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Restricted Rotation Involving the Tetrahedral Carbon. II. 2-Substituted 4,6,8-Trimethylazulenes[1]

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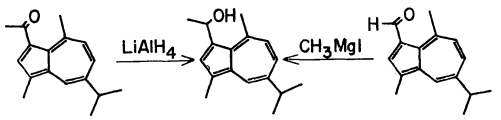
1-(1-Hydroxyethyl)-4,6,8-trimethylazulene (**3**) was prepared by the lithium aluminum hydride reduction of 1-acetyl-4,6,8-trimethylazulene, and by the reaction of methylmagnesium iodide with 1-formyl-4,6,8-trimethylazulene. **3** showed various melting points according to its crystallization conditions and the reaction solvent. Their IR spectra both in solid states and in solutions, the NMR spectra at various temperatures, and the results of X-ray diffraction studies led to a conclusion that this phenomenon is attributable to polymorphism. From the temperature dependence of the NMR spectra of the *t*-butyl protons of 1-*t*-butyl-4,6,8-trimethylazulene, the internal rotation around the C_{Bu}–$C_{azulene}$ was concluded to be slow only at the lower temperature.

In the preceding paper,[2] the restricted rotation about the sp^3–sp^3 carbon-carbon bond was discussed and the possibility of isolating a pair of optical isomers and a *meso*-form of some triptycene-type compounds was mentioned. In the light of this consideration, the sp^2–sp^3 C–C bond should be able to supply another example of resolution into optical isomers provided that the rotation around the bond in question is really restricted and the group involving the very sp^2 carbon atom is directed in relation to the sp^3 part.

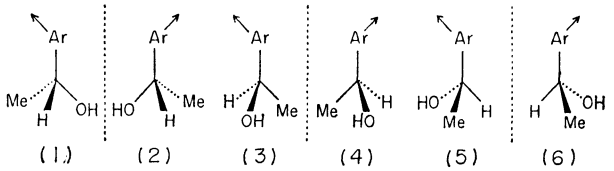
A search of the literature revealed that 3-(1-hydroxyethyl)-*s*-guaiazulene has been reported to show two different melting points and different dehydrative reactivities according to the methods of preparation: the lithium aluminum hydride reduction of 3-acetyl-*s*-guaiazulene and the Grignard reaction of methyl iodide with 3-formyl-*s*-guaiazulene.[3] These phenomena have been suggested to originate from "the isomerism caused by restricted rotation" around the azulene-to-3-substituent bond.



(1)

[70-71°], [72-73°]

If this were really the case, this should be a good example of restricted rotation around the sp^2–sp^3 carbon bond. Thus, we have undertaken an investigation of the isolation of three possible pairs of optical isomers of the afore-mentioned type of compound, which should exist as visualized by the following six models, where



(1) (2) (3) (4) (5) (6)

1) A part of this article was presented at the 22nd annual meeting of the Chemical Society of Japan, Tokyo (1969).

2) M. Ōki and M. Suda, This Bulletin, **44**, 1876 (1971).

3) M. Miyazaki, M. Hashi, and T. Ukita, *Chem. Pharm. Bull.*, **8**, 140 (1960).

Ar is the azulene ring and where the arrow indicates the direction of the azulene group.

The purpose of this paper is to report the results of this investigation which indicate that the rotation around the bond in question is fast and that optical resolution is not possible.

Results and Discussion

4,6,8-Trimethylazulene derivatives were chosen as the model compounds, for the ring system is readily accessible[4] and has the same stereochemical environment as that studied by Ukita and his co-workers.

1-Acetyl-4,6,8-trimethylazulene (**1**) was obtained by the action of acetic anhydride and phosphorus pentoxide on 4,6,8-trimethylazulene and 1-formyl-4,6,8-trimethylazulene (**2**) by the action of the Vilsmeyer-Haak reagent.

Lithium aluminum hydride reduction of **1** in ether afforded blue needles of 1-(1-hydroxyethyl)-4,6,8-trimethylazulene (**3**-L), which melted at 93.5—95.0°C before recrystallization. When recrystallized from petroleum ether, two modifications of the alcohol showing different melting points were obtained according to the crystallization conditions. That is, when the hot solution was chilled quickly to about 0°C, blue granular **3**-L with a mp of 68—78°C was precipitated, while blue crystalline **3**-L with a mp of 81.0—81.1°C was formed when the hot solution was allowed to cool slowly to room temperature.

The reduction of **1** in 1:1 ether-tetrahydrofuran also yielded **3**-L as a dark blue crystalline mass, which changed to tiny violet needles after recrystallization; their melting points were 75.0°C and 87.5—88.5°C before and after recrystallization, respectively.

The reaction of **2** with the methyl Grignard reagent in 1:1 ether-tetrahydrofuran gave **3**-G as a dark blue crystalline mass melting at 80.5—81.5°C before recrystallization. However, the alcohol again changed to tiny violet needles melting at 87.5—88.5°C when the hot solution of the alcohol in petroleum ether was cooled slowly to room temperature.

These phenomena may be accounted for in two different ways. The first is, as has been suggested by Ukita *et al.*, the rotational isomerism, while the second is the polymorphism caused by the different packings in the crystal lattice. Since it is expected that the attacking reagent approaches the reaction site from the least-hindered side, the hydride reduction of **1** will yield **3**-L or its mirror image, as is shown schematically in Fig. 1. Similarly, **2** will afford **3**-Gb or its mirror image and in the case of **3**-Gb the rotation around the C_α–$C_{azulene}$ may be possible at room temperature because of the smaller barrier formed by the hydrogen atom; thus **3**-Gc will exist also.

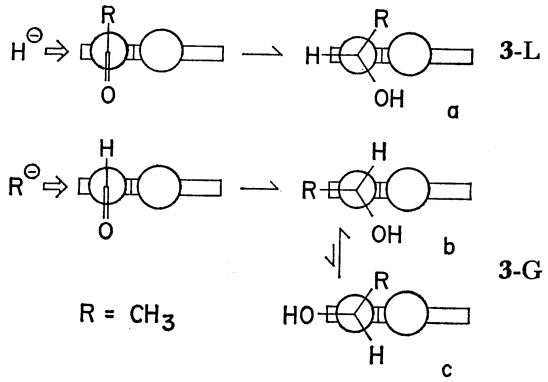


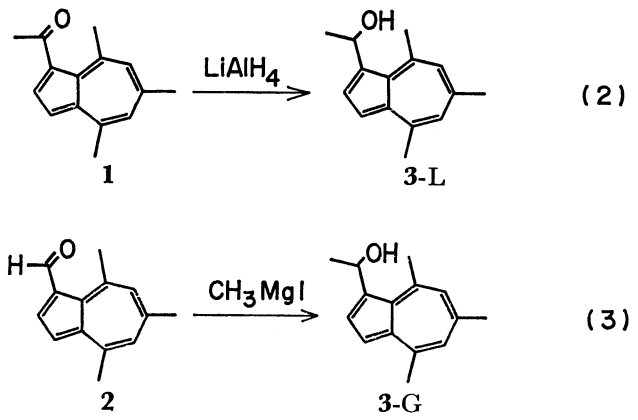
Fig. 1. Possible conformations of **3**-L and **3**-G (Newman type projection). C-1 carbon atom within 5-membered ring and C-8 methyl group attached to 7-membered ring are indicated by circles.

These considerations lead to the idea that, if the rotational isomer is the cause, there should be some differences in IR and NMR spectra among these modifications, because, for example, the force constants of C–O in **3**-Gb and **3**-Gc and the magnetic environments for the methyl protons are considered to be different. Thus, the following spectral studies have been undertaken.

The IR spectra of these compounds were recorded both with solid states and with carbon disulfide solutions, the former being shown in Figs. 2, 3, and 4, and the latter, in Fig. 5.

The correlations of their origins with the mp and IR spectra are summarized in Table 1.

A comparison of Figs. 2 and 4 reveals that, in solid states the difference between **3**-L and **3**-G appears in the spectral ranges of 1340—1260, 1080—1010, and 890—830 cm^{-1} if the reaction solvents differ from each other. When the same solvent is used for the reactions, the spectral difference, as judged by a comparison of



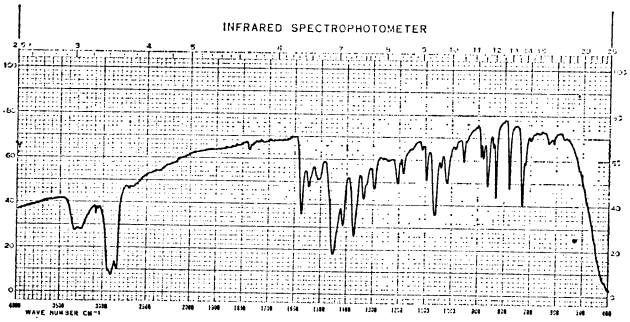


Fig. 2. IR spectrum of **3**-L (Nujol), mp 93.5—95.0°C.

4) K. Hafner and H. Kaiser, "Organic Synthesis," Vol. 44, p. 94 (1964).

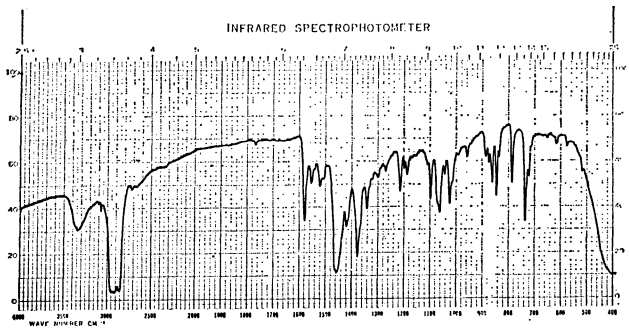


Fig. 3. IR spectrum of **3**-L (Nujol), mp 75.0°C.

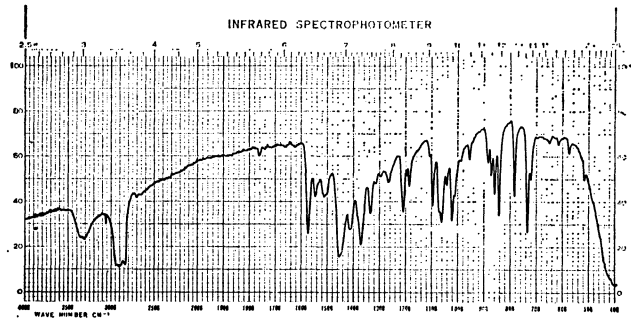


Fig. 4. IR spectrum of **3**-L (Nujol), mp 68—78, 81.0—81.1, 87.5—88.5°C, and **3**-G (Nujol), mp 80.5—81.5, 87.0—89.0°C.

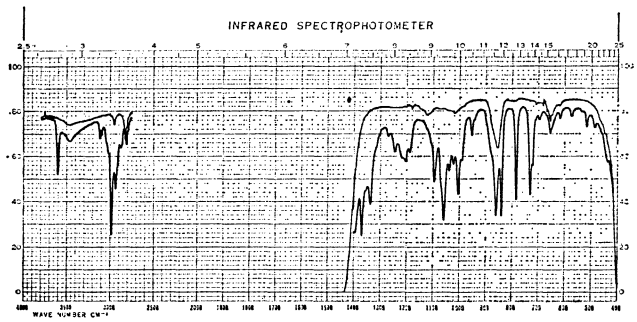
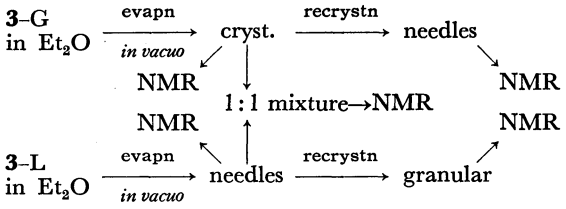


Fig. 5. IR spectrum of **3**-L and **3**-G (CS_2 soln, 0.109 mm KBr cell). The upper line is CS_2 and the lower the CS_2 soln.

Figs. 3 and 4, is confined to around 830 cm^{-1}. The IR spectra of the solution of **3**-L in carbon disulfide, however, were superimposable on those of **3**-G in every respect, one of them being illustrated in Fig. 5.

Some rotational behavior of these compounds is expected to be observable by recording the NMR spectra at various temperatures, since $R_{(a)}$ and $R_{(b)}$ ($R=CH_3$) are in different magnetic environments and a chemical shift difference between them is expected (Fig. 1). Though the NMR sampling was carried out according to Scheme 1, all the NMR spectra are superimposable upon each other; one of them is shown in Fig. 6 (a 1:1 **3**-L-**3**-G mixture in carbon disulfide).



Scheme 1

These results, together with the IR results, may be interpreted by considering that a rapid exchange among the conformers, a, b, and c, is taking place at room temperature.

The NMR spectra of the alcohol, **3**, in carbon disulfide-pyridine was recorded at low temperatures. The methyl proton signal of CH_3-CH< appeared as a sharp doublet ($J=7$ Hz) at room temperature, but as the probe temperature was lowered, the signal decreased in height and increased in width. The changes in signal shape (as in Fig. 7) in the temperature range of −70——90°C apparently indicate that the internal rotation in question becomes sufficiently slow to be observed at these temperatures. Conversely, the internal rotation in question is very rapid, at least at room temperature.

Further evidence supporting the implication that the rotation around the C_α-to-azulene bond was slow at low temperature was obtained from variable-temper-

Table 1. Correlations of reactions with mp and IR

Reaction	Reaction solvent	Before recrystn		After recrystn	
		mp and cryst.	IR (Nujol)	mp and cryst.[a]	IR (Nujol)
$LiAlH_4$ redn	Et_2O	93.5—95.0°C blue needles	Fig. 2	68—78°C (cooled quickly) blue granular crystals 81.0—81.1°C (cooled slowly) blue crystals	Fig. 4
	Et_2O-THF (1:1)	75.0° dark blue crystalline mass	Fig. 3	87.5—88.5°C (cooled slowly) violet needles	Fig. 4
Grignard	Et_2O-THF (1:1)	80.5—81.5°C dark blue crystalline mass	Fig. 4	87.0—89.0°C (cooled slowly) violet needles	Fig. 4

a) The conditions of crystallization were given in parentheses.

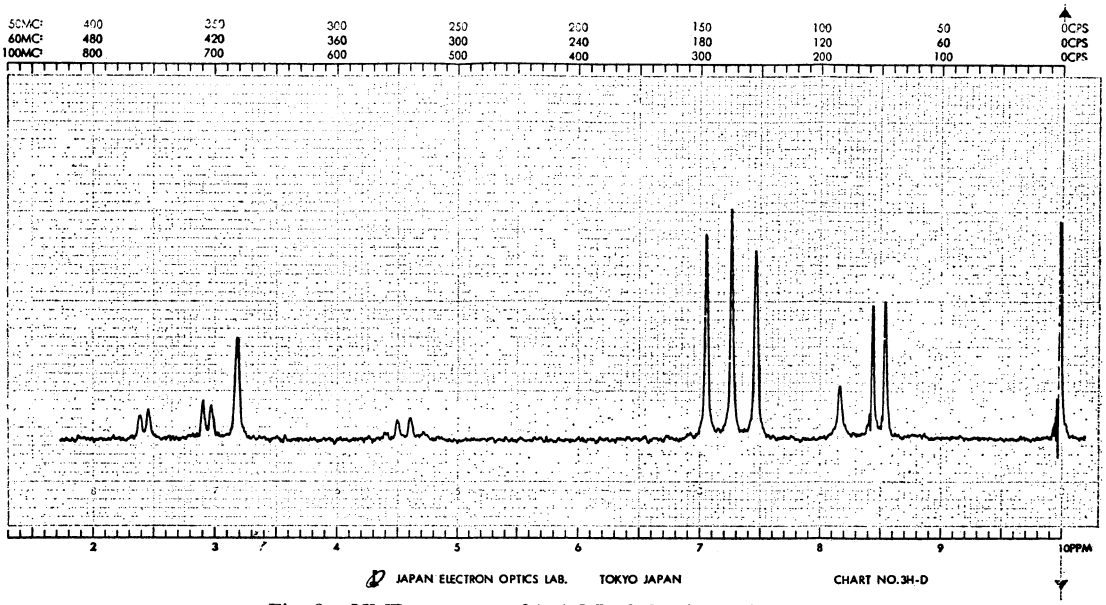


Fig. 6. NMR spectrum of 1: 1 **3**-L-**3**-G mixture in CS_2.

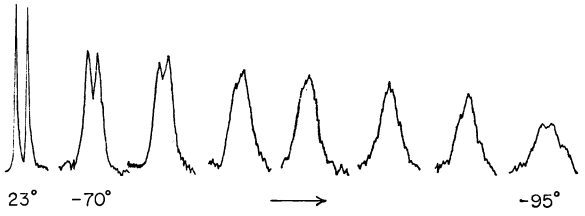
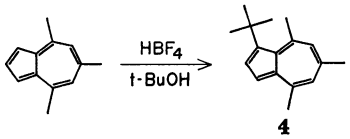


Fig. 7. Temperature dependence of β-methyl signal of 1-(1-hydroxyethyl)-4,6,8-trimethylazulene (1: 1 wt/wt **3**-L-**3**-G in 1: 1 v/v CS_2-C_5H_5N).

ature NMR studies of 1-*t*-butyl-4,6,8-trimethylazulene (**4**), which had been prepared by the reaction of 4,6,8-trimethylazulene with *t*-butyl alcohol in the presence of anhydrous tetrafluoroboric acid. The NMR spec-



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tral data of the *t*-butyl protons are shown in Table 2. Though the *t*-butyl signal was a sharp singlet at room temperature, it became somewhat broader as the temperature was lowered, and below 0°C apparent changes in both its height and half-width were observed. When the temperature reached −80°C, the relative height and the relative half-width were 2.4 and 1.4 respectively, with respect to the ring-methyl signal of the greatest height, and below −80°C there was little change in these figures.

Although no chemical-shift difference among the methyl groups of the *t*-butyl residue was observed in this experiment, those facts given above can be best accounted for by the theory that the internal rotation around the *t*-butyl-to-azulene bond is sufficiently slow only at −80°C on the NMR time scale and that it is too rapid at room temperature for the stable rotamers to be isolated.

Table 2. NMR spectral data of 1-*t*-butyl-4,6,8-trimethylazulene

Temp. °C	Rel. values of *t*-butyl signal[a]	
	height	half-width
23	3.8_4	0.56
−25	3.3_7	0.75
−80	2.3_6	1.3_6
−90	2.3_0	1.2_4

Spectrum was taken with CS_2 solution.
a) Relative values to the ring-methyl group of the greatest height

Thus, it is most probable to ascribe the many modifications of 1-(1-hydroxyethyl)-4,6,8-trimethylazulene to the polymorphism derived by the difference in the mode of crystal packing into the lattice. Indeed, the X-ray diffraction patterns (Fig. 8), whose angles and relative intensities have been obtained with good reproducibilities, show a difference supporting the conclusion.

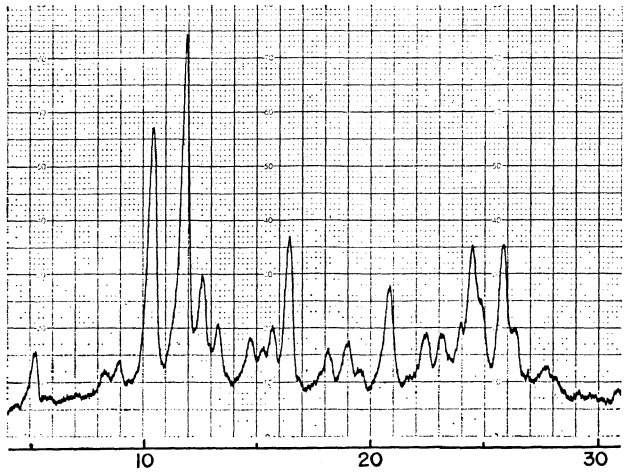
Experimental[5]

The NMR spectra were taken with JEOL 3H-60 and C-60H spectrometer equipped with variable-temperature accessories, the IR spectra, with a HITACHI EPI-G2 grating infrared spectrophotometer, and the X-ray diffraction lines, with a diffractometer, Geigerflex, of the Rigaku Denki Co., Ltd.

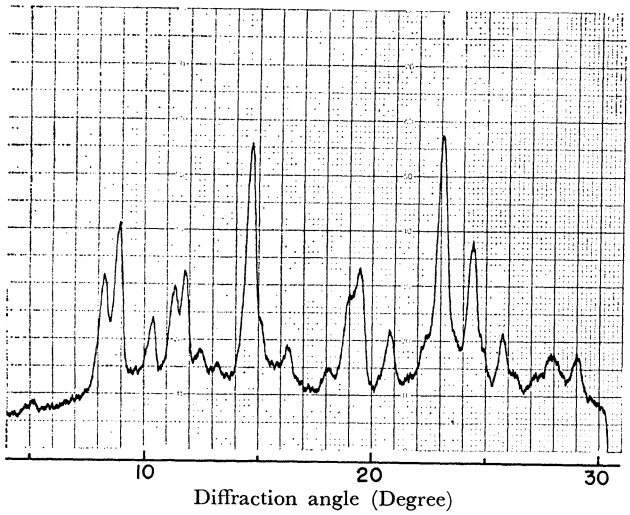
The reduction and Grignard reaction were carried out under dry nitrogen, and the solvents were distilled over lithium aluminum hydride just before use.

1-Acetyl-4,6,8-trimethylazulene (1). From 11.3 g of 4,6,8-trimethylazulene,[4] 200 m*l* of acetic anhydride, and 5.3 g of phosphorus pentoxide, 7.0 g of 1-acetyl-4,6,8-trimethylazulene were formed; mp 72—73°C (reported mp 72—73°C[6]).

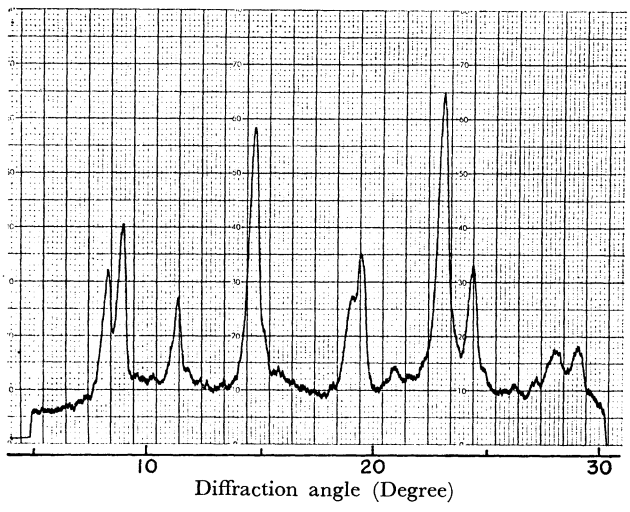
5) All the melting points are uncorrected.
6) K. Hafner, H. Pelster, and J. Schneider, *Ann. Chem.*, **650**, 74 (1961).



a) **3**-L, whose IR spectrum corresponds to Fig. 2



b) **3**-L, whose IR spectrum corresponds to Fig. 3



c) **3**-G, whose IR spectrum corresponds to Fig. 4

Fig. 8. X-ray diffraction patterns of **3**-L and **3**-G.

1-Formyl-4,6,8-trimethylazulene (2). 4,6,8-Trimethylazulene (17.0 g) was formylated with a Vilsmeyer-Haak reagent prepared from 45 m*l* of *N,N*-dimethylformamide and 17.0 g of phosphorus oxychloride to yield 13 g of 1-formyl-4,6,8-trimethylazulene; mp 105°C (reported mp 106—107°C[7]).

1-(1-Hydroxyethyl)-4,6,8-trimethylazulene (3-L): Reduction of **1** *with Lithium Aluminum Hydride.* *a) Reduction in Ether:* To a well-stirred suspension of 0.2 g of lithium aluminum hydride in 30 m*l* of anhydrous ether was added a solution of 1.5 g of **1** in 70 m*l* of anhydrous ether at 0°C; the reaction mixture was then stirred at this temperature for 30 min. At the end of this time, 10 m*l* of methanol and then 20 m*l* of water were added. The mixture was poured into a saturated sodium chloride solution and extracted with ether. The combined ether extracts were washed with water and dried over sodium sulfate. The solvent was evaporated *in vacuo* below 20°C. The blue needles so obtained melted at 93.5—95.0°C and had the IR absorption shown in Fig. 2 (Nujol). Found: C, 84.50; H, 8.81%; Calcd for $C_{15}H_{18}O$: C, 84.07; H, 8.47%.

3-L was recrystallized from petroleum ether (50—60°C fraction). When the hot solution was cooled quickly with ice water, blue granular solid was obtained; mp 68—78°C. However, when it was allowed to cool slowly to room temperature, a blue crystalline product was formed; mp 81.0—81.1°C. These **3**-L's showed identical IR spectra, as is shown in Fig. 4. NMR (δ from TMS in CS_2): 1.50 (3H, doublet, J=6.0 Hz), 1.82 (1H, singlet), 2.53 (3H, singlet), 2.73 (3H, singlet), 2.94 (3H, singlet), 5.44 (1H, quartet, J=6.0 Hz), 6.82 (2H, singlet), 7.05 (1H, doublet, J=4.0 Hz), 7.57 (1H, doublet, J=4.0 Hz).

b) Reduction in 1:1 Ether-Tetrahydrofuran: To a mixture of 0.2 g of lithium aluminum hydride and 30 m*l* of ether, was added a solution of 1.5 g of **1** in 20 m*l* of ether and 50 m*l* of tetrahydrofuran at 0°C. The reaction mixture was then treated as described in a). The blue product, mp 75°C before recrystallization, showed the IR spectrum given in Fig. 3 (Nujol). After recrystallization from petroleum ether, tiny violet needles, mp 87.5—88.5°C, were obtained. The IR spectrum (Nujol) is shown in Fig. 4.

Found: C, 84.36; H, 8.80%; Calcd for $C_{15}H_{18}O$: C, 84.07; H, 8.47%.

1-(1-Hydroxyethyl)-4,6,8-trimethylazulene (3-G): Reaction of **2** *with Methylmagnesium Iodide.* To an ethereal solution of methylmagnesium iodide prepared from 2.2 g of methyl iodide, 0.37 g of magnesium ribbon, and 30 m*l* of anhydrous ether, was added, drop by drop, a soluion of 1.98 g of **2** in 20 m*l* of anhydrous ether and 50 m*l* of anhydrous tetrahydrofuran at 0°C; the reaction mixture was stirred at this temperature for a further 30 min. The mixture was treated with 10 m*l* of methanol and then 20 m*l* of water, poured into a saturated sodium chloride solution, and extracted with ether. The combined extracts were washed with water and dried over sodium sulfate. The solvent was evaporated *in vacuo* below 20°C to yield a dark blue crystalline product, mp 80.5—81.5°C before recrystallization, whose IR spectrum (Nujol) is shown in Fig. 4.

After recrystallization from petroleum ether (50—60°C fraction), it was obtained as tiny violet needles; these needles melted at 87.0—89.0°C (reported mp 87—88°C[8]) and showed the IR spectrum illustrated in Fig. 4 (Nujol).

Found: C, 83.70; H, 8.93%; Calcd for $C_{15}H_{18}O$: C, 84.07; H, 8.47%.

1-t-Butyl-4,6,8-trimethylazulene (4). To a well-stirred mixture of 5.1 g of 4,6,8-trimethylazulene, 68 g of *t*-butyl alcohol, and 150 m*l* of anhydrous ether, 60 m*l* of a 54%

7) K. Hafner and C. Bernhard, *Ann. Chem.*, **625**, 116 (1959).
8) K. Hafner and C. Bernhard, *ibid.*, **625**, 122 (1959).

ethereal solution of anhydrous tetrafluoroboric acid[9] was added, drop by drop under nitrogen. The reaction mixture was allowed to stand at room temperature for 12 days and then poured onto crushed ice. The mixture was extracted three times with ether to recover the starting material. The aqueous layer was made alkaline with a 5% sodium hydroxide solution and extracted with ether. The extracts were washed with water and dried over sodium sulfate-potassium carbonate (2:1). The solvent was then evaporated *in vacuo*, and the residual dark blue oil was chromatographed on alumina to yield *ca.* 1 g of 1-*t*-butyl-4,6,8-trimethylazulene as a dark blue oil.

Found: C, 90.17; H, 9.99%; Calcd for $C_{17}H_{22}$: C, 90.20; H, 9.80%.

NMR (δ from TMS in CS_2): 1.54(9H, sharp singlet), 2.45 (3H, singlet), 2.69 (3H, singlet), 2.95 (3H, singlet), 6.72 (1H, broad singlet), 6.81 (1H, broad singlet), 7.00 (1H, doublet, J=5 Hz), 7.57 (1H, doublet, J=5 Hz). The two protons attached to the seven-membered ring of 1-*t*-butyl-4,6,8-trimethylazulene showed different positions of absorption from each other in their NMR spectra in carbon disulfide. This phenomenon was observed only in the case of **4**. In the case of the other 1-substituted 4,6,8-trimethylazulenes studied, including 1-benzoyl and 1-hydroxymethyl derivatives, the ring protons attached to the seven-membered ring appeared as a broad singlet in the 60 MHz MNR spectra in carbon disulfide.

9) K. Hafner, A. Stephan, and C. Bernhard, *Ann. Chem.*, **650**, 57 (1961).

We are deeply indebted to Dr. Yutaka Kawazoe and Dr. Mitsuhiro Tsuda, National Cancer Center Research Institute, Japan, for measuring the NMR spectra, and also to Dr. Isao Ikemoto, The University of Tokyo, for recording the X-ray diffraction lines.