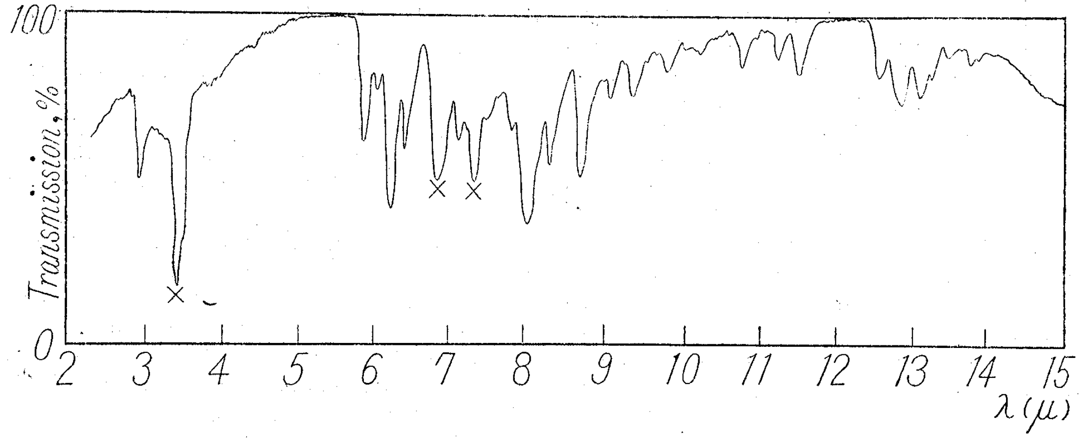

Fig. 3 Infrared Absorption Spectrum of Endocrocin (in Nujol)
× Nujol absorption

its molecule, but negative for S and halogen. *Anal.* Found: C, 71.04; H, 6.02; N, 13.30. Due to its poor yield, further study was not made.

Summary

The metabolic products of *Aspergillus amstelodami* (Mangin) Thom et Church were investigated, and endocrocin and catenarin were newly isolated.

(Received April 20, 1953)

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40. Ken'ichi Takeda and Wataru Nagata: Components of the Root of *Lindera strychinifolia* Vill. V.[1] Azulenes isolated from Linderene by Zinc-Dust Distillation.

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

In the previous paper of this series[2], one of the authors (Takeda) reported the isolation of linderazulene as purple crystals by the zinc-dust distillation of linderene[3]. This azulene can also be obtained by heating linderene with selenium or palladium carbon.

In the present series of experiments, the present authors reconfirmed these facts and also isolated a new azulene, aside from linderazulene, as blue oil. The new azulene, $C_{14}H_{16}$, confirmed as its picrate and a trinitrobenzene complex, did not coincide with any of the azulenes reported in literature and was designated as lindazulene.

I. Isolation of azulenes

a) From linderene: The mixture of azulenes obtained by the zinc-dust distillation of linderene was treated in the usual manner and purified through chromatography, the column being developed carefully with a mixture of petroleum ether and ether (100:3).

The two principal components adsorb at F_2 and F_4 portion of alumina column (Fig. 1). Lindazulene is isolated from the F_2 portion and linderazulene from F_4, showing that the

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* Imafuku, Amagasaki, Hyogo-ken (武田健一, 永田 亘).

[1] Part IV: J. Pharm. Soc. Japan, 64, 154 (1944).

[2] Part III: *Ibid.*, 59, 504 (1939).

[3] For examples of obtaining azulenes by zinc-dust distillation, cf. J. Am. Chem. Soc., 53, 3507 (1941).

latter is more strongly adsorbed than the former. Lindazulene thereby obtained gives a trinitrobenzene complex of m.p. 128° and a picrate of m.p. 109°. There is one zone of adsorption band between F_2 and F_4 and another in the lowest portion of the alumina column (F_3, F_1, Fig. 1). The former gives an azulene containing oxygen, and the latter an azulene of C_{15}. Details of these azulenes, however, could not be examined further due to the small amount of the material available.

b) From the neutral, high-boiling fraction: Zinc-dust distillation of the neutral high-boiling fraction of the extract also yields lindazulene and linderazulene. Lindazulene thereby obtained gives a trinitrobenzene complex of m.p. 132° and a picrate of m.p. 112°, both of which showed no depression of the melting point on admixture with the complexes obtained from the azulene from linderene. The ultraviolet and visible-light absorption spectra of complexes from both were also identical (Figs. 2 and 3).

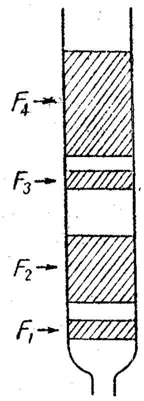

Fig. 1

II. Lindazulene

The new azulene was blue and was clearly different from the color of linderazulene. Lindazulene gives a picrate of m.p. 112° and a trinitrobenzene complex of m.p. 132°, the analytical values of both coinciding well with those for $C_{14}H_{16}$.

Oxidation of lindazulene with potassium permanganate gives acetic and propionic acids. These acids were confirmed by deriving them to esters, then to hydroxamic acid derivatives, and by their paper partition chromatograms described by Inouye, *et al.*[4] (Fig. 4).

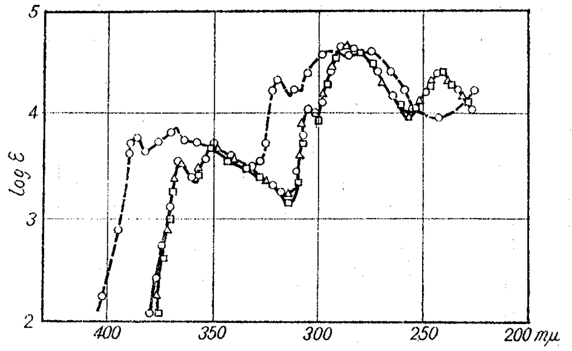

Fig. 2

—○—○—	Lindazulene from high-boiling frac.
—△—△—	Lindazulene from linderene
—□—□—	Guaiazulene
—○—○—	Linderazulene
	(in Hexane)

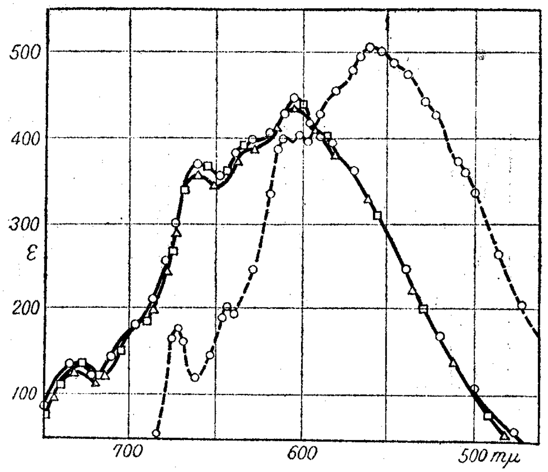

Fig. 3

This result has shown that there are methyl and ethyl groups in this azulene. Ultraviolet and visible absorption spectra both coincide with that of guaiazulene (Figs. 2 and 3). It is assumed, therefore, that the structure of this azulene would be best represented by 1,4-dimethyl-7-ethylazulene (I).

III. Linderazulene

In the previous paper, Kondo and Takeda reported[2] that analytical values of linderazulene itself contained oxygen as $C_{15}H_{16}\cdot xH_2O$. As a result of more detailed experiments, it has been found that the molecular formula of linderazulene corresponds to $C_{15}H_{14}O$, and the values previously reported are herewith corrected, from the analytical values of the azulene itself and its complexes.

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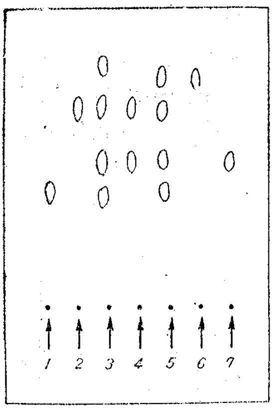
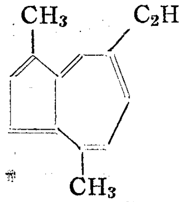
4) Y. Inouye, M. Noda: J. Agr. Chem. Soc. Japan, 24, 291 (1951).



1. Formohydroxamic acid
2. Propio- „ „
3. Formo-, Aceto-, Propio-, Isobutyrohydroxamic acids
4. Material
5. =3
6. Isobutyrohydroxamic acid
7. Aceto- „ „



(I)

This oxygen in the molecule is assumed to form a furan-ring from the results of dehydrogenation of perhydrodesoxy-linderene, $C_{15}H_{26}O$ (cf. Part IV, *loc. cit.*).

Generally, furan ring is completely oxidized by any of the oxidizing agents except alkaline hydrogen peroxide against which the ring is fairly stable[5~7]. By the oxidative decomposition of linderazulene with hydrogen peroxide, in the presence of pyridine to obtain homogeneity[8], the anticipated 4-methylfuran-2,3-dicarboxylic acid was obtained, although in a small amount. Under these conditions, azulene shows a certain amount of resistance to oxidation. 4-Methylfuran-2,3-dicarboxylic acid thereby obtained was identical with the product synthesized by Reichstein[9]. For the sake of further confirmation, it was admixed with furan-2,3-dicarboxylic acid by which the depression of the melting point was clearly observed.

The absorptions at 7.82 μ and 8.82 μ in infrared spectrum indicate the presence of a furan ring, and these results are identical with the absorption of coumarone derivatives and naphthofuran[10] (Fig. 5).

The ultraviolet absorption spectrum of linderazulene is very similar to that of guaiazulene with the former curves slightly located in the longer wavelength range (Fig. 2). Visible absorption spectrum of linderazulene is rather like that of 6,7-benzazulene[11] (cf. Experimental Part and Fig. 3).

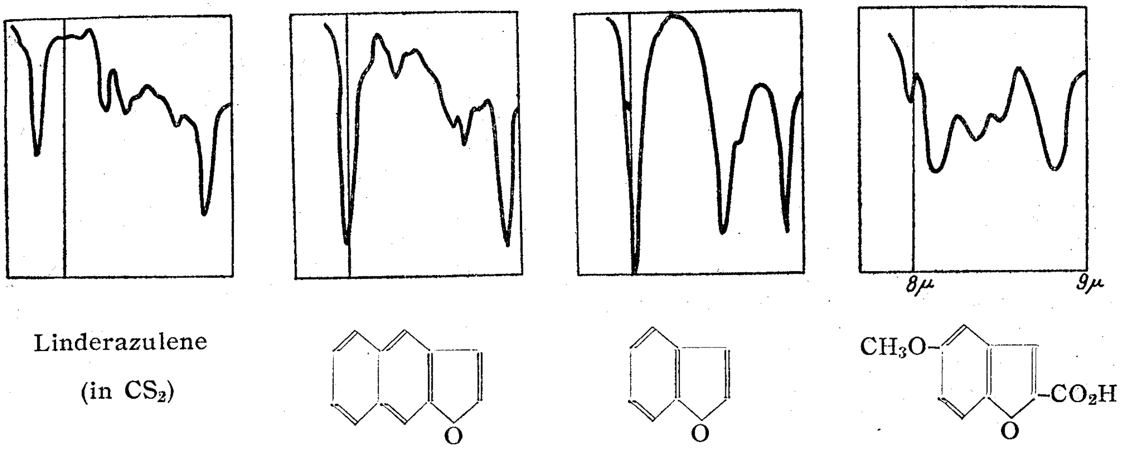


Fig. 5

From these experimental facts and by the fact that eudalene and 1-methyl-6-hydroxynaphthalene[1] were obtained from the dehydrogenation product of linderene reduction product, it can be assumed that linderazulene possesses a structure corresponding to 1,4-dimethyl-6,7-(4′-methylfurano-2′,3′)-azulene (II). This would not only be inconsistent with

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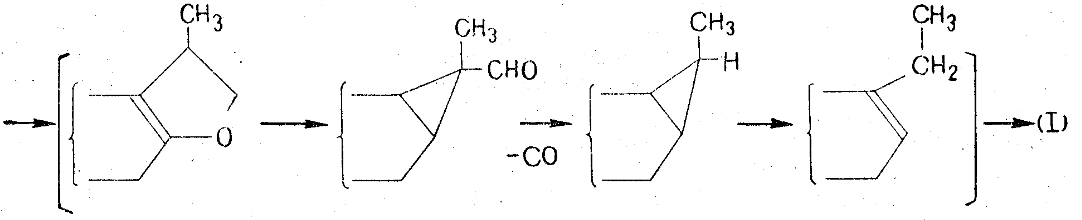
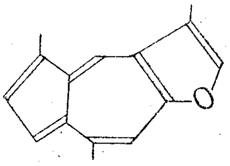
[5] F. Wessely, F. Kallab: Monatsh., 59, 161 (1932).
[6] T. Reichstein, A. Grussner: Helv. Chim. Acta, 16, 555 (1933).
[7] E. Späth, H. Holzen: Ber., 66, 1137 (1933).
[8] cf. Barger: J. Chem. Soc., 113, 218 (1918).
[9] T. Reichstein, H. Zschokke: Helv. Chim. Acta, 14, 1270 (1931).
[10] Private Communication from Mr. Masao Maruyama (Unpublished).
[11] P. A. Plattner, A. Furst, W. Keller: Helv. Chim. Acta, 32, 2426 (1949)

experimental results but would also explain the fact that linderazulene and lindazulene are formed by the high-temperature decomposition of linderene. Lindazulene was probably formed by the loss of -CO from the furan ring of linderene molecule through intermediates with a cyclopropane nucleus[12].

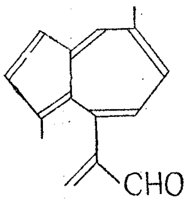


Willstaedt[13] reported the isolation of lactaroviolin, an azulene containing an aldehyde group, from orange agaric (*Lactarios deliciosus*), and assumed for it the structure (IIIa-IIIc). However, it is very interesting that an azulene with a fused hetero ring, such as the furan nucleus, had been isolated from natural products.

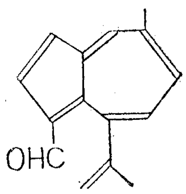
The structure of these azulenes is hoped to be identified by synthesis in the near future.



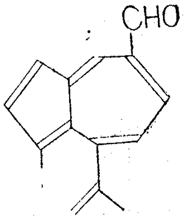
(I)



(IIIa)



(IIIb)



(IIIc)

Deep gratitude of the authors is expressed for the kind guidance of Prof. H. Kondo, Prof. Emeritus, and Prof. Eiji Ochiai of the University of Tokyo, and to Mr. Masao Maruyama of the Technological Faculty, University of Tokyo, for his photographing of infrared absorption spectra and many kind advices. The authors' thanks are also tendered to Messrs. T. Kubota, M. Inaba, T. Iyeki, K. Miyahara, and to Miss N. Morita, of this Laboratory for the photographing of ultraviolet and visible absorption spectra and for microanalyses.

Experimental[14]

I. Isolation of azulene

a) Zinc-dust distillation of linderene (cf. Ref. 1)—A mixture of 1 g. of linderene and 20 g. of zinc dust was packed in a test tube, further 40 g. of zinc dust added, and this mixture was heated at 330~390° (bath temp.). A total of 14 g. of linderene was treated. The oil that distilled out was taken up in petroleum ether, and extracted with 86% phosphoric acid to remove non-azulenic substances. Azulenic substances were distilled and the fraction of b.p$_1$ 120~195° (bath temp.) was collected.

The bluish violet, oily substance was dissolved in petroleum ether, purified through alumina, and the column was developed with a mixture of petroleum ether and petroleum (100:3) (Fig. 1).

The column was further eluted with the same solvent and separated into various fractions.

Fraction F$_4$—This is the linderazulene fraction, which was purified as the trinitrobenzene complex of m.p. 140~143°. Yield, 410 mg. Decomposed to 160 mg. of the free azulene of m.p. 85~90°.

Fraction F$_2$—This portion colors blue. Treatment with 96% phosphoric acid and purification by chromatograpy of the petroleum ether solution gave a few mg. of lindazulene trinitrobenzene complex as dark purple needle crystals of m.p. 128° (from EtOH); picrate of black needles, m.p. 109° (from EtOH). Due to the small amount available, no further purification was possible.

Fraction F$_1$—Further purification of this fraction by chromatography showed it to be a mixture. Trinitrobenzene complex was obtained in a few mg. amount as dark purple needle crystals, m.p. ca. 130°, but impure, showing depression of the melting point when fused with the trinitrobenzene complex of lindazulene. *Anal.* Found: C, 61,75; H, 4.97.

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12) Wilson: J. Am. Chem. Soc., 69, 3002, 3004 (1947).

13) H. Willstaedt: Ber., 68, 333 (1935), 69, 997 (1936); C. A., 34, 3753 (1940); Svensk Kem. Tid., 58, 23, 81 (1946).

14) m.p. uncorrected.

Fraction F_3—This portion colors pinkish violet. A small amount of trinitrobenzene complex of m.p. 154～156° was obtained but no further examination could be made. This substance may be an isomer of linderazulene. *Anal.* Calcd. for $C_{15}H_{14}O \cdot C_6H_3O_6N_3$: C, 59.57; H, 4.02. Found: C, 59.65; H, 3.96.

b) From the neutral, high-boiling fraction—The neutral, high-boiling fraction of the extract was treated with about 60 volumes of zinc dust, exactly in the same manner as for linderene, and lindazulene and linderazulene were obtained in a pure state. From 95 g. of the high-boiling fraction, about 1.5 g. of linderazulene trinitrobezene complex and 1.7 g. of crude lindazulene trinitrobenzene complex were obtained. The purified lindazulene trinitrobenzene complex thereby obtained showed m.p. 132° and gave a picrate of m.p. 112°.

II. Lindazulene—Trinitrobenzene complex: Dark purple needles, m.p. 132°. Picrate, black needles, m.p. 112°. *Anal.* Calcd. for $C_{14}H_{16} \cdot C_6H_3O_6N_3$: C, 60.45; H, 4.82; N, 10.58. Found (TNB-complex from the high-boiling fraction): C, 60.69, 60.79, 60.66; H, 4.79, 5.17, 5.28; N, 10.61, 10.69 Found (TNB-complex from linderene): C, 60.88; H, 4.45. *Anal.* Calcd. for $C_{14}H_{16} \cdot C_6H_3O_7N_3$: C, 58.11; H, 4.63; N, 10.17. Found (Picrate from the high-boiling fraction): C, 58.31, 58.33; H, 4.43, 4.73; N, 10.31.

Ultraviolet and Visible Absorption Spectrum
(in Hexane)
(Beckman Spectrophotometer)

	Lindazulene (I)		Lindazulene (H.B.F.)		s-Guaiazulene	
	λ (mμ)	log ε	λ (mμ)	log ε	λ (mμ)	log ε
Max	368	3.52	368	3.55	368	3.53
Min	362	3.33	362	3.36	362	3.32
Max	350	3.67	351	3.67	350	3.66
Min	316	3.16	316	3.21	316	3.15
Max	304	3.99	304	4.01	304	3.01
Min	302	3.96	302	3.98	302	3.95
Max	286	4.64	286	4.64	286	4.62
Min	258	3.97	258	4.02	258	4.02
Max	245	4.36	245	4.38	245	4.37
	λ (mμ)	ε	λ (mμ)	ε	λ (mμ)	ε
Max	605	429.70	605.0	443.80	605	444.10
Min	650	341.80	650.0	355.00	650	355.60
Max	662.5	356.50	662.5	369.80	660	369.50
Min	720	113.30	717.5	121.30	717.5	122.20
Max	732.5	125.00	735.0	136.10	730.0	134.10

Permanganate oxidation of lindazulene—To a suspension of 115 mg. of lindazulene in 10 cc. of water, 4% aqueous solution of potassium permanganate was added in drops, while stirring the mixture at 3～5°. After about 3 hours, the discoloration became slack, and a total of 24 cc. of the permanganate solution was required. The reaction mixture was filtered, the filtrate neutralized to phenolphthalein, and evaporated. This condensed solution was treated with ether to remove the neutral substances, acidified to Congo red with phosphoric acid, and submitted to steam distillation. The distillate was collected in a well-chilled vessel, and extracted repeatedly with ether. After drying, ether was distilled off, using a distillation column, and esterified with diazomethane. After the decomposition of the excess of diazomethane with dehydrated alcohol saturated with hydrochloric acid, the mixture was neutralized by the addition of an alcoholic solution of 13% sodium ethoxide. To this solution were added 7 cc. of alcoholic solution of 4% hydroxylamine hydrochloride and 7 cc. of alcoholic solution of 13% sodium ethoxide, and the vessel was allowed to stand for about 5 hours after closely stoppered. The mixture was then boiled for 30 minutes on a water bath, cooled, and sodium chloride that separated out was removed by filtration. After evaporation of the filtrate to a small volume, the solution was neutralized to weak alkaline reaction with alcohol saturated with hydrochloric acid, condensed further, and sodium chloride removed. The solution thereby obtained was acidified to Congo red with conc. hydrochloric acid: ethanol (1:2) mixture and used as the sample.

Paper partition chromatography was carried out with 0.005 cc. of this sample and a mixture of hydroxamic acids was used as the control.

Rf values	Control	Sample
Acetohydroxamic acid	0.49	0.49
Propiohydroxamic acid	0.66	0.66
Formohydroxamic acid	0.38	—
Isobutyrohydroxamic acid	0.78	—

Filter paper: Toyo Roshi No. 50, 23×40 cm. Ascending method.
Developing agent: Water-saturated butanol. 13 hrs. at room temp.
Coloring agent: 10% Alcoholic solution of ferric chloride.

III. Linderazulene—Linderazulene, purple plates, m.p. 106.5°. *Anal.* Calcd. for $C_{15}H_{14}O$: C, 85.71; H, 6.66. Found: C, 85.78, 85.52, 85.50; H, 6.46, 6.54, 6.95 (Previous report[2]) gave the values as C, 85.40; H, 7.12).

Trinitrobenzene complex: *Anal.* Calcd. for $C_{15}H_{14}O \cdot C_6H_3O_6N_3$: C, 59.57; H, 4.02; N, 9.91. Found: C, 59.89, 59.70, 60.08, 59.34; H, 4,22, 4.51, 4.48, 4.06; N, 9.89, 9.84.

Visible range absorption

Linderazulene 673^{f}, 645, 610^{f}, 602^{f}, 585, 580, 570, 562^{ff}, 545^{f}, 525, 508 mμ
6,7-Benzazulene 681^{f}, 665, 645, 631, $621\text{-}607^{ff}$ 582^{f}, 570——550^{ff}, 531, 511 mμ

Infrared range absorption

Linderazulene	Naphthofuran	Coumarone	5-Methoxycoumarone-2-carboxylic acid
7.82 μ	7.99 μ	8.0 μ	8.12 μ
8.82 μ	8.92 μ	8.91 μ	8.74 μ

Hydrogen peroxide oxidation of linderazulene—To a solution of 200 mg. of linderazulene dissolved in 25 cc. of pyridine, 15 cc. of 10% sodium hydroxide was added and, while stirring and chilling the mixture with ice, 20 cc. of 30% hydrogen peroxide was added dropwise, with caution, keeping the temperature below 10°. After the completion of the addition, the mixture was stirred in room temperature for about 1.5 hours and further 10 cc. of 30% hydrogen peroxide was added in drops. After about 4 hours, the solution became dark brownish orange, and after 6 hours, pale orange. After allowing the mixture to stand overnight (the color of the solution was pale yellow), 10 cc. of 30% hydrogen peroxide was added, the mixture reacted for 5 hours, warmed to 65°, and further 15 cc. of the peroxide solution was added. Finally, the temperature of the solution was raised to 80° to decompose hydrogen peroxide. The reaction mixture was neutralized to phenolphthalein, condensed to a small volume, and non-acidic substances were removed with ether. The aqueous layer was then alkalized with ammonia, calcium chloride solution added to remove oxalic acid, and the filtrate was acidified with conc. hydrochloric acid. After salting out with potassium chloride, this was extracted with ether. Ether residue gave a positive Ehrlich reaction. This was sublimed at 0.02 mm. pressure by which platelet crystals in the upper layer, and microprisms containing some oil in the lower layer were obtained. The latter was esterified with diazomethane, and distilled to collect a fraction of $b.p_{10}$ 120∼140° (bath temp.) which was saponified in room temperature with 5% methanolic potash.

Ultraviolet and Visible Absorption Spectrum
Linderazulene
(in Hexane)
(Beckman Spectrophotometer)

λ (mμ)	log ε	λ (mμ)	ε
388 max	3.75	562 max	505.6
382 min	3.62	598 min	398.1
370 max	3.83	602.5 max	401.1
332 min	3.45	607.5 min	393.1
320 max	4.32	610.0 max	398.1
292 max	4.61	645.0 max	200.1
282 min	4.56	662.5 min	119.4
278 max	4.58	672.5 max	177.2
245 min	3.97		

Acid substance was washed with a small amount of ether to remove oil, and sublimed at 0.005 mm. pressure at around 120°. The colorless microprisms thereby obtained were washed once with ether and gave approximately 2 mg. of crystals melting at 224∼227° with decomposition. Admixture of these crystals with those of 4-methylfuran-2,3-dicarboxylic acid, m.p. 229∼230°, synthesized according to the report of Reichstein[10]), gave m.p. 227∼229°, showing the two substances to be identical both in crystal form and properties.

The afore-mentioned plate crystals were acid substance of m.p. 114∼118° but no further examination could be made due to the small amount.

Admixture of 4-methylfuran-2,3-dicarboxylic acid and furan-2,3-dicarboxylic acid clearly gave about 20° depression of the melting point.

Summary

A new azulene, corresponding to the formula of $C_{14}H_{16}$, was obtained, together with linderazulene, from the zinc-dust distillation product of linderene, the neutral, crystalline component of the root of *Lindera strychinifolia* Vill. This new azulene was designated as lindazulene. From the fact that the permangnate oxidation of lindazulene yielded acetic and propionic acids and from the examination of the absorption spectra, this new azulene was assumed to be 1,4-dimethyl-7-ethylazulene. Linderazulene was found to correspond to the formula of $C_{15}H_{14}O$ and its oxidation with hydrogen peroxide gave 4-methylfuran-2,3-dicarboxylic acid, from which it was deduced that its structure would probably be 1,4-dimethyl-6,7-(4′-methylfurano-2′,3′)-azulene.

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