

873. Components of the Root of *Lindera Strychnifolia* Vill. Part VIII.¹ Structures of Linderalactone and Isolinderalactone.

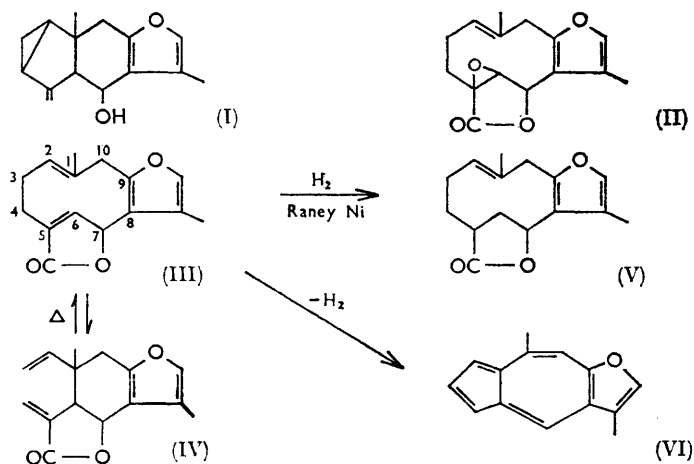
By KEN'ICHI TAKEDA, HITOSHI MINATO, and MAKOTO ISHIKAWA.

Linderalactone and isolinderalactone have been isolated from *Lindera strychnifolia* Vill. and shown to have structures (III) and (IV), respectively.

As already reported, linderene (I)²⁻⁴ and linderane (II),¹ neutral sesquiterpenes, were isolated from the root of *Lindera strychnifolia* Vill.,⁵⁻⁷ and their structures established by our group. On the other hand, on alkaline hydrolysis of the neutral extract of the same plant, Kondo⁵ isolated linderic acid, C₁₅H₁₈O₃, m. p. 205–206°, the structure of which has not been investigated. In order to confirm the structure of linderic acid, we attempted to isolate this acid from the extract of *Lindera strychnifolia* Vill. From the acid fraction of the ether extract at room temperature, linderic acid was not obtained. After the separation of linderane (II) and linderene (I) by crystallization, the neutral fraction of the extract was chromatographed on alumina to isolate linderic acid ester, but again the expected product was not obtained.

However, we obtained two new sesquiterpenic lactones having a furan ring, linderalactone (III) and isolinderalactone (IV) on the repetition of alumina chromatography of the neutral extract, and we now report the results of structural studies of these compounds.

Linderalactone (III), C₁₅H₁₆O₃, gave a positive Ehrlich's colour test and had the following spectral properties: nuclear magnetic resonance (n.m.r.) doublet at 7.90 τ ($J = 1.1$ c./sec.) and quartet at 2.87 τ ($J = 1.1$ c./sec.) (methylfurano-group); infrared (i.r.) 1762 cm.⁻¹ (γ -lactone C:O); and ultraviolet (u.v.) 208 m μ (ϵ 15,200).



When linderalactone (III) was catalytically hydrogenated with Raney nickel in ethanol, dihydrolinderalactone (V) was obtained. This compound showed an i.r. maximum at 1769 cm.⁻¹ (γ -lactone C:O) and a u.v. maximum at 221 m μ (ϵ 6800) (furan ring isolated from the double bond). Moreover, the n.m.r. spectrum of linderalactone showed a doublet

¹ Part VII, Takeda, Minato, and Horibe, *Tetrahedron*, 1963, **19**, 2307.

² Takeda and Shimada, *J. Pharm. Soc. Japan*, 1944, **64**, 154.

³ Takeda, *Chem. and Pharm. Bull. (Japan)*, 1953, **1**, 244.

⁴ Takeda and Ikuta, *Tetrahedron Letters*, 1964, No. 6, 277.

⁵ Kondo and Sanada, *J. Pharm. Soc. Japan*, 1925, **40**, 1047.

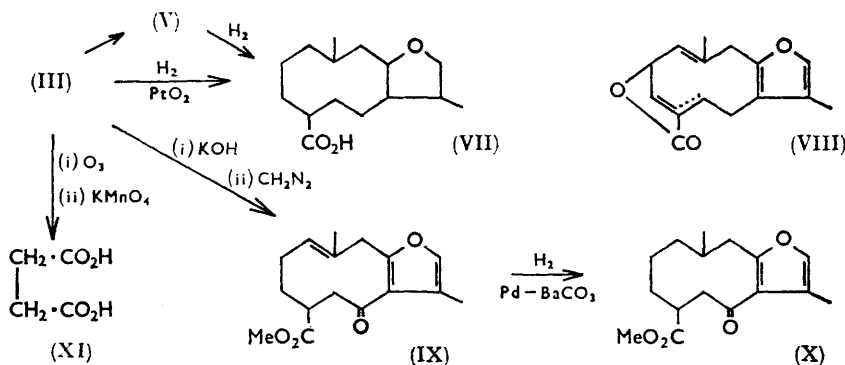
⁶ Suzuki, *J. Pharm. Soc. Japan*, 1930, **50**, 714.

⁷ Kondo and Takeda, *J. Pharm. Soc. Japan*, 1939, **59**, 504.

at 3.18τ ($J = 1.5$ c./sec.) due to an olefinic proton, which was absent from that of dihydro-linderalactone. From these results, it is established that linderalactone has an $\alpha\beta$ -unsaturated γ -lactone function. Since the n.m.r. spectrum of linderalactone (III) or dihydro-linderalactone (V) shows a signal at 8.72 or 8.37τ (methyl group on a double bond), linderalactone has an ethylenic double bond having a methyl group, which is the one isolated from the furan ring, in addition to a double bond in the $\alpha\beta$ -unsaturated γ -lactone system.

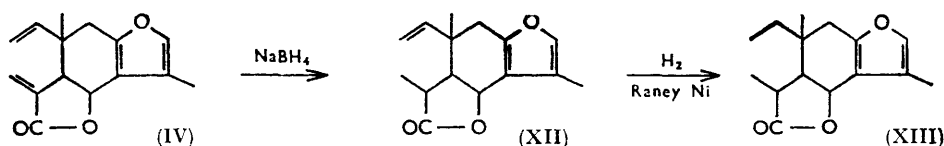
From these facts and from the data of elemental analysis, linderalactone (III) is a ten-membered monocyclic sesquiterpenic lactone having two ethylenic double bonds and a furan ring.

On dehydrogenation of linderalactone with 10% palladium-charcoal, ujacazulene (VI)⁸ was obtained. Therefore, linderalactone has a methyl group at C-1, a 1,2-double bond, an 8,9-furan ring, and a lactonic carbonyl probably at C-5.



When linderalactone was hydrogenated in acetic acid with Adams catalyst, 5 mol. of hydrogen were taken up to give a carboxylic acid (VII), m. p. 163 – 164° . Dihydro-linderalactone (V) also afforded compound (VII) under the same conditions. As these facts are elucidated by hydrogenolysis of the γ -lactone function, the lactonic oxygen must be located at the allylic position of the furan ring or the ethylenic double bond, *i.e.*, at C-3, -7, or -10. As it is impossible to formulate a γ -lactone which has its lactonic oxygen at C-10 and satisfies the above-mentioned experimental results, the γ -lactone function of linderalactone must be situated at C-5,7 or at C-3,5.

The n.m.r. spectrum of linderalactone shows the signal of a proton at C-2 as a triplet centred at 5.05τ ($J = 7.5$ c./sec.). This fact indicates the existence of two protons on the adjacent carbon atom (C-3) of C-2, formula (VIII) is therefore excluded for linderalactone. Moreover, linderalactone afforded the keto-ester (IX) on hydrolysis with 5% potassium hydroxide in methanol, followed by treatment with diazomethane. On hydrogenation with



5% palladium-barium carbonate in ethanol, compound (IX) gave the dihydro-derivative (X) which showed an i.r. maximum at 1673 cm.^{-1} (conjugated C:O) and a u.v. maximum at $267 \text{ m}\mu$ (ϵ 2500).

⁸ Takeda, Minato, Hamamoto, Horibe, Nagasaki, and Ikuta, *J.*, 1964, 3577.

Since these results indicate that the ketonic carbonyl group is conjugated with the furan ring, the γ -lactonic oxygen of linderalactone must be situated at C-7. As mentioned later, from the fact that linderalactone and isolinderalactone (IV) are valence tautomers to each other and the results of the structural studies of isolinderalactone, linderalactone further should not be represented by structure (VIII), but by structure (III).

Lastly, the formation of the ketonic compound (X) on alkaline hydrolysis of linderalactone indicates that the double bond of the $\alpha\beta$ -unsaturated γ -lactone function is situated at C-5,6. Linderalactone afforded succinic acid (XI) in good yield by ozonolysis and oxidation of the ozonide with potassium permanganate. This result confirms the fact that linderalactone has a $\text{CH}_2\cdot\text{CH}_2\cdot$ grouping. The formula incorporating all these observations must be (III) for linderalactone.

Isolinderalactone (IV), $\text{C}_{15}\text{H}_{16}\text{O}_3$, gave a positive Ehrlich's colour test and showed n.m.r. signals at 7.92 and 2.87 τ (methylfuranogroup), an i.r. peak at 1773 cm^{-1} (γ -lactone C=O), and a u.v. peak at 210 $\text{m}\mu$ (ϵ 16,700).

On reduction with sodium borohydride in methanol, isolinderalactone gave dihydroisolinderalactone (XII) which showed an i.r. maximum at 1782 cm^{-1} and a u.v. maximum at 216 $\text{m}\mu$ (ϵ 8050) (furan ring). It is reasonable to suppose that isolinderalactone has an exocyclic methylene $\alpha\beta$ -unsaturated γ -lactone grouping, because it afforded the saturated γ -lactone (XII) on reduction with sodium borohydride.*

The n.m.r. spectrum of isolinderalactone (IV) shows five vinyl protons, whereas that of the dihydro-compound (XII) shows that two vinyl protons, 3.68 and 4.35 τ (both: doublet, $J = 1.5$ c./sec.) out of the five vinyl protons of isolinderalactone, disappear but a new methyl signal at 8.68 τ (doublet, $J = 7.0$ c./sec.) arises. These data also support the above-mentioned chemical evidence.

Dihydroisolinderalactone (XII) shows characteristic strong i.r. bands at 999 and 916 cm^{-1} (RHC:CH_2) and three vinyl protons as eight characteristic n.m.r. signals⁹ at 3.85—5.10 τ (hydrogen atoms of the same type of double bond). Moreover, hydrogenation of the lactone (XII) with Raney nickel in ethanol afforded tetrahydroisolinderalactone (XIII) which lacked the characteristic bands of the double bond in the i.r. and all vinyl proton signals in the n.m.r. spectrum, but showed a new methyl signal at 9.12 τ (triplet, $J = 7.0$ c./sec.). According to these results and the fact that isolinderalactone has a tertiary methyl group at 9.02 τ , isolinderalactone (IV) must be a monocyclic sesquiterpenic $\alpha\beta$ -unsaturated lactone having a furan ring and a vinyl group as a side-chain.

When linderalactone (III) or isolinderalactone (IV) was heated alone at about 160°, both afforded an equilibrium mixture of the two (*ca.* 1 : 1). As this fact is elucidated by valence isomerization¹⁰ between a ten- and a six-membered ring compound, the valence tautomer of linderalactone (III) should be represented by structure (IV), which is completely consistent with the above-mentioned chemical and physical data on isolinderalactone and is therefore assigned to this compound.

As isolinderalactone is a valence tautomer of linderalactone, we have some doubts as to whether the former is a natural product or not. In fact, the yield of isolinderalactone is greater in the case of separation of the components by distillation of the plant extract.

In this report, as the separation of the components was performed as carefully as possible to avoid heating, it is unreasonable to suppose that isolinderalactone is obtained by isomerization of linderalactone.

Although linderane (II) and linderalactone (III) both belong to the germacrane-type sesquiterpenes, it is noteworthy that one of the methyl groups at position 5 is oxidized to the γ -lactone function.

* It is reasonable that a *cis*-enone such as (IV) should be reduced by sodium borohydride and this procedure is very useful for reduction of the exocyclic methylene $\alpha\beta$ -unsaturated γ -lactone system.

⁹ Varian Associates, "High Resolution N.M.R. Spectra Catalog," Palo Alto, California, 1962, No. 35.

¹⁰ Vogel, *Angew. Chem.*, 1962, **74**, 829.

EXPERIMENTAL

Melting points were taken on a Kofler hot-stage apparatus and are corrected. Unless otherwise specified, u.v. spectra were taken in 95% ethanol, i.r. spectra in carbon disulphide, and $[\alpha]_D$ values in dioxan. N.m.r. spectra were taken on deuterochloroform solution with a Varian A-60 spectrometer. Thin-layer chromatography was carried out with "Merck," Kieselgel G and benzene-ethyl acetate (9 : 1) by the ascending method; detection was by Ehrlich's reagent.

Isolation of Linderalactone (III) and *Isolinderalactone* (IV).—The dried and sliced root of *Lindera strychnifolia* Vill. (3 kg.) was extracted with ether (2×7 l.) at room temperature for 5 days. The combined ether solutions were washed with 5% sodium hydroxide to isolate the acid fraction. The aqueous layer was acidified with 2N-sulphuric acid, extracted with ether, and evaporated leaving a dark brown oil (10 g.), which showed no characteristic bands due to a furan ring in the i.r. and u.v. spectra, and gave a negative Ehrlich's colour test. Therefore, linderic acid was not contained in this acid fraction. The ether layer (neutral fraction) was washed with water, dried (Na_2SO_4), evaporated to about 200 ml. *in vacuo*, and left under nitrogen overnight in an ice-box to give crude linderane (II) (2.27 g.). The filtrate was evaporated *in vacuo* and light petroleum (30 ml.) was added and left overnight in an ice-box to give crude linderene (I) (5.9 g.). The mother-liquor was evaporated *in vacuo* leaving a reddish-brown oil (52.1 g.). The residue (44.3 g.) was dissolved in light petroleum (500 ml.) and chromatographed on neutral alumina (Woelm, Activity II) (440 g.) with the results shown in the Table.

Alumina chromatography.

Fraction no.	Solvent	Product	R_F on thin-layer chromatogram *	Yield (g.)
1—5	Light petroleum	Oil	0.69, 0.61	19.57
6—8	Light petroleum-benzene (8 : 2 and 7 : 3)	Oil	0.61, 0.51	2.73
9—10	Light petroleum-benzene 1 : 1	Crystals	0.45, 0.36	3.41
11—17	Light petroleum-benzene (1 : 1) and benzene	Crystals	0.39	4.55
18—19	Benzene-chloroform (9 : 1)	Oil	—	0.72

* Linderane (II) 0.51, isolinderalactone (IV) 0.45, linderene (I) 0.39, and linderalactone (III) 0.36. The structures of the compounds, R_F 0.69 and 0.61, will be reported in Part IX of this series.

Fractions 9 and 10 (3.41 g.) were rechromatographed on neutral alumina and recrystallized to give *isolinderalactone* (IV) (80 mg.), needles, m. p. 118—121° (from acetone), $[\alpha]_D - 224.7^\circ$ (c 0.52), R_F 0.45, λ_{max} . 210 μ (ϵ 16,700), ν_{max} . 1773 cm^{-1} and (in Nujol) 3085, 1752, 1643, 1010, 959, 928, 775 cm^{-1} (Found: C, 73.85; H, 6.7. $\text{C}_{15}\text{H}_{16}\text{O}_3$ requires C, 73.75; H, 6.6%) and *linderalactone* (III) (1.19 g.), needles, m. p. 136—138° (from methanol), $[\alpha]_D + 5.2^\circ$ (c 0.98), R_F 0.36, λ_{max} . 208 μ (ϵ 15,200), ν_{max} . 1762 cm^{-1} (Found: C, 73.75; H, 6.7%).

Hydrogenation of Linderalactone (III) with Raney Nickel.—A mixture of Raney nickel (W-2) (0.1 ml.) in a solution of the lactone (100 mg.) in 95% ethanol (20 ml.) was reduced by catalytic hydrogenation. When 1.2 equiv. of hydrogen had been absorbed, the catalyst and solvent were removed. The residue was extracted with ether, washed with water, dried (Na_2SO_4), and evaporated leaving a crystalline substance (93 mg.), which was recrystallized from pentane to give *dihydrolinderalactone* (V) (23 mg.), needles, m. p. 140—142° (decomp.), $[\alpha]_D - 43.9^\circ$ (c 0.63), λ_{max} . 221 μ (ϵ 6800), ν_{max} . 1769 cm^{-1} (Found: C, 73.1; H, 7.45. $\text{C}_{15}\text{H}_{18}\text{O}_3$ requires: C, 73.15; H, 7.35%).

Dehydrogenation of Linderalactone (III).—When a mixture of the lactone (122 mg.) and 10% palladium-charcoal (60 mg.) was heated at 305—310° for 2 min. under nitrogen, a reddish-purple azulene was obtained. The azulene was extracted with light petroleum and chromatographed on neutral alumina (Woelm, Activity II) (1.5 g.) to give the crude azulene (5.2 mg.), m. p. 80—95°, which was recrystallized from ethanol to give ujacazulene (VI) ⁸ as reddish-purple prisms, m. p. 103—105°, identical (mixed m. p. and ultraviolet, visible, and infrared spectra) with an authentic sample.

Hydrogenation of Linderalactone (III) with Adams Catalyst.—A mixture of Adams catalyst (20 mg.) and the lactone (100 mg.) in acetic acid (20 ml.) was catalytically reduced. When 5 equiv. of hydrogen had been absorbed, the reaction stopped, and the catalyst and solvent were removed. The residue was dissolved in ether and extracted with 2N-sodium carbonate. The ether layer afforded an oil (3.4 mg.). The aqueous layer was acidified with 2N-sulphuric

4582 *Components of the Root of Lindera Strychnifolia Vill. Part VIII.*

acid, extracted with ether, washed with water, dried (Na_2SO_4), and evaporated leaving a crystalline substance (100 mg.), which was recrystallized from acetone to give a *carboxylic acid* (VII) (37 mg.), plates, m. p. 163–164°, ν_{max} . (Nujol) 1722 cm^{-1} (Found: C, 70.95; H, 10.4. $\text{C}_{15}\text{H}_{26}\text{O}_3$ requires: C, 70.85; H, 10.3%).

Hydrogenation of Dihydrolinderalactone (V) with Adams Catalyst.—When the lactone (10 mg.) was catalytically reduced as described for compound (III), 4 equiv. of hydrogen were absorbed, and the acid (VII) (6.3 mg.) was obtained.

Hydrolysis of Linderalactone (III).—A solution of the lactone (90 mg.) in 5% potassium hydroxide–methanol (2 ml.) was refluxed for 1 hr. under nitrogen, evaporated *in vacuo*, and the residue dissolved in water. The aqueous solution was extracted with ether, and the aqueous layer was acidified with acetic acid, extracted with ether, washed with water, dried (Na_2SO_4), and evaporated leaving an oil (98 mg.), which was esterified with diazomethane and purified by alumina chromatography to give the *keto-ester* (IX) (80 mg.), a colourless oil, b. p. 140–145° (bath)/0.3 mm., λ_{max} . 216 (ϵ 11,800), 291 $\text{m}\mu$ (ϵ 1300), ν_{max} . (film) 1734, 1690 cm^{-1} , n.m.r. peaks 4.69 τ (triplet, $J = 7.0$ c./sec.) ($-\text{CH}_2\text{C}<$) (Found: C, 69.85; H, 7.55. $\text{C}_{16}\text{H}_{20}\text{O}_4$ requires: C, 69.55; H, 7.3%).

Hydrogenation of the Ester (IX) with 5% Palladium–Barium Carbonate.—A mixture of 5% palladium–barium carbonate (50 mg.) and the ester (42 mg.) in 95% ethanol (10 ml.) was catalytically reduced. When 0.9 equiv. of hydrogen had been absorbed, the catalyst and solvent were removed. The residue (37 mg.) was chromatographed on neutral alumina to give the *dihydro-keto-ester* (X), a colourless oil, b. p. 140–145° (bath)/0.3 mm., λ_{max} . 214 (ϵ 8700), 267 $\text{m}\mu$ (ϵ 2500), ν_{max} . (film) 1737, 1673, 1603, 1537 cm^{-1} (Found: C, 68.65; H, 7.75. $\text{C}_{16}\text{H}_{22}\text{O}_4$ requires: C, 69.05; H, 7.95%).

Ozonolysis of Linderalactone (III).—The lactone (100 mg.) in methyl acetate (10 ml.) was ozonized at -70° and the solvent removed *in vacuo*. The residue was dissolved in acetone (15 ml.) and oxidized by addition of a solution of potassium permanganate (380 mg.) in acetone (30 ml.) with stirring for 1.5 hr. at room temperature. After filtration, the filtrate was evaporated *in vacuo*, dissolved in 2N-sulphuric acid (2 ml.), evaporated to dryness, and extracted with acetone. The extract was evaporated giving succinic acid (XI) (36 mg.), m. p. and mixed m. p. 189–190° (from acetone).

Reduction of Isolinderalactone (IV) with Sodium Borohydride.—A solution of the lactone (46 mg.) and sodium borohydride (7.2 mg.) in methanol (1.5 ml.) was left for 1 hr. at room temperature, evaporated, extracted with ether, washed with water, dried (Na_2SO_4), and evaporated leaving a crystalline substance (45.6 mg.) which gave *dihydroisolinderalactone* (XII) (33 mg.), needles, m. p. 124–126° (decomp.) (from methanol), λ_{max} . 216 $\text{m}\mu$ (ϵ 8050), ν_{max} . 3075, 1782, 1641, 999, 916, 739 cm^{-1} (Found: C, 73.05; H, 7.45. $\text{C}_{15}\text{H}_{18}\text{O}_3$ requires: C, 73.15; H, 7.35%).

Hydrogenation of Dihydroisolinderalactone (XII) with Raney Nickel.—A mixture of Raney nickel (W-2) (0.1 ml.) in a solution of the lactone (33 mg.) in 95% ethanol (10 ml.) was reduced by catalytic hydrogenation. When 1.3 equiv. of hydrogen had been absorbed the catalyst and solvent were removed. The residue was dissolved in light petroleum and chromatographed on neutral alumina to give tetrahydroisolinderalactone (XIII) (29.5 mg.), a very unstable colourless oil, λ_{max} . 217 $\text{m}\mu$ (ϵ 6400), ν_{max} . 1782 cm^{-1} .

Valence Isomerization of Linderalactone (III) and *Isolinderalactone* (IV).—When the lactone (III) or (IV) was heated alone for 15 min. at 160–170° in an oil-bath or refluxed in *p*-cymene for 1 hr. under nitrogen, the product showed two spots, R_f 0.45 and 0.36, in the thin-layer chromatogram and afforded (III) and (IV) (ca. 1:1) by alumina or preparative thin-layer chromatography.

The authors express their deep gratitude to Dr. K. Tori for his valuable discussion on the n.m.r. spectra.

SHIONOGI RESEARCH LABORATORY, SHIONOGI & CO., LTD.,
FUKUSHIMA-KU, OSAKA, JAPAN.

[Received, February 14th, 1964.]