4.58), 366 sh (3.71), 385 (3.98), 400 (4.07). IR: 1608 cm^{-1} (C=O). NMR: 1.37/3.05 (d, 6H/m, 1H, J=6.8; *i*-Pr), 2.58 (s, 3H; Me$_1$), 3.12 (s, 3H; Me$_4$), 7.40 (d, 1H, J=12.0; H$_5$), 7.65 (dd, 1H, J=2.0 and 12.0; H$_6$), 8.25 (s, 1H; H$_2$), 8.32 (d, 1H, J=2.0; H$_8$), 10.63 (s, 1H; CHO). NMR (CF$_3$COOH)[11]: 1.52/3.47 (d, 6H/m, 1H, J=7.2; *i*-Pr), 2.60 (s, 3H; Me$_1$), 3.23 (s, 3H; Me$_4$), 8.25 (s, 1H; H$_2$), 8.35 (s, 2H; H$_{5,6}$), 8.73 (s, 1H; H$_8$), 9.12 (s, 1H;  $=\mathrm{C}\langle^{\mathrm{O}}_{\mathrm{H}}$).

TABLE 1. YIELDS (%) OF THE THERMAL REACTION PRODUCTS

Products	Carbonyl components			
	HCO	CH$_3$CO[1,2]	C$_6$H$_5$CO[3]	CH$_3$OCO[3]
S-Guaiazulene	9.1	1.4	1.8	0.8
2-Acylgauaiazulene	6.1	16.4	11.3	0.08
1-Acyl-7-isopropyl-3,4-dimethylazulene	—	7.0	5.7	5.3
2-Benzylguaiazulene	—	—	2.5	—
Diazulylethene derivatives	0.3	—	—	—

Thermal Reaction of 3-Formylguaiazulene (I). a) Determination of the Reaction Temperature: Three glass tubes, each containing 50 mg of I, were sealed under a nitrogen atmosphere and heated at 150 °C, 200 °C and 250 °C for 1 hr, respectively. The reaction mixture was, after being dissolved in a small amount of benzene, investigated by tlc (benzene) and vpc (200 °C). The ratio of the reaction products relative to the recovery of I was of 0.8, 15.7 and 108% corresponding to the temperatures of 150, 200 and 250 °C, respectively, on the basis of the vpc. Contrary to these data, in the case of 250 °C we observed tlc spots of degradation products which were spread out over a whole region or did not move from the original point, while those were scarcely apparent in the other cases.

b) The Case of 1 hr Heating. I (1.0255 g) was heated in a sealed tube at 200 °C for 1 hr. The reaction mixture was eluted through a silica-gel column with petroleum ether, subsequently with benzene, and separated into the following three fractions.[12)]

petroleum ether:

Fr. 1 blue oil (106.9 mg)···*S*-guaiazulene (II) (93.5 mg)

benzene:

Fr. 2 greenish-brown oil (140.9 mg)···
···{1,2-(1,3-diazulyl)ethene derivative (V) (0.15 mg)
2-formylguaiazulene (III) (62.25 mg)

Fr. 3 violet crystals (301.1 mg)···
···{*trans*-1,2-(1,4-diazulyl)ethane derivative (IV) (2.74 mg)
3-formylguaiazulene (I) (277.4 mg) (recovered)

c) The Case of 2 hr Heating. I (3.36 mg) was heated at 200 °C for 2 hr. By treating the reaction mixture as described for (b), each product was obtained in the following yield:

II (262.4 mg), V (0.6 mg), III (58.6 mg), IV (21.0 mg).

S-*Guaiazulene (II).* This compound was obtained as a blue oil which showed a single blue spot (R_f, 0.46 in tlc (petroleum ether)). It was identical with an authentic specimen[13)] in tlc and vpc (180 °C).

1,2-(1,3-Diazulyl)ethene Derivative (V). The greenish brown oil from Fr. 2 exhibited violet and blue spots (R_f, 0.37 and 0.34) overlapping each other in tlc (benzene). By means of repeated benzene–silica-gel elution chromatography, it was roughly separated into a red oil (V portion) and a blue oil (III portion), corresponding to each spot in tlc. The red oil, still containing some of the III portion, was then chromatographed on an aluminum oxide column with a mixed solvent of petroleum ether–benzene (7:3); R_f, 0.29]. NMR (90 MHz, accumulated 34 times): 1.28 (d, 6H, J=6.8; *i*-Pr), 2.57, 2.80 and 3.02 (each s, 3H; Me), 6.90—8.43 (10H; aromatic- and vinyl protons), 10.23 (s, 1H; CHO).

2-Formylguaiazulene (III). The blue oily portion described above was purified by repeated benzene–silica-gel elution chromatography to give III as dark red needles, which showed a single blue spot (R_f, 0.34) in tlc (benzene). After being recrystallized from ethanol, it showed a mp of 80.0—81.0 °C. IR: 1666 cm^{-1} (C=O), 2710 and 2795 cm^{-1} (CH: aldehyde). UV: nm (log ε), 251.2 (4.37), 286.5 (4.47), 304.5 (4.58), 312 sh (4.47), 347 (3.74), 361.5 (3.78), 374 (3.41). VS: nm (ε), 392 (223), 416 (70), 570 sh (277), 616 sh (495), 660 (675), 705 (697). NMR: 1.38/3.07 (d, 6H/m, 1H, J=6.9; *i*-Pr), 2.83 (s, 3H; Me_1), 2.90 (s, 3H; Me_4), 7.00 (d, 1H, J=2.1 and 10.4; H_5), 7.46 (dd, 1H, J=2.1 and 10.4; H_6), 7.60 (s, 1H; H_3, 8.35 (d, 1H, J=2.1; H_8), 10.58 (s, 1H; CHO). MS: *m/e* 226 (M, $C_{16}H_{18}O$; 96.4%), m/e 225 (M−H; 11.1%), *m/e* 211 (M−CH_3; base peak), *m/e* 197 (M−CHO: 13.1%).

Reaction of 2-Formylguaiazulene (III) with Diazomethane. To a solution of III (32.00 mg) in ether (1 ml), was added an ethereal solution (2 ml) of diazomethane prepared from nitrosomethylurea (0.4 g); the solution was then kept at room temperature for 25 days. After the remaining reagent was decomposed by adding a few drops of formic acid, the reaction mixture was submitted to benzene–silica gel elution chromatography to afford VI (3.90 mg) as green crystals and the recovery of III (11.56 mg) as dark red crystals. VI, thus obtained, was idetical with an authentic specimen[1)] in tlc (benzene) and vpc (195 °C).

Thermal Reaction of 2-Formylguaiazulene (III). III was sealed in three glass tubes (*ca.* 50 mg in each ampoule), and heated at 150, 200 and 250 °C for 1 hr, respectively. The reaction mixture, dissolved in a small amount of benzene, was investigated by tlc (benzene) and vpc (195 °C). The formations of II, I and an unknown substance were observed in the case of 250 °C, while only unchanged III was detected in the cases of 150 °C and 200 °C. The yield of each compound at 250 °C (III; 46.2 mg) was estimated on vpc (195 °C) to be 7.5 (II), 2.5 (I), 13.7 (unknown) and 76.4% (III; recovered). Successively the reaction mixture was subjected to benzene–silica-gel elution chromatography to be separated into II (15.78 mg), I (1.15 mg) and unchanged III (12.71 mg). These compounds were identical with the authentic specimens in tlc and vpc.

trans-*1,2-(1,4-Diazulyl)ethene Derivative (IV). a) By Thermal Reaction of 3-Formylguaiazulene (I).* The violet crystals from Fr. 3 were chromatographed on a silica-gel column with a mixed solvent of benzene–ether (49:1), and separated into purple crystals of IV and reddish-brown crystals of I (recovered). The former showed a single violet spot (R_f, 0.19) in tlc (benzene), and had a mp of 160.0—160.1 °C after being recrystallized from *n*-hexane. IR: 1620 cm^{-1} (C=O). UV: nm (log ε), 256 (4.40). 262 (4.40), 310 (4.44). VS: nm (log ε), 403 (4.00), 513 (4.21). NMR (90 MHz, accumulated 41 times): 1.36 and 1.42 (each d, 6H, J=7.0; 2*i*-Pr), 2.58 and 2.62 (each s, 3H; 2Me_1), 3.08 (s, 3H; Me_4), 6.97—8.20 (8H; aromatic protons), 7.88 and 8.32 (each d, 1H, J=15.5; vinyl protons), 10.68 (s, 1H; CHO). MS: *m/e* 434 (M, 16.5%), *m/e* 211 (M−CH=CH; base peak).

The semicarbazone of this compound was obtained as a dark brown powder in a usual manner. After being recrystallized from ethanol, it showed a mp of 192.0—194.0 °C.

b) As a By-product in the Preparation of 3-Formylguaiazulene (I). S-Guaiazulene (II) (10.0 g) was formylated with a mixed reagent of dimethylformamide (65 ml) and phosphorous oxychloride (8.7 g).[10)] The reaction mixture was submitted to benzene–silica-gel elution chromatography giving I (3.05 g) and IV (13.32 mg). The IV obtained thereby was identical with that from (a) (thermal reaction product) in tlc and in IR spectrum.

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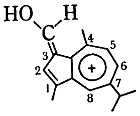

12) Next to the dotted lines are shown the compounds obtained finally from each fraction after it had been further purified.

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