Tetrahedron. Vol. 24, pp. 625 to 631. Pergamon Press 1968. Printed in Great Britain

COMPONENTS OF THE ROOT OF *LINDERA STRYCHNIFOLIA* VILL—XIII[1]

STRUCTURE OF ISOGEMAFURENE AND LINDEROXIDE

H. ISHII, T. TOZYO, M. NAKAMURA and KEN'ICHI TAKEDA

Shionogi Research Laboratory, Shionogi & Co., Ltd.
Fukushima-ku, Osaka, Japan

(*Received in Japan* 19 *April* 1967; *accepted for publication* 16 *May* 1967)

Abstract—Two new furanosesquiterpenes, named isogermafurene and linderoxide, have been isolated from the ether extract of the root of *Lindera strychnifolia* Vill, and structures IV and XVII proposed for isogermafurene and linderoxide, respectively. It is also suggested that the isogermafurene (IV) is not produced naturally, but is an artifact formed by pyrolysis of the germacrene type progenitor XIII.

SUZUKI[2] in 1930 reported in Part II of this series on the fractionation of an ether extract of the root of *Lindera strychnifolia* Vill., purchased from Formosa,* giving four distillation fractions A, B, C and D. Further, from fraction C an oil of b.p. 158°/5 mm together with a small amount of crystalline linderene were isolated. Later the structure of linderene (Ia) was established by one of us (K.T.).[3–5] The other oily fractions were sealed in ampoules and remained untouched, but development of modern chromatograph techniques prompted us to reinvestigate the lower boiling liquids. Suzuki's fractions B and C yielded two new sesquiterpenes having a furan ring, and we now describe the isolation and structure elucidation of isogermafurne and linderoxide.

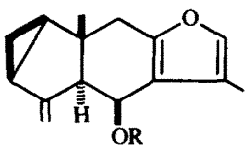
Fractions B (b.p. 100–140°/5 mm) and C (b.p. 140–170°/5 mm) were combined and fractionated by re-distillation into seven aliquots as described in the Experimental. Gas chromatographic inspection of each fraction† showed the presence of two new components besides lindestrene[6] (II) and isolinderoxide[1] (III) in the furanosesquiterpene region. Preparative gas chromatography of a redistilled fraction of b.p. 116–125°/2 mm gave isogermafurene (IV) and lindestrene (II), and the fraction, b.p. 140–145°/2 mm, afforded isolinderoxide (III) and linderoxide (XVII).

Isogermafurene (IV) is a colourless mobile oil, $C_{15}H_{20}O$, and develops a reddish colour in the Ehrlich test. The following spectral properties are similar to those of elemol[7,8] (V) and suggest the presence of a vinyl, an isopropenyl and a furan ring grouping; UV absorptions at 202·5 mμ (ε 7900) and 220 mμ (ε 6300); IR bands at 3067, 1640, 1418, 996, 910 and 892 cm^{-1} (—CH=CH_2 and >C=CH_2), and 1568 cm^{-1} (furan ring); NMR signals at τ 8·95 (3H, singlet), 8·26 (3H, doublet, J = 1 c/s, C=C—CH_3), 8·09 (3H, doublet, J = 1·1 c/s, CH_3 on furan ring), 4·85–5·30 (4H, three

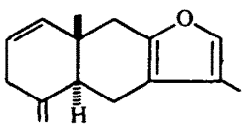
* It was assumed that this material was of Chinese origin gathered from Chekiang Province.

† Details of gas chromatographic analysis of the fractions will be reported in a forthcoming paper.

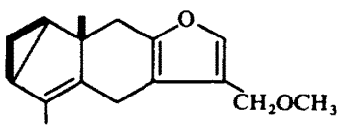
Chart 1



Ia: R = H
b: R = Ac



II



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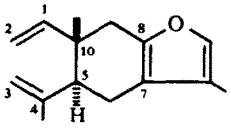
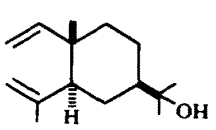


IV



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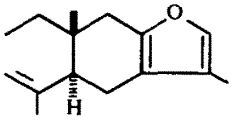

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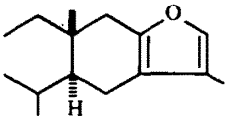
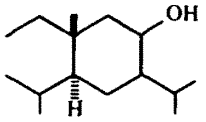
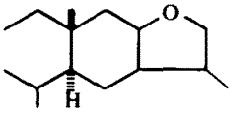


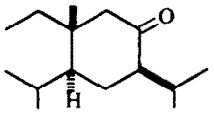
VII



VIII



IX



X

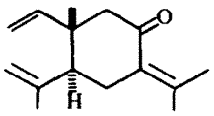
multiplets, —CH=C$\underline{H}_2$ and $\rangle$C=C$\underline{H}_2$), 4·09 (1H, doublet of doublets, J = 10·2; 17·4 c/s, —C$\underline{H}$=CH$_2$) and 2·95 (1H, quartet, J = 1·1 c/s, proton on furan ring).

On selective hydrogenation over palladized barium carbonate catalyst in methanol, isogermafurene (IV) absorbed 1 mole of hydrogen to give a dihydro compound VI, $C_{15}H_{22}O$. In the NMR spectrum, signals related to the three vinyl protons of —CH=CH$_2$ grouping had disappeared, while a Me signal appears as a triplet (J = 7·5 c/s) at τ 9·11. Hydrogenation of IV over Adams' catalyst in methanol gave a tetrahydro derivative VII (isogermafuran), $C_{15}H_{24}O$, the NMR spectrum of which displays no vinyl proton signals, but a newly formed isopropyl signal (9H, triplet, J = 7 c/s) at τ 9·08 overlapped with a triplet signal of the C-2 Me group. These data also support the elemol skeleton for isogermafurene (IV) and this was confirmed by the following sequence of reactions.

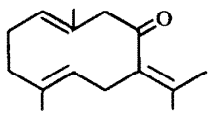
Isogermafurene (IV) when hydrogenated over Adams' catalyst in glacial acetic acid absorbed 4·2 moles of hydrogen to give a hydroxyl compound VIII besides octahydroisogermafurene (IX), $C_{15}H_{28}O$. The hydroxyl compound VIII, separated by chromatography on alumina, was oxidized with Jones' reagent to produce a

ketone, the IR spectrum of which was proved to be identical with that of eleman-8-one (X) of known stereochemistry,[9] thus establishing the furan ring closure to C-8 as well as the stereochemical assignment at C-5 and at C-10 in isogermafurene (IV).

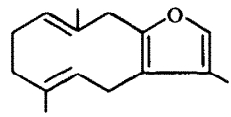
Chart 2



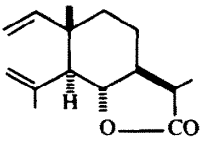
XI



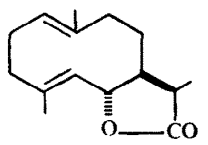
XII



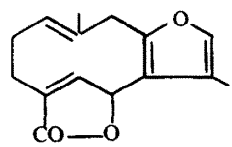
XIII



XIV



XV

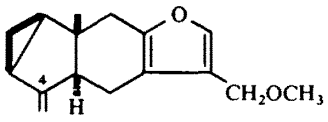


XVI

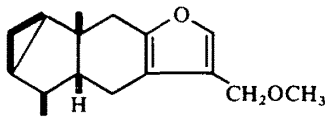
The ketone X obtained from isogermafurene shows a lower specific rotation (—1·5°) than eleman-8-one (—5·2°)[9] derived from optical active natural elemol (V), suggesting that the major part of the ketone X. thus in turn that of isogermafurene, should be racemic. Since formation of (±)-β-elemenone (XI) on pyrolysis of germacrone (XII) has been known,[10,11] it would appear that most of the isogermafurene (IV) is an artifact formed by pyrolysis of the corresponding germacrene type progenitor XIII and only a small part is a natural constituent of the plant. This is also supported by the facts that isogermafurene itself shows a very low optical rotation of −0·7° and that it was recovered unchanged on heating at 160° for 2 hr, not to give the compound XIII. Furthermore, saussurea lactone[12] (XIV) was reported to be an artifact derived from dihydrocostunolide (XV), and a 10-membered ring sesquiterpene, linderalactone[13] (XVI), was previously found in this plant.

Linderoxide (XVII), $C_{16}H_{20}O_2$, has one MeO group (elemental analysis) and gives a purple colour in the Ehrlich test. The IR spectrum shows bands at 3085, 1662 and 882 cm^{-1} ($\rangle C{=}CH_2$), and 1559 cm^{-1} (furan ring). The UV spectrum reveals an absorption at 206·5 mμ (ε 10,010)[4] indicating the presence of a conjugated system besides the furan ring. The NMR spectrum has signals at τ 9·38 (3H. singlet)[4], 6·70 (3H, singlet, OMe)[1], 5·74 (2H, doublet, J = 1 c/s, $=C-CH_2-O$)[1], 5·24 and 5·02 (2H, two multiplets, $\rangle C{=}CH_2$), and 2·77 (1H, triplet, J = 1 c/s, proton on furan ring).[1] These data together with the occurrence of isolinderoxide[1] (III) in the same distillation fraction suggest that linderoxide is a double-bond isomer of isolinderoxide and has the structure XVII.

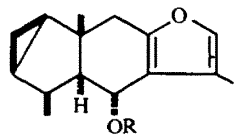
Chart 3



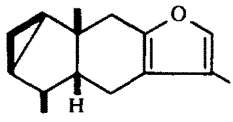
XVII



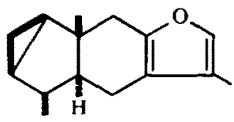
XVIII



XIXa: R = H
b: R = Ac



XX



XXI

Presence of a cyclopropane ring in XVII was verified by inspection of the NMR spectrum of dihydrolinderoxide (XVIII). On hydrogenation over Adams' catalyst in methanol, linderoxide absorbed 1 mole of hydrogen to give a dihydro compound XVIII, $C_{16}H_{22}O_2$. The NMR spectrum lacks the exocyclic methylene signals in XVII at τ 5·24 and 5·02, but displays a signal shifted in a high field at τ 9·47 (1H. triplet of doublets, J = 8·7; 5·6 c/s)[4] due to the proton on a cyclopropane ring, the observation being very similar to that reported in the selective hydrogenation of linderene (Ia) to dihydrolinderene (XIXa).[4]

Location of the OMe group in XVII was given as follows; reduction of dihydrolinderoxide (XVIII) with sodium in liquid ammonia afforded demethoxydihydrolinderoxide (XX), the NMR spectrum of which shows a Me signal on the furan ring as a doublet (J = 1·2 c/s) at τ 8·11 and a proton signal on the furan ring as a quartet (J = 1·2 c/s) at τ 2·97. These data are in good agreement with those for linderene[4] (Ia), thus indicating that demethoxydihydrolinderoxide (XX) has a β-methyl furano grouping and that linderoxide (XVII) consequently has the OMe group on its Me group.

Since the structure XX for demethoxydihydrolinderoxide would correspond to that for dihydrodehydroxylinderene, an attempt was made to reduce dihydrolinderene acetate (XIXb) of known stereochemistry[4,5] with sodium in liquid ammonia to furnish a hydrogenolytic product, dihydrodehydroxylinderene. This compound was found to be identical with XX by comparison of the IR spectra, establishing the structure and stereochemistry of dihydrolinderoxide as given in XVIII. Location of the exocyclic methylene group is limited in C-4, leading to the structure XVII for linderoxide.

Shortage and instability of both samples of the compound XX derived from linderoxide and dihydrolinderene acetate made it impossible to determine their optical activities. Then, linderoxide itself was reduced with sodium in liquid ammonia to afford isodihydrodemethoxylinderoxide (XXI), $[\alpha]_D$ −147·5°. Linderene acetate[6] (Ib) was also reduced by the same procedure to yield isodihydrodehydroxylinderene

(XXI), $[\alpha]_D$ −139·8°. Identity of both reduction products (IR spectrum) confirmed the same absolute configuration of linderoxide (XVII) as that of linderene[4,5] (Ia).

The afore-mentioned oil of b.p. 158°/5 mm obtained by Suzuki[2] was also examined by gas chromatography and proved to consist largely of linderoxide with about 10% of isolinderoxide and other unidentified minor components. Although, about 25 years ago, one of us (K.T.)[14] gave the name "isolinderene" to the oil mainly from the dehydrogenation reaction of this oil and of its hydrogenated substance, the name "isolinderene" is now known to be unsuitable for this component and should not be used hereafter.

EXPERIMENTAL

Rotations were taken in $CHCl_3$ and UV spectra in 95% EtOH. NMR spectra were recorded on a Varian A-60 spectrometer in $CDCl_3$. Gas chromatography was run by the use of an Aerograph Autoprep model A-700 instrument. Alumina used for column chromatography was Aluminiumoxid aktiv neutral (Merck).

Isolation of isogermafurene (IV) *and linderoxide* (XVII). Suzuki's distillation fractions B and C[2] were combined (70 g) and fractionated by redistillation under reduced press of 2 mm to give 7 portions: up to b.p. 116° (14·7 g), b.p. 116–125° (5·0 g), b.p. 125–130° (3·8 g), b.p. 130–135° (4·8 g), b.p. 135–140° (1·3 g), b.p. 140–145° (5·4 g) and distillation residue (32·2 g).

Fraction of b.p. 116–125°/2 mm (5·0 g) was dissolved in light petroleum and chromatographed on grade II alumina (150 g) to yield 3 fractions: fraction 1, light petroleum (1·6 g); fraction 2, light petroleum ether (98:2) (3·0 g) and fraction 3, light petroleum–ether (9:1) (0·4 g). Fraction 2 showed two peaks of retention times 11·6 min (39%) and 31·2 min (61%) on gas chromatography (5% Diethyleneglycol succinate; 150°; He 100 ml/min). The compound of retention time 11·6 min was *isogermafurene* (IV), a colourless mobile oil, $[\alpha]_D^{20}$ −0·7° (±0·3°) (*c* 0·870), the spectral data of which are given above. (Found: C, 83·5; H, 9·4. $C_{15}H_{20}O$ requires: C, 83·3; H, 9·3%). The compound of retention time 31·2 min was lindestrene[6] (II) (identified by the IR spectrum and retention time).

Fraction of b.p. 140–145°/2 mm gave 3 peaks of retention times 27·4 min (12·8%), 41·3 min (20·6%) and 51·2 min (66·6%) on gas chromatography (25% SE-30; 210°; He 100 ml/min). The compound of retention time 41·3 min was the known isolinderoxide[1] (III; identified by the IR spectrum and retention time). The compound of retention time 51·2 min was *linderoxide* (XVII), a colourless oil, $[\alpha]_D^{21}$ −52·5° (±0·9°) (*c* 0·797), the absorptions of which are shown above. (Found: C, 78·9; H, 8·4; MeO 12·6. $C_{16}H_{20}O_2$ requires: C, 78·65; H, 8·25; MeO 12·7%.)

Hydrogenation of isogermafurene (IV) *to dihydroisogermafurene* (VI). A soln of IV (198 mg) in MeOH (10 ml) was hydrogenated over 10% Pd-$BaCO_3$ (50 mg) at room temp. After 1·01 mole H_2 had been absorbed, the reaction stopped. The catalyst and solvent were removed leaving an oil (189 mg), which was purified by alumina chromatography to yield *dihydroisogermafurene* (VI), a colourless oil, ν_{max} (film) 3070, 1640, 1568 and 892 cm^{-1}, NMR τ 9·11 (3H), 9·09 (3H), 8·24 (3H), 8·11 (3H), 5·25 (1H), 5·17 (1H) and 2·97 (1H). (Found: C, 82·35; H, 10·25. $C_{15}H_{22}O$ requires: C, 82·5; H, 10·15%.)

Hydrogenation of isogermafurene (IV) *to tetrahydroisogermafurene* (VII). A mixture of IV (280 mg) and Adams' catalyst (200 mg) in MeOH (15 ml) was hydrogenated at room temp. When 2·05 mole H_2 had been absorbed, the uptake ceased. After removal of the catalyst and solvent, the residue (282 mg) was chromatographed on alumina to give *tetrahydroisogermafurene* (VII), a colourless oil, ν_{max} (film) 1652 and 1569 cm^{-1}, NMR τ 9·10 (3H), 9·08 (9H), 8·05 (3H) and 2·97 (1H). (Found: C, 82·05; H, 10·95. $C_{15}H_{24}O$ requires: C, 81·75; H, 11·0%.)

Conversion of isogermafurene (IV) *into eleman-8-one* (X). Isogermafurene (IV; 104 mg) was hydrogenated over Adams' catalyst (70 mg) in AcOH (6 ml) at room temp to absorb 4·2 moles H_2. Removal of the catalyst and solvent afforded an oil (100 mg) which was chromatographed on grade III alumina (5 g). The first light petroleum eluate gave a hydroxyl-free substance (68 mg) which showed two main peaks with retention times of 5·6 min (63·3%) and 7·7 min (24·5%) on gas chromatography (5% Phenyldiethanolamine succinate; 180°; He 100 ml/min). The compound of retention time 5·6 min was *octahydroisogermafurene* (IX), a colourless oil, $[\alpha]_D^{23}$ −0·89° (±0·05°) (*c* 7·721 dioxan) ν_{max} (film) 1050 cm^{-1}, NMR τ about 9·1 (15H, 5 Me groups) and 6·0–6·8 (3H, protons on the carbon bearing oxygen atom). (Found: C, 80·45; H, 12·45. $C_{15}H_{28}O$ requires: C, 80·3; H, 12·6%.)

The tail eluate with the same solvent produced an alcohol VIII (12 mg), ν_{max} (film) 3400 cm^{-1}. Jones' reagent (0·1 ml) was added to a soln of VIII (44 mg) in acetone (4 ml). After a period of 5 min, the reaction mixture was worked up as usual giving an oil (42 mg), which was chromatographed on alumina to yield a ketone X, a colourless oil, $[\alpha]_D^{23}$ −1·5° (±0·4°) (*c* 0·691), ν_{max} (film) 1710 cm^{-1}. Its IR spectrum was identical with that of the known eleman-8-one.[9] The semicarbazone melted at 176°.[9] (Found: C, 68·25; H, 11·05; N, 15·05. $C_{16}H_{31}ON_3$ requires: C, 68·3; H, 11·1; N, 14·95%.)

Hydrogenation of linderoxide (XVII) *to dihydrolinderoxide* (XVIII). A mixture of XVII (410 mg) and Adams' catalyst (100 mg) in MeOH (15 ml) was hydrogenated at room temp. When 1·1 moles H_2 had been absorbed, the reaction stopped, and the catalyst and solvent were removed. The residue (389 mg) showed two peaks with retention times of 10·6 min (23%) and 14·6 min (77%) on gas chromatography (5% Phenyldiethanolamine succinate; 200°; He 200 ml/min). The compound of retention time 14·6 min was *dihydrolinderoxide* (XVIII), a colourless oil, ν_{max} (film) 1561 cm^{-1}, NMR τ 9·47 (1H), 9·19 (3H), 9·13 (3H), 6·69 (3H), 5·77 (2H) and 2·77 (1H). (Found: C, 77·85; H, 8·7. $C_{16}H_{22}O_2$ requires: C, 78·0; H, 9·0%.)

Reduction of dihydrolinderoxide (XVIII) *with sodium in liquid ammonia.* A soln of XVIII (60 mg) in dry ether (1 ml) was added to a soln of Na (200 mg) in liquid ammonia (10 ml) with stirring at −60° to −70°. After a period of 1·5 hr, EtOH (2 ml) was added dropwise with stirring during 2 hr at the same temp. The solvent was evaporated, and the residue was extracted with light petroleum, washed with water, dried ($NaSO_4$), and evaporated leaving a colourless oil (53 mg). The oil was dissolved in light petroleum and chromatographed on grade III alumina (2 g). Elution with light petroleum gave *demethoxydihydrolinderoxide* (XX), a colourless mobile oil (32 mg), ν_{max} (film) 1625 and 1560 cm^{-1}, NMR τ 9·48 (1H), 9·19 (3H), 9·13 (3H), 8·11 (3H) and 2·97 (1H). (Found: C, 83·15; H, 9·45. $C_{15}H_{20}O$ requires: C, 83·3; H, 9·3%.)

Reduction of dihydrolinderene acetate (XIXb) *with sodium in liquid ammonia.* Dihydrolinderene acetate[4] (XIXb; 100 mg) was treated with Na (400 mg) in liquid ammonia (15 ml) in the manner described above. The reaction product (94 mg) was chromatographed on grade III alumina (3 g). Elution with light petroleum furnished a hydrogenolytic compound (7 mg), which was identical with XX derived from linderoxide (IR spectrum). Subsequent elution with light petroleum–ether (1:1) afforded a crystalline substance (78 mg), which was recrystallized from ether–light petroleum giving dihydrolinderene[4] (XIXa), m.p. 125–127°.

Reduction of linderoxide (XVII) *with sodium in liquid ammonia.* Linderoxide (XVII; 190 mg) was reduced in the manner described for XVIII with the use of Na (900 mg) and liquid ammonia (50 ml). The reaction product (171 mg) was chromatographed on grade II alumina (170 g) to give *demethoxyisodihydrolinderoxide* (XXI), a colourless mobile oil (94 mg), $[\alpha]_D^{21.5}$ −147·5° (±1·6°) (*c* 1·009), ν_{max} (film) 1626 and 1556 cm^{-1}, NMR τ 9·32 (3H), 9·13 (3H), 8·12 (3H) and 2·95 (1H). (Found: C, 83·05; H, 9·6. $C_{15}H_{20}O$ requires: C, 83·3; H, 9·3%.)

Reduction of linderene acetate (Ib) *with sodium in liquid ammonia.* Linderene acetate[6] (Ib; 600 mg) was reduced with Na (1·8 g) and liquid ammonia (60 ml) as described above. The reaction product (485 mg) was chromatographed on grade II alumina (500 g). Elution with light petroleum yielded isodihydrodehydroxylinderene, a colourless mobile oil (40 mg), $[\alpha]_D^{22}$ −139·8° (±1·4°) (*c* 0·887), which was identical with XXI derived from linderoxide (IR spectrum). Further elution with ether–light petroleum (1:19) and (1:9) gave isodihydrolinderene,[5] m.p. 109–112° (219 mg) and linderene,[4] m.p. 145° (124 mg), respectively (mixed m.p. and IR spectrum).

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