Structural Investigation of Lac Resin. Part X.[1] Structure and Stereochemistry of Methyl Laccolate γ-Lactone and its Epimer

By **G. B. V. Subramanian,* N. Sriram, V. S. Chauhan, Javed Iqbal,** and **K. N. Ganesh,** Department of Chemistry, University of Delhi, Delhi-110007, India

The structure and stereochemistry of two lactones obtained by esterification of the gum resulting from the alkaline fission of shellac are discussed. They are the 8-epimers of 9,13-epoxy-10β-hydroxycedrane-12,15-dioic acid 12,10-lactone 15-methyl ester and appear to have been formed from shellolic acid by intramolecular addition of the hydroxymethyl group to the double bond of the αβ-unsaturated carbonyl system. Methyl esters of laksholic and 2-*epi*-laksholic acids, previously described as gums, have been obtained crystalline and characterised as derivatives.

AQUEOUS alkaline hydrolysis of shellac, followed by esterification and chromatography on silica gel, gave two crystalline lactone methyl esters in low yields.[2] These are isomeric terpene derivatives, $C_{16}H_{20}O_5$ (M^+ 292), responding to the Liebermann–Burchard test. Methyl laccolate γ-lactone, m.p. 202—204°, showed $\nu_{max.}$ 1 779 (γ-lactone) and 1 733 cm^{-1} (ester), with no indication of hydroxy-groups or double bonds (either isolated or conjugated). This was confirmed by the absence of any u.v. sorption corresponding to an αβ-unsaturated carbonyl function, and the lack of uptake of hydrogen over platinum oxide. The n.m.r. spectrum had a general resemblance to that of shellolic acid (I) and similar compounds, earlier reported [3,4] from the shellac hydrolysate. Singlets at δ 1.02 (one tertiary Me) and 3.71 (one CO_2Me), an ill-resolved two-proton quartet, partly overlapping

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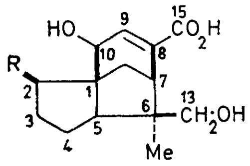
[1] Part IX, V. S. Chauhan, N. Sriram, G. B. V. Subramanian, and H. Singh, *J. Chromatog.*, 1973, **84**, 51.

[2] T. R. Seshadri, N. Sriram, and G. B. V. Subramanian, *Indian J. Chem.*, 1971, **9**, 528.

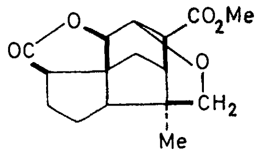
[3] (*a*) P. Yates and G. F. Field, *Tetrahedron*, 1970, **26**, 3135; (*b*) P. Yates, P. M. Burks, and G. F. Field, *ibid.*, p. 3159.

[4] R. C. Cookson, N. Lewin, and A. Morrison, *Tetrahedron*, 1962, **18**, 547.

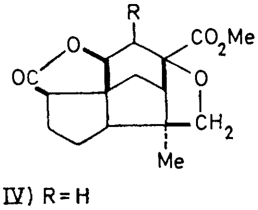
with the CO_2Me signal and centred at δ 3.48 ($CH_2{\cdot}O$), and two one-proton doublets at δ 4.38 (*J* 2.5 Hz) and 4.72 (ill-resolved) were the main features.



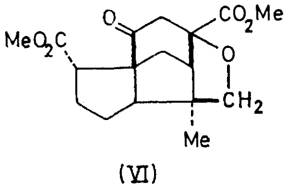
(I) R = CO_2H
(II) R = CH_2OH



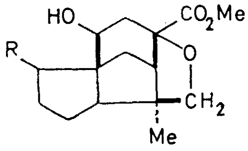
(III)



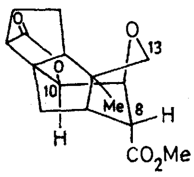
(IV) R = H
(V) R = Br



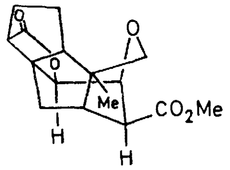
(VI)



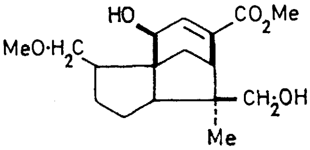
(VII) R = CO_2Me
(VIII) R = CH_2OH



(IX)



(X)



(XI)

Shellolic acid (I) and related terpenes from shellac have a great tendency to undergo lactonisation, during catalytic hydrogenation of the αβ-unsaturated ester function, though the parent olefinic compounds themselves undergo lactonisation only on treatment with Lewis acids.[3,4] This property has also been observed during other reactions leading to addition to the double bond; hence the lactones under consideration might have arisen in a similar fashion.

The lactone ring of the title compounds was readily opened by alkali to give the parent dicarboxylic acid, laccolic acid, as a crystalline solid. The n.m.r. spectrum [solvent $(CD_3)_2SO$] was ill-defined, showing a broad signal centred at δ 3.95 due to overlap with the OH signals. The absence of any signal beyond δ 4.18 indicated the cleavage of the lactone system. Esterification with diazomethane afforded some methyl laccolate γ-lactone along with major amounts of a t.l.c.-pure gum, dimethyl laccolate. The n.m.r. spectrum of the latter showed the presence of two CO_2Me groups (δ 3.67), and two one-proton doublets at δ 3.95 and 4.25, the methylene quartet remaining unaffected. The signal at δ 4.72 can thus be attributed to the proton attached to the γ-lactone function in methyl laccolate γ-lactone. I.r. spectra also confirmed the absence of a γ-lactone system in both laccolic acid and the dimethyl ester.

Of the two possible structures (III) and (IV) for methyl laccolate γ-lactone, structure (III) was favoured for the following reasons. The two one-proton n.m.r. signals between δ 4.0 and 5.0 are not readily reconciled with the environment at C-9 and -10 in structure (IV). Further in all the ether-type compounds already known in this series,[3] the CH_2 signals never appear downfield of δ 4.1. The n.m.r. data of methyl laccolate-γ-lactone are closely similar to the values reported[3,4] for the bromo-lactone methyl ester (V) and the corresponding bromo-hydroxy-ester from dimethyl shellolate, thereby substantiating the assignment. The oxo-ether (VI) from dimethyl 2-*epi*-shellolate on reduction with sodium borohydride gave two products, (VII) and (VIII), identified on the basis of their n.m.r. spectra, whereas the oxo-ether from dimethyl shellolate gave only the corresponding hydroxy-ester.

The compound isomeric with methyl laccolate γ-lactone, m.p. 218—220°, showed strong i.r. absorptions at 1 754 (γ- or δ-lactone) and 1 724 cm^{-1} (ester carbonyl) with no bands corresponding to hydroxy-groups or double bonds (confirmed by the lack of uptake of hydrogen during catalytic hydrogenation), and only end absorption in the u.v. region. In the n.m.r. spectrum the essential difference from the isomer of lower m.p. appeared in the chemical shifts of the methylene protons [δ 3.31 (d)] and the two one-proton doublets (δ 4.10 and 4.95). The behaviour of this lactone towards hydrolysis and reesterification sequence was similar to that of the other one.

Dimethyl sulphoxide, as a solvent in n.m.r. spectroscopy,[5] often nullifies differences[6] between isomeric structures (such as conformational differences or effects due to weak intramolecular hydrogen bonding or anisotropic influences from neighbouring groups) by complexing with polar centres. N.m.r. data for a number of epimeric pairs of these terpenes in $CDCl_3$ and in $(CD_3)_2SO$ (Table) indicate that the allylic proton in the 2-*epi*-series always resonates downfield of that in the shellolate series in $CDCl_3$, whereas the chemical shifts are very similar in $(CD_3)_2SO$. This property may be helpful in configurational assignment where chemical reactions are ambiguous or where no other method is available.

The n.m.r. data of the two lactones of the present investigation indicate that they may well be epimers. However, unlike the other cases, no possibility of hydrogen bonding exists, and hence the difference in spectra in $CDCl_3$ is likely to be a consequence of only anisotropic influence. The relative stereochemistry of the isomers

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[5] (*a*) S. W. Jacob, E. E. Rosenbaum, and D. C. Wood, 'Dimethyl Sulphoxide,' Dekker, New York, 1971, ch. 1; (*b*) B. Casu, M. Reggiani, G. G. Gallo, and A. Vigevani, *Tetrahedron*, 1966, **22**, 3061.

[6] S. V. Eswaran, T. R. Seshadri, N. Sriram, and G. B. V. Subramanian, *Indian J. Chem.*, 1971, **9**, 196.

may be assigned as follows. As both are γ-lactones, they are derived from shellolic acid and not 2-*epi*-shellolic acid. The C-10 proton in structure (IX) [but not in structure (X)] would be expected to suffer shielding from the C-8 ester group in $CDCl_3$. On the other hand the $CH_2{\cdot}O$ protons would come under the influence of the C-8 ester group in (X) but not in (IX). Hence structure (IX) is assigned to methyl laccolate-γ-lactone and (X) to its epimer. The mass spectra of the two compounds showed useful differences in the high mass range. Methyl laccolate γ-lactone gave a significant peak for $M - 31$ (44.5%) whereas the epimer showed an $M - 31$ peak with only 3% abundance. On the other hand, the former showed no $M - 32$ peak of consequence whereas that of the epimer was of 20.2% abundance. Only in the lactone (X) is a hydrogen atom suitably disposed for elimination of CH_3OH, thus confirming the stereochemistry assigned.

N.m.r. data (δ values; *J* in Hz)

Compound	Solvent	$CH_2{\cdot}O$	$CH{\cdot}OH$ (1H, d)	C:CH (1H, d)	$HC{\cdot}O{\cdot}CH_2$ (1H, d)
Dimethyl shellolate	$CDCl_3$	3.36br (q)	4.56 (*J* 2.5)	6.66 (*J* 2.5)	
	$(CD_3)_2SO$	3.18 (s)	4.60 (*J* 2.5)	6.43 (*J* 2.2)	
Dimethyl 2-*epi*-shellolate	$CDCl_3$	3.28br (q)	4.80 (*J* 2.5)	6.69 (*J* 2.5)	
	$(CD_3)_2SO$	3.18 (s)	4.60 (*J* 2.5)	6.53 (*J* 2.5)	
Dimethyl laccishellolate	$CDCl_3$		4.53 (*J* 2.5)	6.61 (*J* 2.5)	
	$(CD_3)_2SO$		4.55 (*J* 2.5)	6.48 (*J* 2.1)	
Dimethyl 2-*epi*-laccishellolate	$CDCl_3$		4.78 (*J* 2.5)	6.70 (*J* 2.5)	
Methyl laksholate	$CDCl_3$	3.30br (q)	4.70 (*J* 2.4)	6.63 (*J* 2.5)	
	$(CD_3)_2SO$	3.2 (s)	4.46 (*J* 2.0)	6.34 (*J* 2.4)	
Methyl 2-*epi*-laksholate	$CDCl_3$	3.31br, q	4.75 (*J* 2.5)	6.68 (*J* 2.5)	
	$(CD_3)_2SO$	3.2 (s)	4.42 (*J* 2.0)	6.39 (*J* 2.0)	
Methyl 2-*epi*-laccilaksholate	$CDCl_3$	3.31br, q	4.72 (*J* 2.0)	6.63 (*J* 2.0)	
Methyl laccolate γ-lactone	$CDCl_3$	3.48 (q)	4.72		4.38 (*J* 2.5)
	$(CD_3)_2SO$	3.14 (s)	4.70		4.22 (*J* 1.5)
Methyl 8-*epi*-laccolate γ-lactone	$CDCl_3$	3.31	4.95		4.10 (*J* 2.5)
	$(CD_3)_2SO$	3.14 (s)	4.70		4.22 (*J* 1.5)
Shellolic acid	$(CD_3)_2SO$	3.24 (s)	4.66 (*J* 2.2)	6.47 (*J* 2.3)	
2-*epi*-Shellolic acid	$(CD_3)_2SO$	3.15 (s)	4.65 (*J* 2.0)	6.53 (*J* 2.0)	
Laksholic acid	$(CD_3)_2SO$	Broad	4.47	6.32 (*J* 2.5)	
2-*epi*-Laksholic acid	$(CD_3)_2SO$	Broad	4.48	6.37 (*J* 2.5)	
Laccolic acid	$(CD_3)_2SO$	Broad and ill-defined			

The methyl esters of laksholic (II) and 2-*epi*-laksholic acids, previously reported as gums,[7] have now been obtained crystalline during the chromatography of shellac hydrolysate. They have been characterised by elemental analysis, optical rotation, and spectral properties. Both underwent hydrogenation and bromination reactions similar to those reported [3] for shellolates. Methyl laksholate was also obtained by reduction of dimethyl shellolate with borohydride. In some of these reduction experiments a pure (t.l.c.) gummy product was obtained formulated as the dihydroxy-ester (XI) on the basis of spectral characteristics.

Some differences were noticeable amongst various lac samples, the lacci-series reported [8] being absent in some shellac samples.

The trimethylsilyl derivatives of methyl laksholate, 2-*epi*-laksholate, and 2-*epi*-laccilaksholate were not separable on a number of g.l.c. columns (1% HI-EFF-8BP on GasChrom Q, 15% EGGS-X on GasChrom P, and 3% SE-30 on GasChrom WHP or GasChrom P); the separation of the trimethylsilyl derivatives of dimethyl shellolate and 2-*epi*-shellolate was best carried out on 3% SE-30 on GasChrom P (see Figure).

EXPERIMENTAL

T.l.c. of methyl esters was carried out in chloroform–methanol (96 : 4) and of the free acids in toluene–ethyl formate–formic acid (5 : 4 : 1) on silica gel plates. Spots

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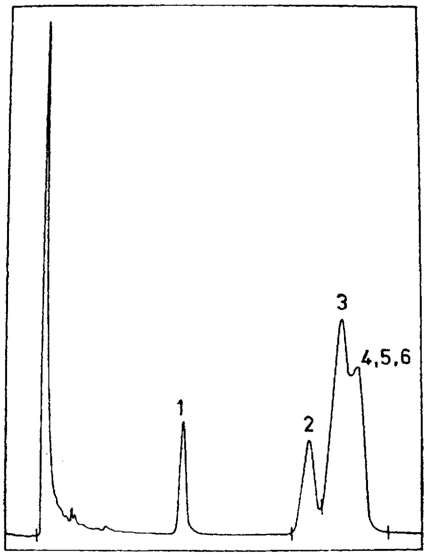
[7] M. S. Wadia, R. G. Khurana, V. V. Mhaskar, and S. Dev, *Tetrahedron*, 1969, **25**, 3841.

[8] A. N. Singh, A. B. Upadhye, M. S. Wadia, V. V. Mhaskar, and S. Dev, *Tetrahedron*, 1969, **25**, 3855.

were located by spraying with 50% aqueous sulphuric acid followed by charring.

Isolation of Constituent Acids. Superblonde shellac (200 g) was dissolved in aqueous sodium hydroxide (20%; 800 ml) and kept at room temperature for 14 days. The free acids obtained on acidification were esterified and the esters were chromatographed over silica gel as described earlier.[2] Elution with 2% ethyl acetate–benzene (4 × 500 ml) gave 9,13-*epoxy*-10β-*hydroxy*-8βH-*cedrane*-12,15-*dioic acid* 12,10-*lactone* 15-*methyl ester* (IX) (*methyl laccolate* γ-*lactone*) (100 mg), which crystallised from benzene–petroleum as needles, m.p. 202—204°, $[\alpha]_D$ −99.3° (*c* 1.0 in MeOH) (Found: C, 65.3; H, 7.1. $C_{16}H_{20}O_5$ requires C, 65.7; H, 6.9%). Hydrolysis of the lactone (80 mg) with aqueous sodium hydroxide (15%; 1 ml) (24 h) at room temperature gave 9,13-*epoxy*-10β-*hydroxy*-8βH-*cedrane*-12,15-*dioic acid* (*laccolic acid*) as a solid (60 mg), m.p. 198—200° (Found: C, 61.3; H, 7.1. $C_{15}H_{20}O_6$ requires C, 60.8; H, 6.8%).



Gas–liquid chromatogram of pure trimethylsilyl derivatives [3% SE-30 on GasChrom P (100—200 mesh); 195 °C; detector temp. 220 °C; injection port temp. 220 °C; flow rate (He) at 40 cm³ min⁻¹ at 30 lb in⁻², H_2 + air 40 cm³ min⁻¹ at 50 lb in⁻²]: 1, dimethyl laccishellolate; 2, Dimethyl 2-*epi*-shellolate; 3, dimethyl shellolate; 4, methyl 2-*epi*-laksholate; 5, methyl laksholate; 6, methyl 2-*epi*-laccilaksholate

Elution of the column with 4% ethyl acetate–benzene (4 × 500 ml) yielded the epimeric 8αH-*lactone* (X) (100 mg), which crystallised from benzene–petroleum as fibrous needles, m.p. 218—220°, $[\alpha]_D$ −94° (*c* 1.0 in $CHCl_3$) (Found: C, 65.0; H, 7.0. $C_{16}H_{20}O_5$ requires C, 65.7; H, 6.9%). Hydrolysis of the lactone (60 mg) with aqueous sodium hydroxide (15%, 1.5 ml) (24 h) at room temperature gave the 8αH-*acid* (35 mg), m.p. 207—209° (Found: C, 60.9; H, 6.6. $C_{15}H_{20}O_6$ requires C, 60.8; H, 6.8%).

Elution with 25% ethyl acetate–benzene gave *methyl* 10β,12,13-*trihydroxycedr*-8-*en*-15-*oate* (*methyl laksholate*) (2.5 g) as a crystalline solid, m.p. 124°, $[\alpha]_D$ +84.12° (in EtOH) (Found: C, 65.3; H, 8.6. $C_{16}H_{24}O_5$ requires C, 64.8; H, 8.2%), $\lambda_{max.}$ (MeOH) 230 nm (ε 5 700); $\nu_{max.}$ (KBr) 3 420, 1 680, and 1 640 cm⁻¹. Hydrolysis of methyl laksholate (500 mg) with aqueous sodium hydroxide (15%; 2 ml; 24 h) gave laksholic acid (II) (400 mg), m.p. 189° (lit.,[7] 181—183°); $[\alpha]_D$ +46.01° (in EtOH) (Found: C, 63.3; H, 7.8. Calc for $C_{15}H_{22}O_5$: C, 63.8; H, 7.9%). Re-esterification with diazomethane gave crystalline methyl laksholate.

Elution with 30% ethyl acetate–benzene gave *methyl* 2-epi-*laksholate* (2.5 g), m.p. 124°, $[\alpha]_D$ +34.60° (in EtOH) (Found: C, 64.9; H, 8.1%); $\lambda_{max.}$ (MeOH) 229 nm (ε 5 800); $\nu_{max.}$ (KBr) 3 450, 1 700, and 1 630 cm⁻¹. Hydrolysis with aqueous sodium hydroxide gave 2-*epi*-laksholic acid as an amorphous solid, m.p. 198—200° (lit.,[7] 202—203°), $[\alpha]_D$ +143.3° (in EtOH) (Found: C, 63.3; H, 8.1%).

Re-esterification of Laccolic Acid.—(i) *With diazomethane.* Esterification of laccolic acid (30 mg) in absolute methanol (2 ml) with ethereal diazomethane gave a gummy residue which was chromatographed over silica gel (5 g). Elution with pure benzene gave a solid (5 mg), m.p. 201°, not depressed by admixture with authentic methyl laccolate γ-lactone. Elution with 2% ethyl acetate–benzene gave a gummy product (t.l.c.-pure) which could not be induced to crystallise; $\nu_{max.}$ (film) 1 739 cm⁻¹; δ 1.0 (s, CMe), 3.4 br ($CH{\cdot}O{\cdot}CH_2$), 3.67 (d, $2CO_2Me$), 3.95 br (CH·OH), and 4.25 br ($CH{\cdot}O{\cdot}CH_2$).

(ii) *With methanolic hydrogen chloride.* Esterification of laccolic acid (25 mg) with methanolic hydrogen chloride (24 h; 10 °C) gave a gummy residue which was chromatographed over silica gel. Elution with 2% ethyl acetate–benzene gave the gummy dimethyl ester. 8-*epi*-Laccolic acid gave similar results on re-esterification by above methods.

Reduction of the Oxo-ether (VI). The oxo-ether (VI) (100 mg) in absolute methanol (5 ml) was treated with sodium borohydride (50 mg) for 15 min at room temperature. The solution was neutralised with dilute hydrochloric acid (1 : 1), concentrated under reduced pressure, and extracted with ethyl acetate (2 × 20 ml). Removal of solvent left a gummy residue which was chromatographed over silica gel. Elution with 6% ethyl acetate–benzene gave *dimethyl* 8,13-*epoxy*-10-*hydroxy*-2βH-*cedrane*-12,15-*dioate* (VII) (40 mg), m.p. 135° (Found: C, 63.2; H, 7.4. $C_{17}H_{24}O_6$ requires C, 63.0; H, 7.5%), $\nu_{max.}$ (KBr) 3 450 and 1 724 cm⁻¹; δ 1.09 (s, CMe), 3.64 (CO_2Me overlapping with $CH_2{\cdot}O$ signal), 3.70 (s, CO_2Me), and 4.32 (q, CH·OH). Elution with 10% ethyl acetate–benzene gave *methyl* 8,13-*epoxy*-10,12-*dihydroxycedran*-15-*oate* (VIII) (50 mg), which crystallised from ethyl acetate–petroleum; m.p. 140° (Found: C, 64.5; H, 7.8. $C_{16}H_{24}O_5$ requires C, 64.8; H, 8.2%), $\nu_{max.}$ (KBr) 3 460 and 1 724 cm⁻¹; δ 1.08 (s, CMe), 3.37 (s, $CH_2{\cdot}O$), 3.55 (q, $CH_2{\cdot}OH$), 3.65 (s, CO_2Me), and 4.31 (q, CH·OH).

The epimeric oxo-ether from dimethyl shellolate (200 mg) on similar reduction gave a gummy product which was chromatographed over silica gel. Elution with 10% ethyl acetate–benzene gave a solid (150 mg) which crystallised from ethyl acetate–petroleum; m.p. 155° (Found: C, 65.1; H, 7.4. Calc for $C_{16}H_{24}O_5$: C, 64.8; H, 8.2%), $\nu_{max.}$ (KBr) 1 715—1 700 cm⁻¹.

Reduction of Dimethyl Shellolate.—Dimethyl shellolate (500 mg) in absolute methanol (10 ml), on reduction with sodium borohydride (120 mg) (30 min) gave a gummy residue which on chromatography over silica gel gave the following fractions: 5% ethyl acetate–benzene (3 × 100 ml), no product; 10% ethyl acetate–benzene (2 × 100 ml), dimethyl shellolate (150 mg); 15% ethyl acetate–benzene (3 × 100 ml), dimethyl 2-*epi*-shellolate(20 mg); 25% ethyl acetate–benzene (3 × 100 ml), methyl laksholate (250 mg). In some experiments the 5% ethyl acetate–benzene fraction yielded *methyl* 10β,13-*dihydroxy*-12-*methoxycedr*-8-*en*-15-*oate* (XI) as a gum (t.l.c.-pure) (dimethyl *epi*-shellolate was not isolated from these experiments); $\nu_{max.}$ (BKr) 3 550, 1 730, and 1 639 cm^{-1}; δ 1.2 (s, CMe), 3.27br (CH$_2$·OH), 3.39 (s, CH$_2$·O·CH$_3$), 3.58br (CH$_2$·O·CH$_3$), 3.76 (s, CO$_2$Me), 4.58 (d, (*J* 2.6 Hz, CH·OH), and 6.65 (d, *J* 2.3 Hz, C:CH).

Hydrogenation of Methyl 2-epi-*Laksholate*.—A solution of methyl 2-*epi*-laksholate (150 mg) in ethyl acetate (50 ml) was hydrogenated over Adams catalyst for 8 h. Removal of catalyst and solvent left a gummy residue which was chromatographed over silica gel (5 g). Elution with 20% ethyl acetate–benzene yielded methyl 8,9-*dihydro*-2-epi-*laksholate* (100 mg), which was recrystallised from ethyl acetate–petroleum, m.p. 135—136° (Found: C, 63.9; H, 8.4. $C_{16}H_{26}O_5$ requires C, 64.4; H, 8.8%).

Methyl laksholate, by a similar reaction, gave 8,9-*dihydrolaksholic acid* 15,13-*lactone*, m.p. 159—160° (Found: C, 66.9; H, 8.1. $C_{15}H_{22}O_4$ requires C, 67.6; H, 8.3%), $\nu_{max.}$ (KBr) 3 370 and 1 730 cm^{-1} (δ-lactone); δ 1.19 (s, CMe), 3.99 (m, CH$_2$·OH), 4.08 (CH·OH), and 4.42 (m, CH$_2$·O·CO).

Bromination of Methyl Laksholate.—Powdered methyl laksholate (200 mg) was treated with liquid bromine (6 drops) at room temperature for 24 h. The dark reddish residue was extracted into chloroform and the solution was washed with aqueous 10% sodium thiosulphate and water. Drying and concentration gave, a gummy residue which was chromatographed over silica gel (8 g). Elution with 1% ethyl acetate–benzene gave a solid (100 mg), which crystallised from ethyl acetate–petroleum as needles of *methyl* 9-*bromo*-8,13-*epoxy*-10,12-*dihydroxycedran*-15-*oate*, m.p. 146—148° (Found: C, 51.3; H, 5.8. $C_{16}H_{23}BrO_5$ requires C, 51.2; H, 6.1%), $\nu_{max.}$ (KBr) 3 550 and 1 756 cm^{-1}.

Methyl 2-*epi*-laksholate (200 mg) under similar conditions yielded the corresponding 2-epi-*bromo-ether* (120 mg), m.p. 145° (Found: C, 51.7; H, 6.0%), $\nu_{max.}$ (KBr) 3 500 and 1 740 cm^{-1}.

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