Absolute Configuration of Isolinderalactone, Dihydroisolinderalactone, and *epi*-Dihydroisolinderalactone

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ISOLINDERALACTONE[1] is one component of the root of *Lindera strychnifolia* Vill. and its structure has been established as (I). This compound was easily isomerised to linderalactone [1] (II) by a Cope rearrangement. Therefore, if the stereochemistry of isolinderalactone is elucidated, those of furanogermacrane type compounds[2,3] will also be clarified. The absolute stereochemistry of isolinderalactone (I) is described.

We have recently isolated isofuranogermacrene[4,5] (III), most of which is racemic owing to its synthesis, from the same plant. That portion which was optically active proved that its absolute configuration is represented by formula (III). We therefore attempted to relate isolinderalactone (I) to isofuranogermacrene (III).

Hydrogenation of isofuranogermacrene (III), $[\alpha]_D$ $-1\cdot7°$, with 10% palladium–charcoal in ethanol gave tetrahydroisofuranogermacrene (IV)[4], $[\alpha]_D$ $-0\cdot6°$, while hydrogenation of (III) with Adams catalyst in acetic acid gave two octahydroisofuranogermacrenes in the ratio *ca.* 3 : 1, (Va)[4], retention time 14·0 min., $[\alpha]_D$ $-0\cdot89°$, and (Vb), retention time 20·0 min., $[\alpha]_D$ $-0\cdot4°$.

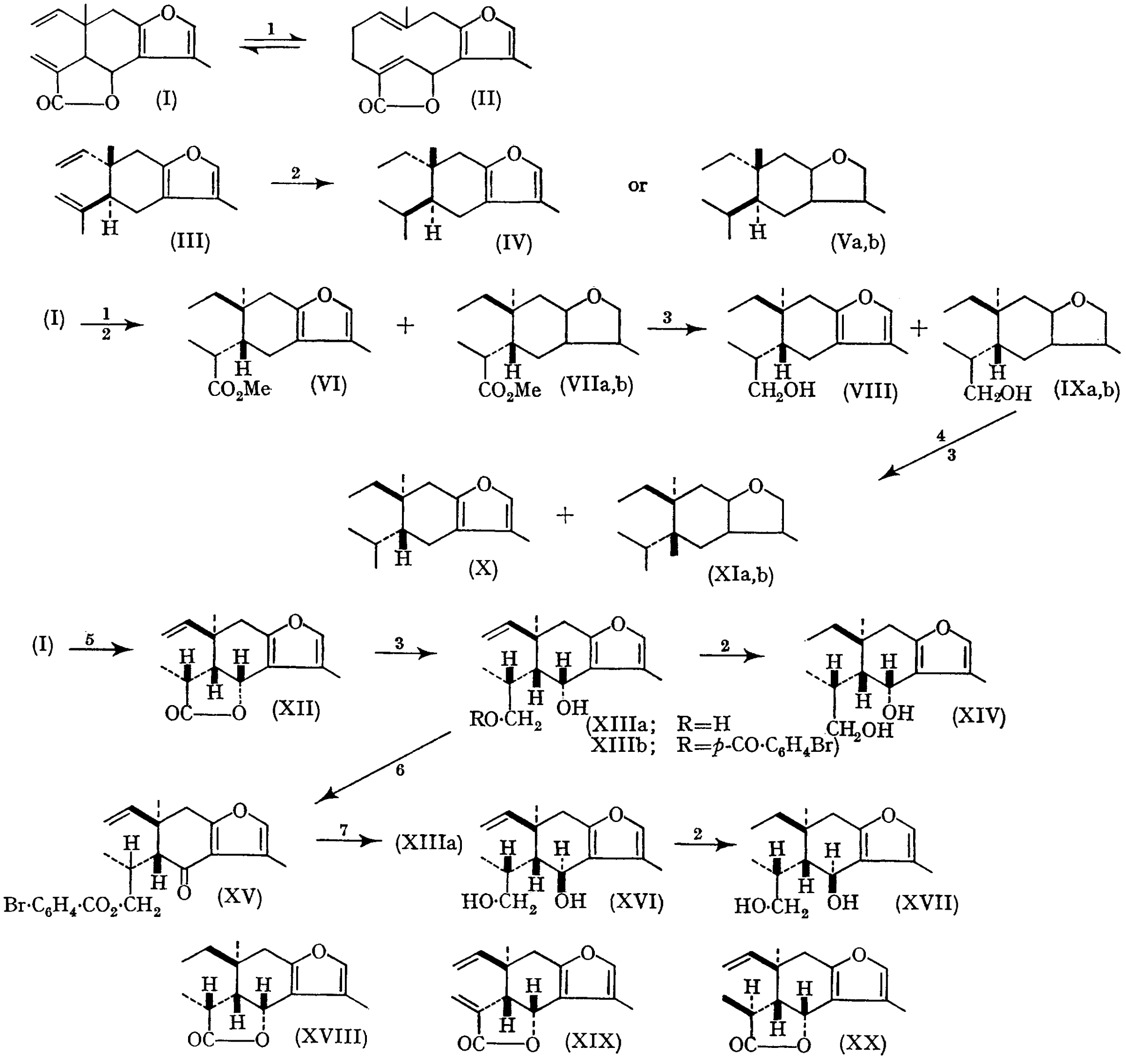
On the other hand, when isolinderalactone (I), $[\alpha]_D$ $-247°$, was hydrogenated with Adams catalyst in ethanol, it afforded an oily mixture of carboxylic acids, which was esterified to give a mixture of (VI), (VIIa), and (VIIb) by the action of diazomethane. The ester mixture was reduced by lithium aluminium hydride in ether to an alcohol mixture (VIII, IXa, and IXb) in ether. This mixture, with toluene-*p*-sulphonyl chloride in pyridine, followed by lithium aluminium hydride reduction afforded tetrahydroisofuranogermacrene (X), $[\alpha]_D$ $+17\cdot6°$, and two octahydroisofuranogermacrenes, (XIa), retention time 14·0 min., $[\alpha]_D$ $+41\cdot8°$, and (XIb), retention time 20·0 min., $[\alpha]_D$ $+9\cdot1°$, at *ca.* 2 : 3.

On comparison of gas chromatographic retention times, i.r., n.m.r., and/or u.v. spectra, these hydrogenated compounds were found to be identical with the corresponding compounds derived from isofuranogermacrene (III).

However, spite the fact that all the derivatives of isofuranogermacrene (III) showed negative rotations, the corresponding derivatives of isolinderalactone (I) revealed positive rotations. This shows that the derivatives of isolinderalactone (I) are enantiomeric to those of isofuranogermacrene (III), although absolute values of optical rotations were not identical in corresponding compounds. Isolinderalactone should consequently be represented by formula (XIX) except for the configuration of the lactonic oxygen.

In the n.m.r. spectrum tetrahydroisolinderalactone[1] (XVIII) showed a doublet–triplet signal at τ 4·70 (J 6·2, 1·2 c./sec.) due to the proton on the carbon carrying the lactonic oxygen. The value of 6·2 c./sec. suggests the fact that this proton and the adjacent proton are in a *cis*-relationship. To confirm this assumption, dihydroisolinderalactone[1] (XII) was reduced with lithium aluminium hydride to give a diol (XIIIa), m.p. 116—118°, which was hydrogenated to give a dihydro-derivative (XIV), m.p. 133—135°. As compound (XIV) showed a doublet-triplet signal at τ 5·05 (J 4·7, 1·2 c./sec.) due to the proton on the carbon carrying the secondary hydroxyl, this proton and the adjacent proton may be in *cis*-relation and the hydroxyl-group may possess the α-axial-like configuration. Moreover, the mono-*p*-bromobenzoate (XIIIb) of (XIIIa) gave a ketone (XV) on oxidation with Jones reagent. This ketone gave a mixture of (XIIIa) and its isomer (XVI) in the ratio *ca.* 2 : 3 by sodium–liquid ammonia reduction, while it afforded only (XIIIa) on lithium aluminium hydride reduction. When the mixture was hydrogenated and chromatographed on silica gel, it afforded compound (XIV) and a new diol (XVII). This compound (XVII) is an isomer of (XIV) and shows a signal at τ 5·33 (doublet–multiplet, J 8·2 c./sec.) due to the proton on the carbon carrying the secondary hydroxyl. These values, J 8·2 c./sec. and τ 5·33, lead to the conclusion that the hydroxyl group in (XVII) has the β-equational-like configuration. The fact that compound (XVII) is a major product of the sodium–liquid ammonia reduction of (XV) is in agreement with the n.m.r. results, the absolute configuration of isolinderalactone should therefore be represented by formula (XIX). Thus isolinderalactone is the first example of the antipodal elemane-type sesquiterpene.

Lastly, it was reported[6] that *epi*-dihydroisolinderalactone (XX), a viscous oil, $[\alpha]_D$ $-60·3°$, ν_{max} 1769, 1641, 1569, 968, 920, 807, and 729 cm.$^{-1}$, n.m.r. τ 8·78 (Me), 8·58 (Me, J 7·0), 7·97 (Me on furan), 4·65 (–CH·OCO, J 6·0 c./sec.), 4·21—5·18 (3 vinyl protons), and 2·95 (H on furan), was isolated from this plant. When compound (XX) was heated with 10% potassium hydroxide in



Reagents: 1, Isomerisation; 2, H_2; 3, $LiAlH_4$; 4, toluene-p-sulphonyl chloride–pyridine; 5, $NaBH_4$; 6, CrO_3; 7, Na–liquid NH_3.

TABLE

Chemical shifts (p.p.m.) of the methyl group on the lactone ring

	Chemical shift in $CDCl_3$	Chemical shift in C_6D_6	$\delta(CDCl_3)-\delta(C_6D_6)$
Dihydroisolinderalactone (XII)	1·309	1·092	+0·217
epi-Dihydroisolinderalactone (XX) ..	1·417	1·076	+0·341

ethanol for 6 hr., it was isomerised to dihydroisolinderalactone (XII). This fact indicating that compound (XX) is epimeric to (XII), with respect to the methyl-group on the lactone ring.

The n.m.r. spectra of (XII) and (XX) were investigated in deuteriated chloroform and deuteriated benzene solutions and the chemical shifts of the methyl-group on the lactone ring were shown in the Table.

According to the n.m.r. study by Narayanan and Venkatasubramanian,[7] based on the differences between the δ-values in chloroform and benzene, the methyl group in (XII) has the α-*pseudo*-equatorial configuration and that in (XX) the β-*pseudo*-axial.

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