Four-point assay design was found to be insufficient in respect to the precision of potency, unless the number of mice or the slope of the regression line was increased.

Applying a six-point assay design to this method, a sufficient result was obtained which statistically suggested the possibility of the usage of this mouse-convulsion assay as a bioassy of insulin.

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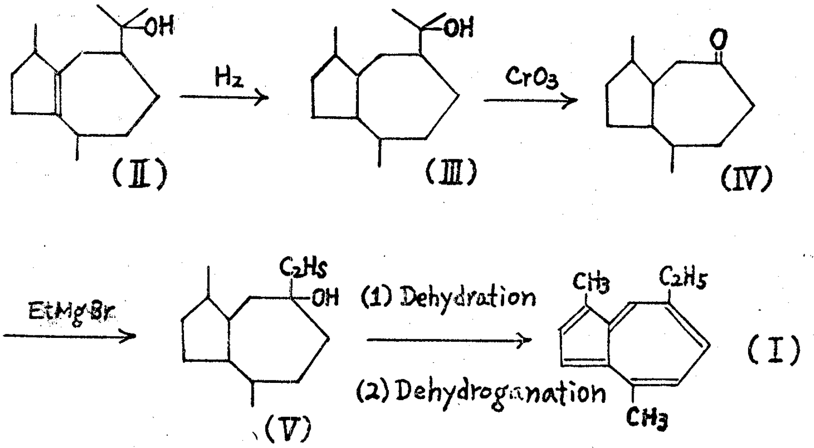
58. **Ken'ichi Takeda, Tokuo Kubota, and Wataru Nagata:** Studies on Seven-membered Ring Derivatives. III[1]. Partial Synthesis of 1,4-Dimethyl-7-ethylazulene (Lindazulene).

(*Research Laboratory, Shionogi & Co., Ltd.**)

Recently, Takeda and Nagata isolated[2] an unknown, new azulene from the product of zinc-dust distillation of linderene, a crystalline component of *Lindera strychnifolia* Vill. This azulene was designated lindazulene. From the fact that its composition corresponded to $C_{14}H_{16}$, that its permanganate oxidation provided acetic and propionic acids, and from ultraviolet and visible absorption spectra, the structure of lindazulene was assumed to be 1,4-dimethyl-7-ethylazulene (I) for whose confirmation the present synthesis was carried out.



Following the method of Plattner, *et al.*[3], guaiol (II) was catalytically reduced to dihydroguaiol (III) and oxidized with chromic acid in acetic acid solution to 1,4-dimethylbicyclo(0,3,5)decanone-7[4] (IV). The dihydroguaiol used for this oxidation showed m.p. 77~78°, and $[\alpha]_D^{23}$: $-53.9°$, as reported by Plattner. Application of ethylmagnesium bromide to this ketone compound (IV) gave the tertiary alcohol (V) which is an oily substance of b.$p_{0.3}$ 83~85° whose dehydration followed by dehydrogenation with sulfur finally gave the objective 1,4-dimethyl-7-ethylazulene (I). This azulene formed trinitrobenzene complex of dark purple crystals, m.p. 132°, and a picrate of black needles, m.p. 112°, both of which showed no depression of the melting point on respective admixture with the trinitrobenzene complex and picrate from lindazulene. The ultraviolet and visible absorption spectra also gave identical results (Figs. 1 and 2, Table I).

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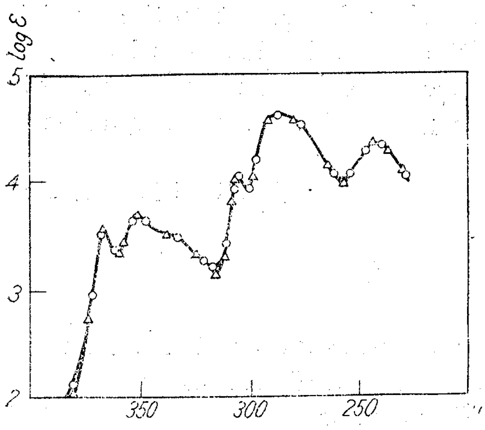
* Imafuku, Amagasaki, Hyogo-ken (武田健一, 久保田德夫, 永田 亘).

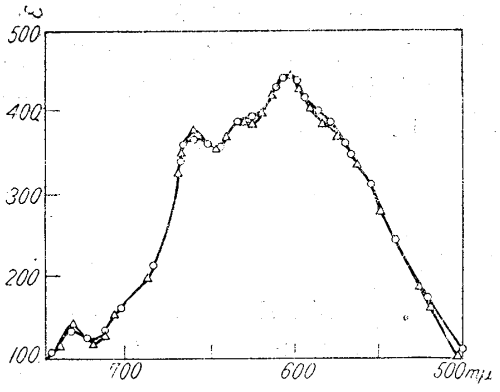
1) Part II: J. Pharm. Soc. Japan, **72**, 1482(1952).

2) This Bulletin, **1**, 164(1953).

3) Pl. A. Plattner, G. Magyer: Helv. Chim. Acta, **25**, 581(1942).

4) Numbering used here is that according to Treibs (Ann., **570**, 165).





——○——○——○—— Lindazulene ——Δ——Δ——Δ—— 1,4-Dimethyl-7-ethylazulene

Fig. 1. Fig. 2.

TABLE I Spectra of Lindazulene (in hexane). (Beckman Spectrophotomer)

	Lindazulene		Lindazulene (Synthesized)	
	λ(mμ)	log ε	λ(mμ)	log ε
max.	368	3.55	368	3.57
min.	362	3.36	362	3.36
max.	351	3.67	350	3.68
min.	316	3.21	316	3.17
max.	304	4.01	304	4.01
min.	302	3.98	302	3.97
max.	286	4.64	286	4.64
min.	258	4.02	258	4.01
max.	245	4.38	245	4.37
	λ	ε	λ	ε
max.	605.0	443.8	605	443.0
min.	650.0	355.0	650	354.4
max.	662.5	369.8	662.5	377.4
min.	717.5	121.3	717.5	119.7
max.	735.0	136.1	735.0	141.5

TABLE II Melting Points of Trinitrobenzene Complexes

Substance	m.p. °C
2-Methyl-azulene	140~141
2-Ethyl-	107
2-Propyl-	118
2-Isopropyl- (Bis-TNB)	113~114
1,4,7-Trimethyl-	177~178
1,4-Dimethyl-7-ethyl-	132
1,4-Dimethyl-7-isopropyl-	148~149
2,4,8-Trimethyl-*	177~178
2-Ethyl-4,8-dimethyl-	118~119
2-Isopropyl-4,8-dimethyl-	151~152

* W. Herz: J. Am. Chem. Soc., 73, 4923(1951).

Of the azulene nucleus substituted with an alkyl group in the same pasition, the melting point of the trinitrobenzene complex of the one substituted with ethyl radical is the lowest compared to those substituted with methyl or isopropyl group, as shown in Table II. This is characteristic of such azulenes and may be assumed to be due to the difference of each alkyl group in its steric figure.

These experimental results have confirmed the structure of lindazulene to be 1,4-dimethyl-7-ethylazulene and consequently, the position of the side-chains in linderene has been clarified as being at 1, 4, and 7 of decahydroazulene nucleus.

The authors extend their thanks to Mr. M. Inaba of this Laboratory for taking the absorption spectra, and to Messrs. T. Ieki and K. Miyahara and Miss N. Morita for carring out the elemental analyses.

Experimental⁵⁾

Dihydroguaiol (III)—Sixty g. of guaiol, m.p. 89~91°, $[\alpha]_D^{23}$: −28.3°, was dissolved in 225 cc. of 99% alcohol, 21.6 g. of Raney nickel added, and reduced with initial hydrogen pressure of 96 kg/cm^2 and heating to 100°. The hydrogen was saturated in about 3 hours. The distillate of b.p$_{11}$ 151~

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5) m.p.s are not corrected.

152° was obtained in 52 g. amount (86%) and did not color with tetranitromethane. This fraction was crystallized from acetone and the crystals were collected after chilling the acetone solution to −10°. The product, 21 g.(34.7%), thereby obtained melted at 77∼78°; $[\alpha]_D^{23}$: −52.9°.

1,4-Dimethyl-bicyclo(0,3,5)decanone-7 (IV)—To a mixture of 11.2 g. of dihydroguaiol, m.p. 77∼78°, and 55 g. of glacial acetic acid, a solution of 9.6 g. of anhydrous chromic acid, 55 cc. of water, and 118 cc. of glacial acetic acid was added in drops, maintaining the temperature at 68∼70°. The reaction mixture was steam-distilled and the distillate was extracted with ether. Ether residue was derived to the semicarbazone, m.p. 205∼206°(decomp.), by the usual method, purified, and decomposed by heating with oxalic acid to the ketone compound. Yield, 2.2 g.(24.4%) of b.p$_{10}$ 125∼126°. n_D^{20}: 1.4879, $[\alpha]_D^{21}$: −108.2°.

1,4-Dimethyl-7-ethyl-bicyclo(0,3,5)decanol-7 (V)—The Grignard reagent prepared from 3.3 g. of ethyl bromide and 0.9 g. of magnesium was applied to 2.7 g. of the ketone compound in ether solution, decomposed with ammonium chloride solution, and treated in the usual manner by which 2.5 g.(79.5%) of oily alcohol was obtained. It remained a colorless, viscous oil, refused to crystallize, and failed to yield any crystalline phenylisocyanate or *p*-nitrobenzoate. Analysis was carried out on a fraction of b.p$_{0.3}$ 83∼85° obtained by the redistillation of the chief fraction of b.p$_1$ 95∼100°. *Anal.* Calcd. for $C_{14}H_{26}O$: C, 79.93; H, 12.46. Found: C, 80.16; H, 12.28. n_D^{20}: 1.4936, $[\alpha]_D^{24}$: −11.7°(EtOH).

1,4-Dimethyl-7-ethyl-bicyclo(0,3,5)decene—A mixture of 3.1 g. of the foregoing alcohol and 1.9 g. of potassium bisulfate was heated for 10 minutes under a slightly low pressure, in an oil bath of 180°. The reaction mixture was then distilled at 50-mm. pressure, the distillate taken up in ether, dried, and distilled. Yield, 1.1 g. of a fraction of b.p$_9$ 113∼115°. *Anal.* Calcd. for $C_{14}H_{24}$: C, 87.42; H, 12.58. Found: C, 87.54; H, 12.82. n_D^{20}: 1.4883.

1,4-Dimethyl-7-ethylazulene (Lindazulene) (I)—To 4.2 g. of the combined initial and chief distillate of the dehydrated product, 2.2 g. of sulfur was mixed thoroughly and heated at 170∼175° for 2 hours by which the generation of hydrogen sulfide virtually ceased. The reaction product was distilled under a reduced pressure and 1.5 g. of blue oil, b.p$_4$ 100∼110°, was obtained. This fraction was dissolved in petroleum ether and the azulene was extracted with 84% phosphoric acid. This azulene portion was again dissolved in petroleum ether, washed with 5% sodium bicarbonate solution, dried, and purified through chromatography.

Trinitrobenzene complex: Dark purple needles, m.p. 131∼132° (from alcohol). *Anal.* Calcd. for $C_{14}H_{16}\cdot C_6H_3O_6N_3$: C, 60.45; H, 4.82; N, 10.58. Found: C, 60.55; H, 4.50; N, 10.82.

Picrate: Black needles, m.p. 111∼112° (from alcohol). *Anal.* Calcd. for $C_4H_{16}\cdot C_6H_3O_7N_3$: C, 58.11; H, 4.63; N, 10.17. Found: C, 58.16; H, 4.70; N, 10.39.

These complexes were in good coincidence with those of lindazulene.

Summary

Partial synthesis of 1,4-dimethyl-7-ethylazulene was carried out, starting with guaiol and following the report of Plattner and others. The compound thereby obtained, its trinitrobenzene complex, m.p. 132°, and picrate, m.p. 112°, and the ultraviolet and visible absorption spectra, all confirmed it to be identical with lindazulene.

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