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SHELLOLIC ACID AND *EPI*-SHELLOLIC ACID

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Abstract—Saturation of the double bond in shellolic acid by hydrogenation, hydroxylation or bromination results in the formation of δ- and γ-lactones, the further reactions of which are discussed in the light of the structure for the acid recently established by Yates and Field. The diol from reaction with osmium tetroxide is degraded by periodate to an aldehyde with three less carbon atoms. The ester group in this aldehyde and the corresponding secondary ester group in dimethyl shellolate and another of its oxidation products can be epimerized by base.

The results are consistent with a common stereochemistry for shellolic acid and cedrene.

BY alkaline hydrolysis of shellac, the resin[1] secreted by the Lac insect, *Laccifer lacca*, Harries and Nagel[2] isolated shellolic acid, $C_{15}H_{20}O_6$, and characterized it as an unsaturated dihydroxydicarboxylic acid.[2,3] A few years ago we interrelated the functional groups of shellolic acid,[4] but the failure to isolate products from attempted dehydrogenation or drastic degradation prevented the derivation of a unique structure for the whole molecule. Recently Yates and Field[5] obtained a product (I) still containing all fifteen carbon atoms of shellolic acid, and with that crucial evidence and further transformations were able to establish structure II (R = H). Since our results compliment Yates and Field's and also have a bearing on the stereochemistry of shellolic acid, we now report them.

The conjugation of the double bond with one of the carboxyl groups was immediately revealed by the spectra of the acid and its derivatives, e.g. dimethyl ester: λ_{max}230 mμ, ε 6,400; ν_{max}* 1704 and 1692 cm^{-1}. The carbonyl stretching bands of the conjugated and unconjugated ester and carboxyl groups were easily resolved, and the carbon–carbon double bond appeared as a weak band at about 1630 cm.$^{-1}$ The appearance of the ultra-violet maximum at about 13 mμ longer wave length than usual[6] (cf. cyclohexen-1-carboxylic acid, λ_{max} 217 mμ, ε 10,000) is probably mainly due to strain, perhaps assisted slightly by the presence of the allylic hydroxyl group.

One of the most striking properties of shellolic acid is the ease with which γ- and δ-lactones are formed by the carboxyl groups and the two hydroxyl groups whenever the double bond is saturated. Thus hydrogenation of shellolic acid (III; R = H)† over Adams's catalyst gave the dihydro- δ-lactone (IV; R = X = H), showing

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* Infra-red frequencies for chloroform solutions unless otherwise indicated.

† For the sake of clarity probable stereochemistry (discussed later) is shown in this and subsequent formulae.

[1] For interesting accounts see E. J. Parry, *Shellac*. Pitman, London (1935); *Shellac* Angelo Bros., Calcutta (1956).

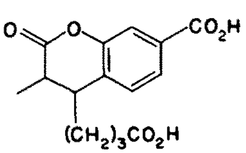
[2] C. Harries and W. Nagel, *Ber. Dtsch. Chem. Ges.* **55**, 3833 (1922).

[3] W. Nagel and W. W. Mertens, *Ber. Dtsch. Chem. Ges.* **70**, 2173 (1937); **72**, 985 (1939).

[4] N. Lewin, Ph.D. Thesis, London (1958).

[5] P. Yates and G. F. Field, *J. Amer. Chem. Soc.* **82**, 5764 (1960).

[6] A. T. Nielson, *J. Org. Chem.* **22**, 1539 (1957).



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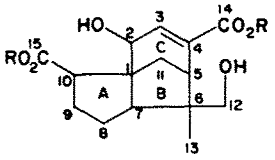

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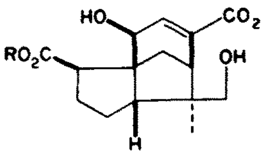

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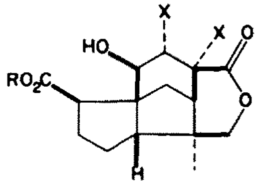

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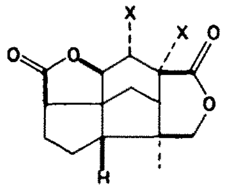

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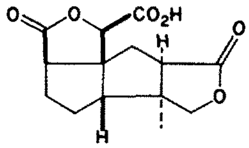

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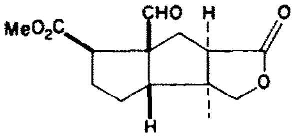

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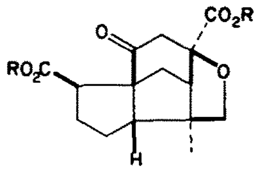

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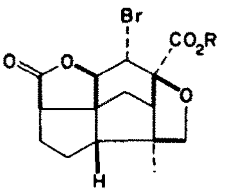

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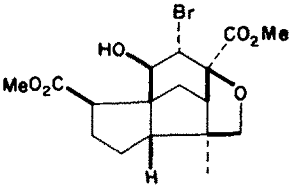
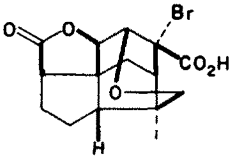
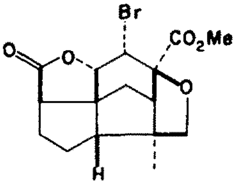


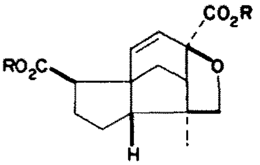
X



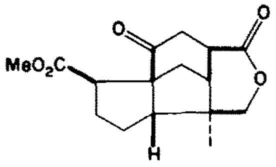
XI



IX a



XII



XIII

bands due to the δ-lactone at 1740 cm^{-1} and the carboxyl group at 1700 cm^{-1} (nujol), which was converted by acid, by sublimation or even by diazomethane into the $\gamma\delta$-dilactone (V; $X = H$), with bands at 1775 and 1750 cm^{-1}. Hydrogenation of dimethyl shellolate (III; $R = Me$) similarly led to the dilactone (V; $X = H$) and methyl ester δ-lactone (IV; $R = Me, X = H$; ν_{max} 1741 and 1720 cm^{-1}).

Osmium tetroxide oxidized shellolic acid to the dihydroxydilactone (V; X = OH; ν_{max} 1776 and 1746 cm^{-1}), also produced in poor yield with potassium permanganate.[3] The derived secondary monoacetate was stable to chromic acid, confirming that the $\alpha\beta$-unsaturated carboxylic acid in shellolic acid bears an α-substituent. Dimethyl shellolate with osmium tetroxide gave the sparingly soluble methyl ester δ-lactone (IV; R = Me, X = OH; ν_{max} 1725 cm^{-1} in nujol), which formed the dilactone (V; X = OH) on sublimation. Further oxidation of the dilactone (V; X = OH) with potassium permanganate yielded Nagel and Mertens's C_{14} acid[3], now formulated by Yates and Field[5] as VI. The infra-red spectrum of the methyl ester clearly showed the three carbonyl groups at 1790, 1780 (γ-lactones) and 1745 cm^{-1} (ester).

On titration the dilactone (V; X = OH) and the ester monolactone (IV; R = Me, X = OH) both took up one mole of periodic acid over about 10 hours, further reaction being very slow. Treatment of the latter, however, with a suspension of a large excess of sodium metaperiodate in aqueous dioxan gave a product that had lost three carbon atoms, so that under these conditions two more moles of periodate must have been consumed. In agreement with structure VII the product, which contained no hydroxyl group, had bands in its spectrum characteristic of an aldehyde (λ_{max} 289 mμ, ϵ 20; ν_{max} 2700 and 1718 cm^{-1}), ester (1736 cm^{-1}) and γ-lactone (1762 cm^{-1} in nujol). Its oxime exhibited only the bands from the ester (1735 cm^{-1}) and γ-lactone (1765 cm^{-1}).

Active manganese dioxide oxidized dimethyl shellolate smoothly to the saturated ketone (VIII; R = Me) as already reported by Yates and Field,[5] the primary hydroxyl group having added to the double bond β to the carbonyl group. The same ketone (VIII; R = Me) was formed in poor and erratic yield when dimethyl shellolate was oxidized with chromic oxide in pyridine. (Attempted Oppenauer oxidation of dimethyl shellolate with acetone and aluminium t-butoxide in benzene gave only the monomethyl ester, indentified by re-esterification with diazomethane to the original di-ester).

Addition of bromine to shellolic acid in sodium hydrogen carbonate solution gave Nagel and Mertens[3] bromolactonic acid, the spectrum of which showed that it too was a γ-lactone (ν_{max} 1775 and 1735 cm^{-1}). The empirical formula and the absence of a hydroxyl group from the derived methyl ester indicated that the primary hydroxyl group had been involved in the addition reaction. (When the esterification was carried out with excess of diazomethane in the presence of methanol the methyl ester lactone was accompanied by the di-ester of the corresponding hydroxy-acid X). The increased acidity of the bromo-lactonic acid (pK_a 3·4: shellolic acid and the dihydro-δ-lactonic acid had pK_a 4·9) did not distinguish between the alternative modes of addition to the double bond (IX; R = H, or XI), because the strengths of α-alkoxy-β-bromo- and β-alkoxy-α-bromo-acids are very close;[7] but only formula IX (R = H) explains the behaviour of the bromolactone on reduction and with alkali.

Treatment of the bromolactone with zinc dust in dilute acid yielded a bromine-free dicarboxylic acid analysing for shellolic acid less a molecule of water, presumably Nagel's "desoxyshellolic acid" (although it could not be obtained by the published

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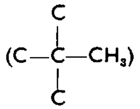
[7] H. C. Brown, D. H. McDaniel and O. Häfliger in *Determination of Organic Structures by Physical Methods.* (Edited by E. A. Braude and F. C. Nachod) p. 567 Academic Press, New York (1955).

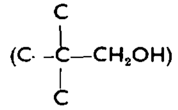
method[3]). The anhydro-acid contained an unconjugated double bond, revealed by immediate decolorization of permanganate, high end-absorption in the ultra-violet, and bands at 1640 (weak) and 715 cm^{-1} (strong) in the infra-red spectrum of the dimethyl ester. Since the same treatment of shellolic acid with zinc and acid gave a gum from which none of the anhydro-acid could be separated, the reaction could not have proceeded by reversal of the addition of bromine to regenerate shellolic acid, which then lost water. The bromine must therefore be eliminated with the lactone, leaving the ether ring intact, so that the anhydro-acid is XII (R = H). Potassium or lithium carbonate solution eliminated hydrogen bromide from the bromo-lactone (IX; R = H) to form a di-acid,[3] the dimethyl ester of which was none other than the ketone VIII (R = Me).

The proton magnetic resonance spectra of the two dimethyl esters, kindly measured by Dr. A. Melera, were consistent with the proposed relationship of anhydroshellolic acid (XII; R = H) to shellolic acid (III; R = H). In deuterochloroform containing 5 per cent of trifluoroacetic acid to catalyse rapid exchange of the protons of the hydroxyl groups, dimethyl shellolate showed singlets at 8·79τ



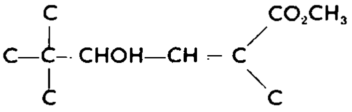
$$(\mathrm{C{-}\overset{\displaystyle C}{\underset{\displaystyle C}{C}}{-}CH_3})$$

6·50τ (2 × OH) and 6·19 and 6·22τ (2 × COOCH_3), a quartet centred at 6·65τ



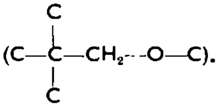
$$(\mathrm{C{-}\overset{\displaystyle C}{\underset{\displaystyle C}{C}}{-}CH_2OH})$$

and two doublets at 3·33 and 5·44τ (J = 2·5 c/s). The last two peaks, taken with the ultra-violet spectrum, clearly show the presence[5] of the group



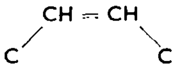
$$\mathrm{C{-}\overset{\displaystyle C}{\underset{\displaystyle C}{C}}{-}CHOH{-}CH{=}C{\begin{smallmatrix}\diagup CO_2CH_3\\ \diagdown C\end{smallmatrix}}}$$

Dimethyl anhydroshellolate (XII; R = Me) had the singlets at 8·76, 6·19 and 6·25τ from the three methyl groups and a quartet centred at 6·16τ



$$(\mathrm{C{-}\overset{\displaystyle C}{\underset{\displaystyle C}{C}}{-}CH_2{-}O{-}C}).$$

The two olefinic protons



$$\mathrm{\underset{\diagup\atop C}{CH}{=}\underset{\diagdown\atop C}{CH}}$$

suggested by the infra-red spectrum, appeared as two doublets at 3·75 and 4·52τ, with J 9·6 c/s. However each of the four peaks was split again (J ~ 1·0 and 1·4 c/s) by interaction with a third X proton, presumably from coupling at long range with one of the tertiary protons or one of the II-protons.

Treatment of anhydroshellolic acid (XII; R = H) with bromine in bicarbonate solution gave a bromolactonic acid isomeric with IX (R = H) which formed a methyl ester with peaks in its infra-red spectrum at 1805 and 1740 cm^{-1}.

At one stage the isolation of an isomer of shellolic acid from hydrolysed shellac caused some confusion, because of the coincidence in some physical properties of the two dimethyl esters (the form in which most material was extracted). The new diester happened to have the same melting point and almost the same rotation (+39°, against +32° in ethanol) as dimethyl shellolate. However, it depressed the m.p. of dimethyl shellolate and in chloroform the two rotations differed widely (+36°, against −28°). The two esters had the same ultra-violet spectrum and, although obviously different, the infra-red spectra suggested the presence of the same functional groups. The presence of the hydroxyl groups was confirmed by its formation of a crystalline diacetate, while hydrogenation afforded a methyl ester δ-lactone. Oxidation of the isomeric ester with manganese dioxide to a saturated keto-ether resembling VIII strikingly extended the analogy with dimethyl shellolate.*

The relationship between the two isomers became clear when treatment of the ketone from dimethyl shellolate (VIII; R = Me) with sodium methoxide gave the isomeric ketone: the only possible base-catalysed isomerization in the structure VIII (R = Me) is epimerization of the secondary methoxycarbonyl group. The new acid then is 10-*epi*-shellolic acid. Sodium methoxide converted dimethyl shellolate into dimethyl *epi*-shellolate amongst other products: quite likely therefore the *epi*-acid is not one of the esterifying hydroxy-acids of intact shellac. Once hydrolysed the sodium salt is probably fairly stable, but while the shellolic acid is still held in combination as a poly-ester it must be vulnerable to epimerization by alkali.

From treatment of dimethyl shellolate with methoxide Yates and Field[5] isolated a substance to which structure XIII was assigned. However, it melts 20° lower than our compound of that structure made unambiguously by oxidation of the dihydro-δ-lactone (IV; R = Me, X = H), so that here too the 10-hydrogen atom has probably epimerized under the alkaline conditions.

Stereochemistry

For the purpose of this discussion the carbon atoms of shellolic acid have been numbered as in formula II. The formation of ethers between C-12 and C-4, and of δ-lactones between C-12 and C-14 obviously requires the fusion of ring C on to the same side of ring B as the 12-hydroxymethyl group (designated β). In the absence of any direct evidence we assume that the 7-H atom also has the β-configuration, as in cedrol:[8] the alternative *trans*-fusion of rings A and B is considerably more strained, although not impossibly so. The γ-lactone ring in structures V and IX would clearly be impossible if C-15 were α and the 2-hydroxyl β, since the two bonds are roughly anti-parallel. Examination of models makes one extremely sceptical whether spontaneous lactonization could occur with C-15 α and even an α 2-OH. Epimerization at C-10 of dimethyl shellolate and especially of the ketone (VIII; R = Me), which is almost completely epimerized at equilibrium, confirms that the 15-ester group is β: the ester group would surely be more stable when opposed to the 11-methylene (α) than to the 2-carbonyl group (β), the C=O bond of which is almost parallel with the 10β bond.

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[*] *Epi*-shellolic acid and its derivatives were first isolated and characterised by Mr. G. Klee at Birkbeck College in 1956–1957.

[8] G. Stork and F. H. Clarke, *J. Amer. Chem. Soc.* **83**, 3114 (1961).

The ester group in the aldehyde (VII) also has the less stable configuration. Hydrolysis with dilute acid yields an acid that forms an isomeric ester on treatment with diazomethane. Although isomerization at C-1 and C-5 is conceivable through a reversed Michael reaction and re-addition, it seems unlikely and we suppose that the isomeric ester is epimeric at C-10.

The sensitivity of the optical rotation of dimethyl shellolate to change in solvent ($[\alpha]_D$-28° in chloroform, 0° in benzene, +34° in methanol) compared with that of the *epi*-ester, which hardly varies, may perhaps be partly due to a variable intramolecular hydrogen bond between the 2-OH and the 15-ester group in the former, possible when the ester is β, but not α.

The remaining doubt is the configuration of the 2-OH group, formation of the γ-lactones being possible with either configuration. The β-side of the double bond in a model of shellolic acid is much more hindered than the α, and in spite of the possibility of participation by several of the oxygen-containing groups it can hardly be doubted that bromine, like hydrogen, osmium tetroxide and permanganate, will attack from the α-side to give either IX or IXA. Either the reduction with zinc to anhydroshellolic acid (XII; R = H) or the conversion to the keto-acid (VIII; R = H) with mild base must involve a *cis*-elimination. If IX is correct then the overall *cis*-elimination of hydrogen bromide with base could be explained by prior displacement of bromide by the etherial oxygen followed by loss of a proton. Although the lactone may be a better leaving group than the etherial oxygen and reductive *cis*-eliminations are not unknown, reduction of a compound with the alternative structure (IXA; giving the possibility of either *cis*- or *trans*-elimination) would probably result in *trans*-elimination to regenerate shellolic acid (III; R = H) rather than in *cis*-elimination to form the anhydro-acid (XII; R = H). On balance, then, this evidence tends to favour IX as the configuration of the bromolactone.

Shellolic acid thus becomes III (R = H), with the secondary hydroxyl group β. Two independent lines of argument based on molecular rotation differences support this configuration.

The optical rotatory dispersion of the three ketones (VIII, R = Me; *epi*-VIII, R = Me and XIII), measured in Professor W. Klyne's laboratory, support the absolute configurations written. Although it alters the sign of the background rotation and the size of the Cotton effect, epimerization of the 15-ester group in VIII (R = Me) does not alter the sign of the effect. The only conformation free of angle-strain for ring C in VIII (R = Me) is a distorted boat with C-3 and C-11 at the bow and stern. Because of its lower ionization potential and diffuse lone-pair orbitals and its asymmetry to the carbonyl group, one might expect[9,10] the axial, etherial oxygen atom in the far upper left octant to overpower the opposite contribution from the predominance of hydrocarbon groups in the far upper right octant,[10] giving the observed positive Cotton effect. In the lactone (XIII) ring C can adopt either a chair-like or a boat conformation. Especially in the former the lactone oxygen atom, which will have a higher ionization potential, is further away from the carbonyl group, so

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[9] R. C. Cookson and J. Hudec, *J. Chem. Soc.* 429 (1962); R. C. Cookson and S. MacKenzie, *Proc. Chem. Soc.* 423 (1961); K. Mislow, M. A. W. Glass, A. Moscowitz and C. Djerassi, *J. Amer. Chem. Soc.*. **83**, 2771 (1961).

[10] W. Moffitt, R. B. Woodward, A. Moscowitz, W. Klyne and C. Djerassi, *J. Amer. Chem. Soc.* **83**, 4013 (1961).

that the hydrocarbon groups in the upper right octant exert their full influence, giving the large negative Cotton effect.

Application of the Hudson–Klyne Lactone Rule[11] suggests that the secondary hydroxyl group in shellolic acid is β. In the case of each of the three γ-lactones V (X = H or OH) and IX (R = Me) the lactone itself is more laevo-rotatory than the corresponding hydroxy-methyl ester. Acetylation of the primary hydroxyl group is likely to cause only a small change in rotation, so that the large increase in dextro-rotation attending conversion of dimethyl *epi*-shellolate into the diacetate is probably derived mainly from the allylic acetate: Mills's generalization[12] then also points to a β-configuration for the secondary hydroxyl group.

O.R.D. IN METHANOL $[\phi]$

Ketone	Background rotation	Peak	Trough
	400–600 mμ		
VIII (R = Me)	−ve	+905 (310 mμ)	+300[a] (280 mμ)
Epi-VIII (R = Me)	+ve	+2350 (312·5 mμ)	−1650 (277·5 mμ)
XIII	−ve	+1090[a] (277·5 mμ)	−3840 (305 mμ)

[a] $[\phi]$ at λ named, extremum not reached.

EXPERIMENTAL

U.V. spectra were measured on a Unicam SP.500 or SP.700 for solutions in ethanol, and I.R. spectra on a Unicam SP.100. Proton magnetic resonance spectra of solutions in $CDCl_3$ were measured on a Varian A.60 at 60 Mc/s with tetramethylsilane as internal reference.

Isolation of shellolic acid

The following method was adopted after published procedures had been found unsatisfactory. Angelo's dewaxed and decolourized shellac ("Patina" grade) was dissolved in 20% aqueous sodium hydroxide (1 l. per Kg of shellac). After 10–14 days the liquor was diluted with ½ of its volume of water, and sodium aleuritate was filtered off. Saturated zinc sulphate in water was gradually added to the filtrate with vigorous swirling until further addition caused no precipitation. The precipitated zinc salts were removed (Filtrate A), suspended in saturated zinc sulphate solution and filtered again (Filtrate B). 4 l. Portions of Filtrate A were acidified to Congo Red with 6N H_2SO_4 and continuously extracted with two 2 l. amounts of ether (ca. 50 hr each). Concentration of the extract caused the deposition of a succession of gums, from the later crops of which crystals of shellolic acid separated, freed from impurities by trituration with ethyl acetate (yield 0·8%). Filtrate B was processed separately in the same way, because it yielded a purer product. All the gums and residues from the extraction were then dissolved in methanol and treated with an excess of diazomethane in ether. On slow evaporation of a solution of the product in ether dimethyl shellolate crystallized out. The material from the mother liquors was chromatographed on silica gel (20 g per g). Benzene eluted a gum, followed by more dimethyl shellolate with 5% ethyl acetate, and dimethyl *epi*-shellolate with 10% ethyl acetate. The total yield of dimethyl shellolate was 3–4%, and of dimethyl *epi*-shellolate about 0·35%.

On one occasion Filtrate A was heated and the precipitate that came down was treated with dry hydrogen chloride in methanol for 3 days. The residue from evaporation of the solvent was extracted

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[11] W. Klyne, *Chem. & Ind.* 1198 (1954).

[12] J. A. Mills, *J. Chem. Soc.* 4976 (1952).

with light petroleum and chromatographed on alumina to give crystals of a third *ester*, m.p. 82–83°. (Found: C, 66·3; H, 7·8; $C_{17}H_{24}O_5$ requires: C, 66·2; H, 7·85%), having ν_{max} 3500, 1704 and 1640 (weak) cm^{-1}.

Dimethyl shellolate (Found: C, 63·0; H, 7·4; OMe, 18·75; active H, 0·66; Calc. for $C_{17}H_{24}O_6$: C, 62·95; H, 7·5; OMe, 19·15; active H, 0·62%) had m.p. 149–150°; $[\alpha]_D$ −28° in $CHCl_3$, 0° in C_6H_6, +34° in MeOH, and +32° in EtOH; λ_{max} 230 mμ, ε 6,400; ν_{max} 3500, 1714, 1702 and 1636 cm^{-1} (weak) in CCl_4, and 3500, 1704 and 1692 cm^{-1} in $CHCl_3$.

Shellolic acid (Found: C, 60·6; H, 6·7; 2 × equiv. wt. 296; Calc. for $C_{15}H_{20}O_6$: C, 60·8; H, 6·8%; mol. wt. 296) was obtained directly from hydrolysed shellac or by boiling the dimethyl ester for 3 hr with 1N NaOH, followed by acidification and concentration of the solution. Recrystallized from aqueous acetone it had m.p. 206–207° decomp; $[\alpha]_D$ +18° in EtOH; pK_a 4·96; λ_{max} 230 mμ, ε 6,200; ν_{max} 3450, 3200, 1725, 1680, 1625 cm^{-1} in nujol.

Dimethyl epi-*shellolate* separated from ethanol or ethyl acetate as needles with m.p. 151–152°; $[\alpha]_D$ +36° in $CHCl_3$ and +39° in ethanol; λ_{max} 231 mμ, ε 5,700; ν_{max} 3600, 3500, 1728 and 1692 cm^{-1} in $CHCl_3$ (Found: C, 63·0; H, 7·4; OMe, 18·4; $C_{17}H_{24}O_6$ requires: C, 63·0; H, 7·5; OMe, 19·15%).

Epi-*shellolic acid*, formed in good yield by hydrolysis of the ester with 1N aqueous NaOH, was less soluble in most solvents than shellolic acid, especially in water, from which it crystallized in hexagonal plates, m.p. 232–233° decomp, with $[\alpha]_D$ +49° in ethanol. (Found: C, 60·9; H, 6·9; $C_{15}H_{20}O_6$ requires: C, 60·8; H, 6·8%).

Monomethyl shellolate

Dimethyl shellolate (1 g) and aluminium t-butoxide (5 g) were boiled in benzene (150 ml) and acetone (100 ml) for 10 days (after 1 day only unchanged diester was isolated). The product was poured into water, made acid and extracted successively with ether, benzene and ethyl acetate. Chromatography of the residue from evaporation of the solvents gave the *mono-ester*, m.p. 223–224° after recrystallization from ethyl acetate; $[\alpha]_D$ −40° (ethanol); λ_{max} 231 mμ, ε 5,800; ν_{max} 3480, 3380, 1705 and 1645 cm^{-1} (nujol). (Found: C, 62·0; H, 7·1; OMe, 8·35. $C_{16}H_{22}O_6$ requires: C, 61·9; H, 7·15; OMe, 10·0%). Treatment with diazomethane regenerated the di-ester.

Hydrogenation of dimethyl shellolate

The di-ester (1·0 g) in ethyl acetate (100 ml) containing acetic acid (2 drops) was reduced by hydrogen (1·1 atm press) over Adams' catalyst. After 8 hr, when almost 1 mole had been taken up, the product was recovered and chromatographed in benzene on silica gel. Elution with benzene containing increasing proportions of ethyl acetate first removed a small amount of *dihydroshellolic dilactone* (V; X = H), m.p. 152–153° after recrystallization from ethyl acetate or benzene, $[\alpha]_D$ −57° ($CHCl_3$), ν_{max} 1775 and 1750 cm^{-1} ($CHCl_3$). (Found: C, 68·8; H, 7·0; $C_{15}H_{18}O_4$ requires: C, 68·7; H, 6·9%).

Recrystallization of the later fractions from ethyl acetate–light petroleum yielded *methyl dihydroshellolate-δ-lactone* (IV; R = Me, X = H; 0·70 g). After further recrystallization the needles had m.p. 155°, $[\alpha]_D$ +13° ($CHCl_3$), ν_{max} 3460, 1741 and 1720 cm^{-1} ($CHCl_3$), or 3420 and 1740 cm^{-1} (nujol). (Found: C, 65·4; H, 7·6; OMe, 10·4. $C_{16}H_{22}O_5$ requires: C, 65·3; H, 7·5; OMe, 10·6%). Use of ethanol as solvent for the hydrogenation increased the yield of dilactone at the expense of the ester monolactone. Short boiling in methanol containing hydrogen chloride converted the ester monolactone almost entirely into the dilactone.

Hydrogenation of shellolic acid in ethyl acetate over Adams' catalyst gave *dihydroshellolic acid δ-lactone* (IV; R = X = H), m.p. 150–153° after recrystallization from ethyl acetate, $[\alpha]_D$ +44° (ethanol), pK_a 4·9, ν_{max} 3300, 1740 and 1700 cm^{-1} nujol. Found: C, 62·2, H, 7·3. $C_{15}H_{20}O_5$, $\frac{1}{2}H_2O$ requires: C, 62·25; H, 7·3%). Treatment of this acid with diazomethane in ether–methanol formed the dilactone in high yield.

Oxidation of methyl dihydroshellolate δ-lactone

A solution of the lactone (IV; R = Me, X = H; 500 mg) in pyridine (10 ml) was added to chromium trioxide (550 mg) in pyridine (7 ml). 19 hr later the mixture was diluted with water, and sulphur dioxide was bubbled through until the colour changed to green. Extraction with chloroform yielded a gum (255 mg) that solidified on trituration with ethyl acetate. Recrystallizations from ethyl acetate (charcoal) gave needles of the *ketone* (XIII; 150 mg), melting at 174–174·5°, ν_{max} 1732 (broad) and 1715 cm^{-1} (nujol). (Found: C, 65·7; H, 7·0; $C_{16}H_{20}O_5$ requires: C, 65·7; H, 6·9%).

More of the ketone (160 mg) was obtained by another extraction of the oxidation mixture with ethyl acetate. Chromatography of the material from the mother liquors gave unchanged ester δ-lactone and dihydro-dilactone (11 mg).

The dihydroxy-dilactone (V; X = OH)

(a) Potassium permanganate (1 g) in water (20 ml) was dropped over 2 hr into a stirred solution of shellolic acid (1 g) in water (20 ml) and 5N KOH (4 ml). 6 hr later the manganese dioxide was filtered off and washed with hot water. The residue from evaporation of the combined filtrates under red press was just acidified with dil sulphuric acid. Dioxan precipitated potassium sulphate, which was filtered off. Evaporation of the solvent left the dilactone,[8] recrystallized from a small amount of ethanol and water (yield 20%).

(b) Shellolic acid (1·3 g) in dioxan (100 ml) was treated with osmium tetroxide (1 mole). 6 Days later the mixture was saturated with hydrogen sulphide. Dioxan was distilled from the filtered solution, and the residual dark gum was boiled with charcoal in ethanol. On evaporation of the solvent and addition of some water the product crystallized (80% yield).

From either reaction, after crystallization from aqueous ethanol, the *dihydroxy-dilactone* (V; X = OH) melted at 115°, solidified and remelted at 165°, and had $[\alpha]_D$ −120° (ethanol), ν_{max} 3500, 1776 and 1746 cm^{-1} ($CHCl_3$), or 3450, 3200 and 1750 cm^{-1} (nujol). (Found: C, 57·7; H, 6·4; $C_{15}H_{18}O_6$, H_2O requires: C, 57·7; H, 6·5%).

The monoacetate,[8] from reaction of the dihydroxy-dilactone with acetic anhydride in pyridine at room temp, after recrystallization from ethanol had m.p. 253–254°, $[\alpha]_D$ −90° ($CHCl_3$), ν_{max} 3550, 1785 and 1765 cm^{-1} ($CHCl_3$). The product from oxidation of the dihydroxy-dilactone with sodium meta-periodate in aqueous ethanol could not be induced to crystallize.

The dilactonic acid (VI)

Oxidation of the dihydroxy-dilactone (V; X = OH) in water at 100° by gradual addition of slightly acid potassium permanganate solution[8] gave the dilactonic acid. Recrystallized from aqueous methanol it had m.p. 251–253°, ν_{max} 1785 cm^{-1} ($CHCl_3$) or 1780 cm^{-1} (nujol).

The methyl ester (from diazomethane) had m.p. 144–145°, $[\alpha]_D$ −96°, ν_{max} 1790, 1780 and 1745 cm^{-1} ($CHCl_3$).

Methyl dihydroxy-δ-lactone (IV; R = Me, X = OH)

(a) The filtrate from oxidation of shellolic acid with alkaline permanganate as above was evaporated to dryness under red press. Methanol (150 ml) was added to the residue which had been acidified with 6N H_2SO_4. After removal of potassium sulphate the filtrate was kept at 5° over night. The sparingly soluble ester separated on partial evaporation of the solvent (30% yield).

(b) Dimethyl shellolate (1·3 g) was treated with osmium tetroxide (1 g) in dioxan (100 ml). After 6 days the mixture was saturated with hydrogen sulphide, filtered and evaporated. The resulting *methyl ester-δ-lactone* (0·8 g) recrystallized from aqueous dioxan, was identical with that from (a), having m.p. 249° decomp, $[\alpha]_D$ −40° (20% water in dioxan), ν_{max} 3550, 3480, 3400 and 1725 cm^{-1} (nujol). (Found: C 58·65; H, 6·9; OMe, 9·3; $C_{16}H_{22}O_7$ requires: C 58·9; H 6·8; OMe 9·5%).

The methyl aldehydo-γ-lactone (VII)

A suspension of the ester δ-lactone (IV; R = Me X = OH; (350 mg) and sodium metaperiodate (3 g) in dioxan (5 ml) and water (70 ml) was shaken for 24 hr. The mixture was then extracted repeatedly with chloroform which was evaporated. Chromatography of the residue in benzene on silica gel produced the *aldehyde* (VII), crystallizing from a small volume of chloroform and ether (30% yield). It had m.p. 144–145°; $[\alpha]_D$ −107° ($CHCl_3$); λ_{max} 289 mμ, ε 20; ν_{max} 2720, 1735 and 1775 cm^{-1} ($CHCl_3$), or 2700, 1762, 1736 and 1718 cm^{-1} (nujol). (Found: C, 62·45; H, 7·2; OMe, 11·2. $C_{14}H_{18}O_5$ requires: C, 63·1; H, 6·8; OMe, 11·8%), and sublimed unchanged at 150° and 5 × 10^{-3} mm.

After recrystallization from ethyl acetate–light petroleum the *oxime* had m.p. 164–165°, $[\alpha]_D$ −112°, ν_{max} 3600, 1765 and 1735 cm^{-1} ($CHCl_3$). (Found: C, 59·2; H, 7·2; N, 4·75; OMe, 11·3; $C_{14}H_{19}O_5N$ requires: C, 59·8; H, 6·8; N, 5·0; OMe, 11·0%).

The aldehyde (VII; 61 mg) in 10% sulphuric acid (10 ml) was warmed until a clear solution was obtained. After 20 hr the crystals that had separated were removed and the filtrate was extracted with chloroform. More crystals resulted from evaporation of the chloroform. After recrystallization from chloroform the *aldehydo-acid* (53 mg) had m.p. 200–201°, ν_{max} 3470, 1775 and 1760 cm^{-1} (nujol). (Found: C, 62·0; H, 6·4. $C_{13}H_{16}O_5$ requires: C, 61·9; H, 6·4%).

Treatment of this acid with diazomethane in ether–methanol, chromatography in benzene on silica gel, and crystallization from ethyl acetate–light petroleum gave a *methyl ester*, m.p. 129–131°, ν_{max} 2740, 1779 and 1735 cm^{-1} ($CHCl_3$). (Found: C, 62·9; H, 7·1; OMe, 11·4; $C_{14}H_{18}O_5$ requires: C, 63·1; H, 6·8; OMe, 11·8%).

Bromolactonic acid (IX; R = H)

Bromine vapour in nitrogen was passed through a solution of shellolic acid (4·6 g) and sodium hydrogen carbonate (10 g) in water (100 ml) until a yellow colour persisted. After 15 min the solution was acidified with dil sulphuric acid and concentrated *in vacuo* until the product crystallized (or sometimes separated as a gum that later solidified). Recrystallization from aqueous ethanol gave colourless needles of the bromolactonic acid[3] (IX; R = H; 4·1 g), partly melting at 125–128°, then m.p. 230° decomp (Found: C, 47·9; H, 5·3; Br, 22·4; equiv. wt. 357; $C_{15}H_{17}O_6Br, H_2O$ requires: C, 48·0; H, 5·1; Br, 22·35%; equiv. wt. 357). It had pK_a 3·4, $[\alpha]_D$ −110° in $CHCl_3$, ν_{max} 3600, 1775 and 1730 cm^{-1} in nujol, and 3450, 1775 and 1735 cm^{-1} in $CHCl_3$.

The acid (1·55 g), dried at 150° in a stream of nitrogen, in methanol (10 ml) was treated at 0° with a slight excess of diazomethane in ether. After 15 min at 0° the solvents were evaporated, and the residue was twice extracted with boiling light petroleum (200 ml) for 30 min. The solid crystallized from methanol as colourless needles of the monomethyl ester (1·20 g), m.p. 174–174·5° after further crystallization from ethanol (Found: C, 51·45; H, 5·25; Br, 21·8; OMe, 8·55; $C_{16}H_{19}O_6Br$ requires: C, 51·8; H, 5·2; Br, 21·5; OMe, 8·35%): $[\alpha]_D$ −100° in $CHCl_3$; ν_{max} 1775 and 1730 cm^{-1} in nujol.

When the acid was treated with a larger excess of diazomethane in methanol–ether at room temp a mixture of mono- and di-ester was produced.[8] The dimethyl ester was extracted into light petroleum from the less soluble mono-ester and chromatographed on silica gel. Benzene containing 5% ethyl acetate eluted the diester (X), m.p. 138–140° after recrystallization from light petroleum (Found: C, 51·3; H, 5·6; Br, 20·1; OMe, 15·2; $C_{17}H_{23}O_6Br$ requires: C, 50·55; H, 5·7; Br, 19·8; OMe, 15·4%): $[\alpha]_D$ −90° in $CHCl_3$; ν_{max} 3500 and 1718 cm^{-1} in nujol.

The *chlorolactonic acid*, made like the bromolactone, crystallized from dil ethanol in needles of the hydrate, which lost water at 135° and melted at 243–244° decomp; $[\alpha]_D$ −93° in $CHCl_3$ (Found after drying over P_2O_5 *in vacuo*: C, 57·6; H, 5·6; $C_{15}H_{17}O_6Cl$ requires: C, 57·6; H, 5·8%).

Anhydroshellolic acid (XII; R = H)

Zinc dust (ca. 0·5 g) was gradually added to a solution of the bromolactonic acid (IX; R = H; 1·4 g) in boiling 0·4N HCl (25 ml) over 8 hr. The cooled solution (A) was decanted from the solid residue, which was then extracted with dil sulphuric acid. The extract was filtered from unreacted zinc and concentrated under red press. The oil (227 mg) that separated almost completely solidified after several days at 0°. Concentration of the decanted solution (A) also yielded a solid (495 mg) when left at 0°. The product could not be induced to crystallize from numerous solvents. After repeated separation from water as an oil that solidified the combined crops of anhydroshellolic acid had m.p. 179–182°, $[\alpha]_D$ −14° in ethanol, ϵ 3000 at 202 mμ, ν_{max} 3170, 2650, 1750 and 1650 cm^{-1} in nujol. (Found: C, 63·9; H, 6·7; $C_{15}H_{18}O_5$ requires: C, 64·7; H, 6·5%).

In one experiment the crude gum (250 mg) from the bromolactonic acid (1·0 g) was chromatographed on silica gel. Benzene with 10% ethyl acetate eluted flakey crystals (30 mg), m.p. 187–188·5°, with ν_{max} 3310, 3015, 1740, 1727 and a shoulder at 1715 cm^{-1}. (Found: C, 68·7; H, 6·85; $C_{15}H_{18}O_4$ requires: C, 68·7; H, 6·9%).

Dimethyl anhydroshellolate (XII: R = Me)

The acid (200 mg) in methanol (10 ml) was treated at 0° with diazomethane in ether. The resulting gum was chromatographed on silica gel. The fractions (198 mg) eluted with benzene containing 1% ethyl acetate were triturated with n-pentane, which was decanted from an insoluble residue. Prisms of the dimethyl ester (98 mg) separated from the concentrated solution, m.p. 65·5–66·5° after recrystallization from n-pentane. (Found: C, 66·7; H, 7·4; OMe, 19·9; $C_{17}H_{22}O_5$ requires: C, 66·65; H, 7·2; OMe, 20·3%). They had ν_{max} 1750, 1640–1650 (weak) and 715 cm^{-1} (strong) in nujol.

Bromination of anhydroshellolic acid

A gum (345 mg) was produced on bromination of anhydroshellolic acid (900 mg), in the same way as shellolic acid. It was less soluble in water than the bromolactonic acid (IX; R = H) from shellolic acid, and could not be induced to crystallize. An amorphous sample, m.p. ca. 160°, had ν_{max} 3070, 2630 (weak), 1800 and 1745 cm^{-1}. After treatment of the gummy acid with diazomethane the isomeric *methyl bromolactonic ester* crystallized from methanol at 0° in needles (35 mg). Chromatography of the evaporated mother liquors on silica gel gave more needles (163 mg), eluted with benzene containing 2% of ethyl acetate. Recrystallized from aqueous ethanol the needles of the ester melted at 151–154° (Found: C, 51·7; H, 5·1; Br, 21·2; OMe, 7·7. $C_{16}H_{19}O_5Br$ requires: C, 51·75; H, 5·1; Br, 21·6; OMe, 8·5%), and had ν_{max} 1805 (broad) and 1740 cm^{-1} in nujol.

The keto-ester (VIII; R = Me)

(a) The bromolactonic acid hydrate (0·8 g) was heated with lithium carbonate (0·3 g) in water (4 ml). The solution was made acid with hydrobromic acid, concentrated and extracted with ether. The extract yielded prisms of the keto-diacid, m.p. 239° decomp after recrystallization from water. (Found: C, 60·9; H, 6·4; $C_{15}H_{18}O_6$ requires: C, 61·2; H, 6·2%). It had $[\alpha]_D$ −36° in water and 28·5° in ethanol, and ν_{max} 1730 cm^{-1} (broad) in nujol.

The dimethyl ester separated from light petroleum in needles, m.p. 122°. (Found: C, 63·5; H, 6·7; $C_{17}H_{22}O_6$ requires: C, 63·3; H, 6·9%); ν_{max} 1750 (shoulder) and 1730 cm^{-1} (broad) in nujol.

(b) Dimethyl shellolate (500 mg) and active manganese dioxide (5 g) in boiling chloroform were stirred for 22 hr. Evaporation of the filtered solution left a gum (405 mg) that crystallized (45 mg) after 2 days at 0° under methanol. Chromatography of the mother liquors on silica gel gave more crystalline ketone (205 mg), eluted with benzene containing 5–10% of ethyl acetate. Further recrystallization from benzene–light petroleum gave clusters of needles, m.p. 122·5–124·5°, $[\alpha]_D$ −62° in ethanol, identical with the compound described above.

Dimethyl epi-*keto-ester* (epi-VIII)

Dimethyl *epi*-shellolate (250 mg) was oxidized with manganese dioxide as in the previous experiment. Evaporation of the chloroform left a crystalline solid (145 mg), which on repeated recrystallization from benzene–light petroleum gave colourless needles of the epi-*ketone*, m.p. 150–151·5°. (Found: C, 63·5; H, 6·8; $C_{17}H_{22}O_6$ requires: C, 63·3; H, 6·9%); $[\alpha]_D$ +39° in ethanol; λ_{max} 284 mμ, ε 26; ν_{max} 1740 cm^{-1} in nujol.

Epimerization of the dimethyl keto-ester (VIII; R = Me)

The diester (40 mg) was boiled for 3 hr in magnesium-dried methanol (10 ml) containing sodium methoxide (from 15 mg of sodium). The solution was poured into dil sulphuric acid, and the product was salted out and extracted with ether. The neutral fraction (9 mg) of the gummy product crystallized from benzene–light petroleum in needles, m.p. 142–144°, depressed to 105° by the starting material. The infra-red spectrum was identical with that of the dimethyl *epi*-keto-ester, which did not depress the m.p. The acid fraction (15 mg) on methylation with diazomethane yielded more needles of the *epi*-ester, m.p. 149–150°.

Epimerization of dimethyl shellolate

The diester (250 mg) was boiled for 3 hr in dry methanol (12 ml) containing sodium methoxide (from 100 mg of sodium). The neutral fraction (153 mg) of the product crystallized from ethyl acetate–light petroleum as prisms and needles, which were sorted by hand. The needles had m.p. 176–177°, and ν_{max} 1760 and 1735 cm^{-1} in nujol, after recrystallization from the same solvent. (Found: C, 65·3; H, 6·9; $C_{18}H_{20}O_5$ requires: C, 65·7; H, 6·9%).

The prisms (31 mg) recrystallized as needles (23 mg), m.p. 154°, undepressed by dimethyl *epi*-shellolate, which had an identical infra-red spectrum.

The acidic fraction (58 mg) was methylated, combined with the product from the mother liquors of the neutral fraction, and chromatographed on silica gel. Benzene containing 10–20% ethyl acetate eluted the compound, m.p. 176–177°, followed by more dimethyl *epi*-shellolate.

Treatment of dimethyl *epi*-shellolate with methoxide under the same conditions gave only unchanged ester and *epi*-acid.

Dimethyl *epi*-shellolate was heated on a steam-bath for 30 min with acetic anhydride and pyridine. Chromatography of the isolated product on silica gel gave (with benzene + 5% ethyl acetate) the *diacetate*, m.p. 108–109° after recrystallization from cyclohexane. (Found: C, 61·8; H, 7·0. $C_{21}H_{28}O_8$ requires: C, 61·75; H, 6·9%). It had $[\alpha]_D$ +102° in $CHCl_3$; λ_{max} 224·5 mμ, ε 7000 in cyclohexane; ν_{max} 1730 cm^{-1} in $CHCl_3$.

*Hydrogenation of dimethyl-*epi*-shellolate*

Dimethyl *epi*-shellolate took up 1 mole of hydrogen over platinum oxide in ethanol in about 2 hr. Chromatography on silica gel produced *methyl dihydro-*epi*-shellolate δ-lactone* (*epi*-IV; R = H), m.p. 109–110° after recrystallization from ether–cyclohexane. (Found: C, 65·5; H, 7·4; OMe, 9·9; $C_{16}H_{22}O_5$ requires: C, 65·3; H, 7·5; OMe, 10·5%), having $[\alpha]_D$ +75° in $CHCl_3$ and ν_{max} 3600 and 1737 cm^{-1} in $CHCl_3$.

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