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LAC—II

THE STEREOCHEMISTRY OF SHELLOLIC AND EPISHELLOLIC ACIDS

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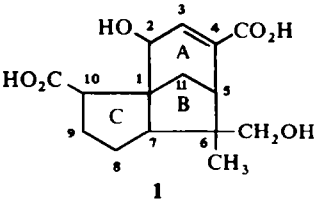
Abstract—The relative configurations of shellolic and epishellolic acids are established as in **2** and **23**, respectively.

Shellolic acid

SHELLOLIC acid, a component of the hydrolysate from lac resin, has been shown to have the gross structure **1**.[1] In the preliminary communication describing this work,[2] the relative configuration shown in **2** was tentatively assigned. Subsequently, Cookson *et al.*[3, 4] have presented chemical and spectroscopic evidence that confirmed this assignment and have also assigned the absolute configuration as in **2**. An x-ray crystallographic study by Gabe[5]† of the bromo lactonic acid[6] formed by treatment of shellolic acid with aqueous sodium hydrogen carbonate and bromine has shown it to have structure **3** (or its mirror image), again confirming the relative configuration of shellolic acid to be that shown in **2**. We describe here our experiments[7] that relate to the assignment of the relative configuration as in **2** to shellolic acid. In some respects these observations are closely related to those of Cookson *et al.*[3, 4] and we shall not discuss these aspects *in extenso*.



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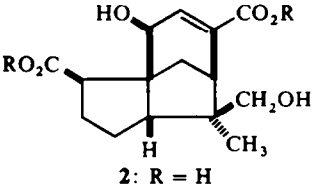
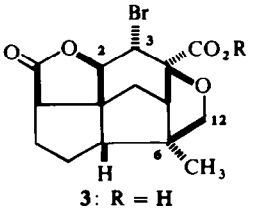
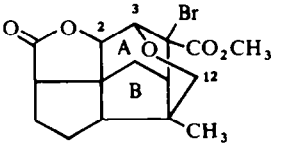


2: R = H
5: R = CH_3



3: R = H
4: R = CH_3



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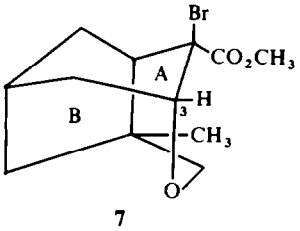
† We thank Dr. E. J. Gabe, National Research Council of Canada, for informing us privately of his results after our preliminary publication[2] had appeared.

Treatment of a solution of shellolic acid in aqueous sodium hydrogen carbonate with bromine vapor[6] gave the hydrate of the bromo lactonic acid **3**, which formed an unsolvated monomethyl ester (**4**) on treatment with diazomethane in dichloromethane. The ester was obtained more conveniently and in higher yield when dimethyl shellolate (**5**) was treated with bromine in the absence of solvent. The IR spectrum of the bromo lactonic ester (5·63, 5·78 μ; no OH band) is in accord with the assignment of structure **4** or **6**. Its PMR spectrum ($CDCl_3$) shows two one-proton doublets at δ 4·57 and 4·19 and a two-proton singlet at δ 4·10 that can be assigned to the protons at C-2, C-3, and C-12 respectively.* These assignments require the assumption that the signals due to the methylene protons at C-12 are accidentally degenerate. The doublets assigned to the protons at C-2 and C-3 show a coupling constant, J_{23} = 11·0 Hz, demonstrating that these protons both have axial dispositions.[9] In the case of **6**, the ether bridge between C-3 and C-6 requires that rings A and B have the geometry shown in **7**,† and that the hydrogen atom at C-3 have an equatorial disposition with respect to ring A; this structure is therefore inadmissible for the bromo lactonic ester.‡ On the other hand, the formation of an ether bridge between C-4 and C-6, as in **4**, permits rings A and B to take up the geometry shown in **8** in which the H atom at C-3 has an axial disposition with respect to ring A. The gross structures corresponding to **3** and **4** are therefore assigned to the bromo lactonic acid and its methyl ester, respectively.



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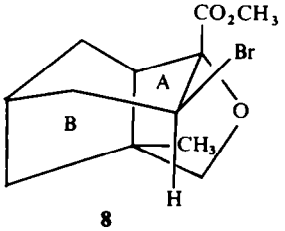

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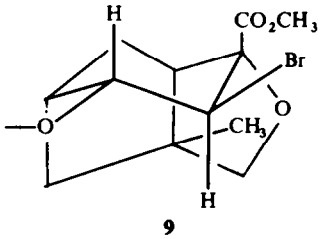
Several stereochemical conclusions follow from the assignment of these structures. First, ether formation requires that the hydroxymethyl group in shellolic acid be situated on the same side of ring B as the 3-carbon bridge (C-2, C-3, and C-4) that forms ring A (both termini of this bridge must, of course, lie on the same side of ring B). Second, the OH group at C-2 must have the relative configuration shown in **2** to account for the observation that the H atom at this carbon in the bromo lactonic ester has an axial disposition (cf. **9**). Third, the ring fusion of rings B and C must be *cis* and the carboxylic acid group at C-10 must lie on the same side of ring C as C-2 to account for the formation of the 5-membered ring lactone. Any variation in these assignments would demand that the lactone ring be very highly strained and that its

* We adopt the numbering scheme used by Cookson[3] for shellolic acid, but prefer to designate the rings as shown in **1** because of established usage in the cedrene series.[8]

† No absolute configuration is implied by this and other part-stereoformulas.

‡ When the PMR spectrum of the bromo lactonic acid is recorded in pyridine, the accidental degeneracy of the C-12 two-proton singlet at δ 4·10 in the spectrum in deuteriochloroform is removed and this signal is replaced by two one-proton doublets at δ 4·20 and 3·98 with J = 9·5 Hz; the doublets due to the protons at C-2 and C-3 now appear at δ 4·71 and 4·63 with J = 11 Hz. Even if the assignments were reversed and the two-proton singlet observed in deuteriochloroform was due to the accidental degeneracy of the C-2 and C-3 signals, the magnitude of this newly observed coupling constant would also require that the C-2 and C-3 protons both be axial.[9]

geometry be such as to inhibit greatly the interaction of the CO group with the unshared electrons on the annular O atom. Since lactone formation occurs with facility, and the position (5·63 μ) of the lactone CO-stretching band in the IR spectrum of the bromo lactonic ester is normal for a 5-membered lactone, alternative assignments are inadmissible. The bromo lactonic ester can then be represented as **10**, corresponding to the complete relative configuration of shellolic acid in **2**.



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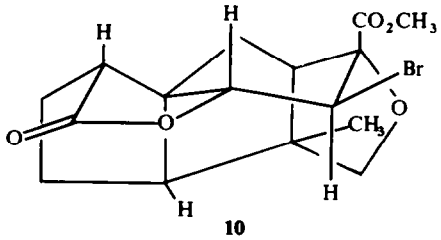
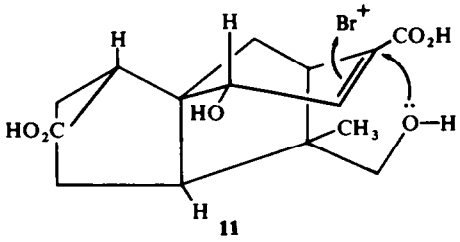


10

The conversion of shellolic acid (**2**) to the bromo lactonic acid **3** on treatment with bromine is in accord with expectation. Thus it may be anticipated that **2** will adopt the conformation in which ring A is in a quasi-chair form (cf. **11**) and that attack by hypobromous acid or bromine will be initiated from the less hindered, upper side of this ring. Intramolecular attack by an unshared pair of electrons on the O atom of the primary OH group at the electron-deficient site from the underside of ring A (cf. **11**) will then lead to **3**. Such a process finds analogy, for example, in the bromination of a product obtained in the synthesis of reserpine (cf. **12**).[10] The reaction course depicted in **11** leads to an intermediate bromohydrin in which ring A is in a boat-like conformation and the bromine and ether oxygen substituents are of the axial type. Formation of the γ-lactone ring then results in a conformational change in this ring, which is then locked in a chair-like conformation as shown in **10**.



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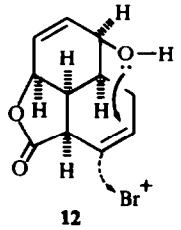
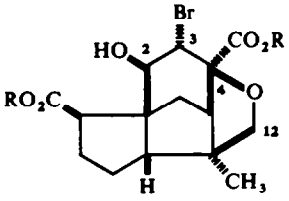


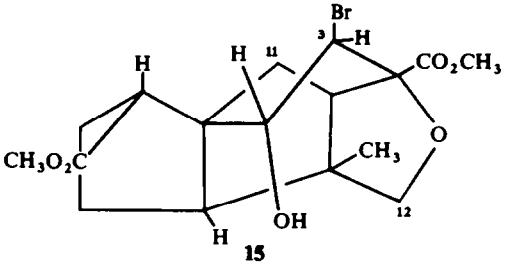
12

Esterification of the bromo lactonic acid **3** with diazomethane in the presence of methanol[6] gave the bromo lactonic ester **4** as the major product together with a low yield of the dimethyl ester, **13**, of the acid **14**, the intermediate bromohydrin postulated above. The ester **13** was obtained in better yield by mild basic hydrolysis of **3** followed by immediate methylation of the resulting acid ester with diazomethane. That no epimerization had taken place during the hydrolysis was shown by the fact that **13** was reconverted to **3** on treatment with *p*-toluenesulfonic acid in boiling benzene. A one-proton doublet at δ 4·22 in the PMR spectrum ($CDCl_3$) of **13** is assigned to the proton at C-3, and a one-proton doublet of doublets at δ 4·51 is assigned to the proton

at C-2, which is coupled with both the C-2 and the OH protons. The coupling constant J_{23} is 3 Hz, in marked contrast to that in the case of the lactone 3 (J_{23} = 11 Hz). This difference is interpreted as being due to the existence of compound **13** in the conformation **15** in which ring A is boat-like. The preference for a boat-like rather



13: R = CH_3
14: R = H



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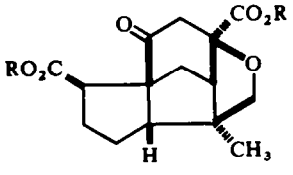
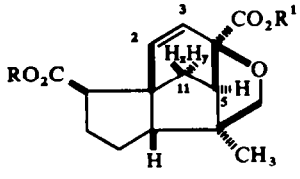
than a chair-like conformation for ring A can be attributed to the circumstance that this ring is free of angle strain only in the former conformation. *A priori*, this factor might have been offset by a bowsprit-flagpole[11] repulsive interaction between the Br atom at C-3 and a H atom at C-11 in the boat-like conformation. That this is not the case may be due to the assumption of a twist-boat conformation by ring A in which the interaction between the H and Br atoms represents a very small repulsion or, indeed, is slightly attractive.[12] It may be noted that Cookson[3] has concluded that ring A has a distorted boat conformation in the ketone **16**, formed by oxidation of dimethyl shellolate (**5**) under mild conditions.



16: R = CH_3
20: R = H



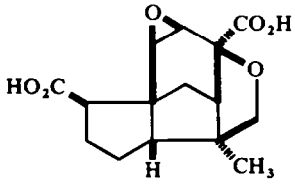
17: R = R′ = H
18: R = R′ = CH_3
19: R = H, R′ = CH_3

The difference in conformation of ring A in the lactone **4** (**10**) and the hydroxy ester **13** (**15**) accounts for the very similar positions of the PMR signals assigned to the protons at C-2 in the two compounds. It would normally be expected that conversion of the >CH—OCO— group to the >CH—OH group would lead to an upfield shift of the signal due to the tertiary proton. However, in the present case this effect could be offset by a downfield shift of the C-2 proton signal on conversion of **4** to **13** due to removal of this proton from the anisotropic shielding region of the ester group at C-4. Another reflection of the conformational difference may be seen in the PMR signals assigned to the protons at C-12 of the ether rings. It has already been mentioned that in the spectrum of **3** in deuteriochloroform these protons give rise to a singlet at δ 4·10, due to accidental degeneracy. In the spectrum of **13** in deuteriochloroform they give

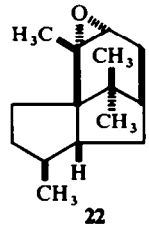
rise to two doublets at δ 3·59 and 3·89 with J = 8·5 Hz. This change can be attributed to the markedly different relationships of the C-12 protons to the ester group at C-4 and the bromine substituent at C-3 in the two conformations. The magnitude of the geminal coupling constant is in accord with expectation for a methylene group in a 5-membered ether ring.[9]

Treatment of the bromo lactonic acid **3** with activated zinc in acetic acid gave a low yield of Nagel and Mertens' "deoxyshellolic acid" (**17**),[6*] which was converted by diazomethane to its dimethyl ester, **18**. A more satisfactory yield of the latter compound was obtained by reduction of the bromo lactonic ester **4** under the same conditions to give the ester acid **19**, followed by treatment of this with diazomethane. The spectra of these products are in good accord with the structures assigned (Experimental). One feature of the PMR spectrum of **18** merits further comment. The vinylic proton signals appear at δ 5·43 and 6·22 and are coupled, as expected, with J = 9·7 Hz; in addition, each of the resulting doublets is further split (J' = 1·1 Hz, J'' = 1·4 Hz), as noted by Cookson.[3] The further splitting of the C-2 proton signal can be attributed to long-range coupling with the proton H_y at C-11 (cf. **18**) on the basis of the studies of Jefford *et al.* on bicyclo[3.2.1]oct-2-ene derivatives;[13] the further splitting of the C-3 proton signal may be due to similar coupling with H_y or with the proton at C-5.

Treatment of the bromo lactonic acid **3** with hot aqueous potassium carbonate[6] gave a product that was shown to be the keto acid **20** by the demonstration that its dimethyl ester was identical with **16**, the product obtained on mild oxidation of dimethyl shellolate.[1] The species from which hydrogen bromide is eliminated to give **20** is most probably the dianion of **14**, in which the lactone ring of **3** is open. The course of the reaction is unexpected in terms of the stereochemistry of **14** (cf. **15**) in that it apparently involves *cis* elimination to give **20** rather than concerted *trans* elmination to give the epoxide **21**, a pathway that it was anticipated would be favoured by the approximately *anti*-periplanar relationship of the C-O and C-Br bonds in **14** (cf. **15**).† Cookson[3] has suggested that the overall *cis* elimination could result from initial displacement of bromine by the ether O atom. An alternative possibility is that the epoxide **21** is in fact formed, but subsequently undergoes rearrangement to the ketone **20** in the acid work-up. Exceptionally facile rearrangement of such an epoxide



21: R = H



22

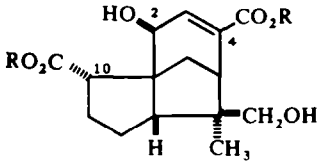
finds analogy in the case of **22**, which has been observed to undergo rearrangement to a ketone upon chromatography on alumina.[15]

* Cookson *et al.*[3] have designated this more appropriately as anhydroshellolic acid. We, like they, could not obtain it by the published method.[6]

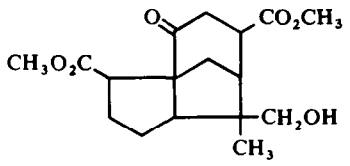
† Although recent work by Sicher *et al.* has shown that *cis* eliminations occur much more frequently than had previously been suspected, such an elimination is unlikely in the present case both because a six-membered ring is involved and the reagent is a relatively weak base.[14]

Epishellolic acid

An isomer of shellolic acid can also be obtained from the lac hydrolysats.[3, 7, 16, 17] Cookson[3] has named this epishellolic acid and has assigned it structure **23**, i.e., the C-10 epimer of shellolic acid. We have come to the same conclusion;[7] again we shall treat in detail only those aspects of our investigations that complement that of Cookson.



23: R = H
24: R = CH_3



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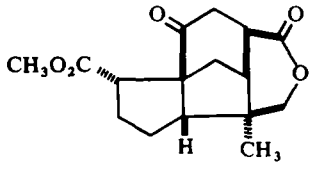
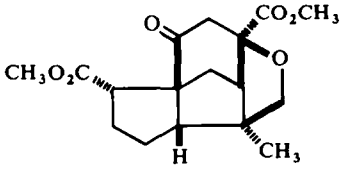
The spectra of dimethyl epishellolate (**24**) (Experimental) and the fact that it forms a diacetate demonstrate that epishellolic acid has the same functional groups as shellolic acid. That the acids are diastereomers was established by the observation that treatment of dimethyl shellolate (**5**) with methanolic sodium methoxide gives dimethyl epishellolate together with other products. Proton removal by base would be anticipated at C-2 and C-10. Because C-2 also bears an OH group, which will be largely converted to the corresponding alkoxide ion in the presence of excess methanolic sodium methoxide, it would be expected that proton removal from C-10 would be faster than from C-2. Further, while the former process could lead to epimerization, the latter would be expected to lead to rearrangement to a γ-keto ester **25** by reprotonation at C-4.[18] The formation of dimethyl epishellolate from dimethyl shellolate thus leads to the conclusion that they differ only in their configuration at C-10 and establishes **23** as the structure of epishellolic acid. The major product from the reaction of dimethyl shellolate with methanolic sodium methoxide was not obtained in crystalline form, but its IR spectrum was in accord with its formulation at **25**. Under more vigorous conditions a lactone related to **25** is obtained, which most probably has the stereoformula **26**,[1, 3] rearrangement of the allylic alcohol system to a ketone being accompanied by epimerization at C-10.



26

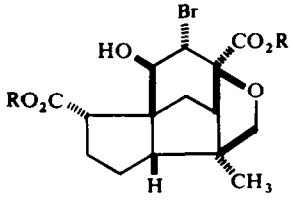


27

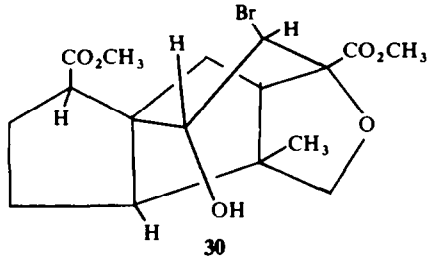
Confirmation that dimethyl shellolate and dimethyl epishellolate are epimeric at C-10 was obtained by oxidation of the latter with "activated" manganese dioxide to the keto ether **27**, which could also be obtained in good yield by epimerizationn of **16**, the product obtained from the corresponding reaction with dimethyl shellolate,[1] with methanolic sodium methoxide. That **27** should be considerably favoured over **16** at

equilibrium is in accord with the stereochemical assignments in that the ester group at C-10 in **16**, but not in **27**, is opposed to the ketonic CO group. The stability relationship is less clearly defined in the case of dimethyl shellolate and dimethyl epishellolate because of the possibility of a compensating effect due to H-bonding between the OH group and the C-10 ester group in the former.

Bromination of epishellolic acid (**23**) in aqueous sodium bicarbonate followed by acidification gave the bromohydrin **28**, which was converted to the dimethyl ester **29** on treatment with diazomethane. This ester was also obtained when dimethyl epishellolate (**24**) was treated with bromine in the absence of solvent. It shows in its PMR spectrum a doublet of doublets at δ 4·54 and a doublet at δ 4·22, assigned to the protons at C-2 and C-3, respectively. The coupling constant, J_{23}, between these protons is ca. 3·5 Hz; the additional splitting of the C-2 signal is attributed to coupling with the OH proton. The magnitude of J_{23} indicates that **29**, like the analogous compound **13** from dimethyl shellolate, adopts an angle-strain-free boat-like conformation, **30**.



28: R = H
29: R = CH_3



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All attempts to convert epishellolic acid or the bromohydrin **28** to lactones were unsuccessful, in contrast to the case of shellolic acid and in accord with the relative configuration assigned to epishellolic acid. Had the configuration at both C-2 and C-10 in epishellolic acid been the opposite of that in shellolic acid, lactonization would have been expected to occur.

EXPERIMENTAL

M.ps were determined on a Fisher–Johns micro hot stage and are uncorrected. Solns in organic solvents were dried over Na_2SO_4.

Isolation of dimethyl shellolate (**5**) *and dimethyl epishellolate* (**24**)

The methods used were patterned after earlier procedures.[1, 19, 28] (i) Kusmi seedlac (500 g) was dissolved in a warm KOH aq (145 g) in water (500 ml), and the resulting purple soln was allowed to stand at room temp for 1–2 weeks. The viscous soln was diluted with water (250 ml) and filtered through Supercel to remove debris and precipitated potassium aleuritate. A buffer soln (500 ml) made from $NaH_2PO_4 \cdot H_2O$ (250 g) and K_2HPO_4 (100 g) in water (1 l) was added to the filtrate. Phosphoric acid (70 ml of an 85% soln in water) was added, and the soln was extracted with a mixture of ether (1·3 l), EtOAc (500 ml), and t-BuOH (200 ml). The aqueous phase (pH ca. 6) was then emulsified with EtOAc (700 ml), made more acidic with 150 ml of 85% phosphoric acid, and re-extracted with EtOAc (2 × 500 ml). The organic extracts were combined and dried. Removal of the solvent under reduced press afforded 100–135 g of a brittle red solid. This was esterified with anhyd MeOH (3 l) containing Hcl (100–120 g). After standing for 3 days to one week the soln was neutralized with methanolic NaOH with the use of bromothymol blue as external indicator. The NaCl was filtered, and the filtrate was concentrated under reduced press to a gum. This was taken up

in $CHCl_3$ (600–700 ml), and the soln was passed through Florisil (140 g), the column being eluted with a further 500 ml of $CHCl_3$. Removal of the solvent from the eluates gave a brown gum (50–104 g), which was taken up in ether (100–200 ml). Crude dimethyl shellolate (8·8–12·2 g) separated when the soln had stood in the refrigerator for ca. 1 week. Recrystallization from acetone–water afforded the pure product, m.p. 154–155°, undepressed when mixed with a sample obtained previously[1]; $\lambda_{max}^{CHCl_3}$ 2·90, 5·8–5·9, and 6·10 μ; λ_{max}^{EtOH} 231 mμ (ε 6200).

When a portion of the mixture which remained in the mother liquors from the crystallization of dimethyl shellolate was chromatographed on acid-washed alumina (Woelm, grade I), a small amount of dimethyl epishellolate was obtained on elution with ether. Recrystallization from benzene gave an analytical sample as long needles, m.p. 154·5–155°, depressed to 130–135° on admixture with dimethyl shellolate; $\lambda_{max}^{CHCl_3}$ 2·78, 2·88, 5·78, 5·81 (sh), 5·89, and 6·11 μ; λ_{max}^{KBr} 2·90, 3·00, 5·77, 5·96, and 6·15 μ; λ_{max}^{EtOH} 232 mμ (ε 5800); $[\alpha]_D^{25}$ 39·8° (in $CHCl_3$). (Found: C, 62·47; H, 7·53%. Calc. for $C_{17}H_{24}O_6$: C, 62·95; H, 7·46%).

(ii) Seedlac (500 g) was saponified in hot alcoholic soln.[28] Neutralization with CO_2, and evaporation of the aqueous soln gave a solid residue which was extracted with hot 95% EtOH (2 l). The Na salts obtained from this soln were dissolved in water (6 l), and the stoichiometric quantity of 10% $ZnSO_3$ aq was added. The precipitated Zn salts were filtered off and the filtrate was treated with solid Na_2CO_3 uptil the soln was alkaline to litmus paper. The residue remaining after removal of the basic Zn salts and evaporation of the soln to dryness was extracted with 95% EtOH (1 l). Treatment of the remainder of the Na salts with lead acetate (74 g) in hot EtOH resulted in the precipitation of the alcohol-insoluble Pb salts (56 g) as a light yellow powder. Methylation afforded dimethyl shellolate (1·74 g) identified by its IR spectrum.

One half (9·0 g) of the gum obtained from the mother liquors after deposition of dimethyl shellolate was taken up in benzene and chromatographed on acid-washed alumina (Woelm, grade III). Elution with 0·5–1% MeOH in benzene gave dimethyl shellolate (315 mg). MeOH in benzene eluted dimethyl epishellolate (253 mg).

(iii) A sample (200 g) of bleached shellac that had been repeatedly extracted with ether and light petroleum was allowed to stand at room temp for 5 days in aqueous 20% NaOH aq (200 ml). The sodium aleuritate which separated was filtered, and the filter cake was washed with water (200 ml). The combined aqueous solns were cooled in ice and neutralized with cold 10% H_2SO_4. The soln was then acidified to pH 4–5 with AcOH and extracted with EtOAc (3 × 500 ml). The organic extracts were dried and evaporated. The residue (100 g) was methylated and worked up as before to give the crude mixed esters (51 g) as a red gum. On standing in the refrigerator for 4 days this gum deposited methyl aleuritate (7·7 g), m.p. 69–70° after recrystallization from light petroleum. Chromatography of a portion (30 g) of the remaining gum on acid-washed alumina (grade III, 300 g) gave dimethyl epishellolate (840 mg) on elution with 1% MeOH in benzene.

Shellolic acid (2)

Dimethyl shellolate (2·00 g) was heated at 80–90° for 3 hr with 1 N NaOH (30 ml). An exactly equivalent amount (21·0 ml) of 1 N HCl was then added. Concentration of the soln to one third of its volume over P_2O_5 gave shellolic acid (1·6 g, 87%) as large rectangular crystals, m.p. 206–207°; λ_{max}^{KBr} 2·9, 3–4, 5·80, 5·97, and 6·15 μ.

Dimethyl shellolate, identified by mixed m.p. and IR spectrum, was reformed when a portion of shellolic acid was esterified with diazomethane in ether–MeOH.

*Dimethyl shellolate monomethanesulfonate**

A soln of dimethyl shellolate (0·972 g, 0·0034 mole) in freshly distilled dry pyridine (5 ml) was cooled to 0–5°. To this was added a cooled soln of methanesulfonyl chloride (0·75 g, 0·0066 mole) in pyridine (2 ml). The mixture was allowed to stand at 0–5° for 6 hr, then poured into cold water (50 ml), and extracted with $CHCl_3$ (3 × 50 ml). The $CHCl_3$ extracts were washed with ice-cold dil H_2SO_4, 10% $NaHCO_3$ aq, and water, dried, and evaporated. Crystallization of the residue from EtOH gave the monomethansulfonate (0·51 g, 42%), m.p. 115–118°. The yield was raised to 65% in a second experiment when MeOH was used as the crystallization solvent. Recrystallization from light petroleum–benzene gave an analytical sample, m.p. 119–120°; λ_{max}^{KBr} 2·85, 5·8–5·9, 6·10, 7·40, and 8·50 μ. (Found: C, 53·92; H, 6·63; S, 7·92. Calc. for $C_{18}H_{26}O_8S$: C, 53·72; H, 6·51; S, 7·95%).

* No reference is made to this product in the discussion; its conversion to a γ-lactone (5·65 μ) indicated that mesylation had occurred at the primary hydroxyl group of dimethyl shellolate.

Bromination of shellolic acid

Formation of bromo lactonic acid 3. The procedure followed was similar to that employed by Nagel and Mertens.[6] Shellolic acid (2·70 g) and $NaHCO_3$ (5·40 g) were dissolved in water (54 ml), and Br vapour was passed through the soln until a permanent yellow colour remained. The mixture was allowed to stand overnight and then acidified with conc HCl. The hydrated bromo lactone (2·14 g), m.p. 227–232°, crystallized on standing. Concentration of the mother liquor afforded a further 1·05 g of the crystalline product (total yield, 92·5%). Recrystallization from water–acetone and vacuum-drying over P_2O_5 for 48 hr gave an analytical sample of the anhydrous bromo lactonic acid, m.p. 234–235°; λ_{max}^{KBr} (hydrated acid) 2·90, 3–4, 5·64, and 5·80 μ. (Found: C, 50·22; H, 4·85; Br, 23·05. Calc. for $C_{15}H_{17}O_5Br$: C, 50·43; H, 4·78; Br, 22·38%).

Less extensive drying gave a product containing varying amounts of water of crystallization as indicated by elemental analytical data.

Bromo lactonic methyl ester 4

(i) *Methylation of bromo lactonic acid* 3. The hydrate of 3 was methylated with diazomethane in ether–MeOH. Evaporation of the solvent gave a gum, which was extracted with hexane; the extract gave a small amount of crystalline product, $\lambda_{max}^{CHCl_3}$ 2·90 and 5·78 μ, which was shown to be identical with 13 (*vide infra*). The residue from the hexane extraction was crystallized from 95% EtOH to give 4. Two recrystallizations from the same solvent gave an analytical sample, m.p. 174·5–175·5°; λ_{max}^{KBr} 5·63 and 5·78 μ. (Found: C, 51·64; H, 5·11; Br, 22·16. Calc. for $C_{16}H_{19}O_5Br$: C, 51·76; H, 5·14; Br, 21·53%).

When the esterification was carried out in cidhloromethane the minor product was not formed.

(ii) *Bromination of dimethyl shellolate* (8). Dimethyl shellolate (1·00 g) was allowed to stand overnight in excess liquid Br_2 in an open flask. The resulting brown gum was dissolved in $CHCl_3$ (75 ml), and the soln was washed with $Na_2S_2O_3$ aq and water, and dried. Evaporation of the solvent gave a gum which crystallized from ether to give 4 (0·90 g, 78%), m.p. 175–177°; its IR spectrum was identical with that of the product obtained by methylation of 3.

Bromohydrin dimethyl ester 13

The bromo lactonic ester 4 (200 mg) was allowed to stand at room temp for 3 hr with 1 N NaOH (5·0 ml). The soln was acidified to pH 2–3 with 1 N H_2SO_4 and immediately extracted with EtOAc (4 × 20 ml). The combined extracts were dried and esterified by addition of diazomethane in ether. Evaporation of the solvents gave a crystalline solid which was recrystallized from benzene–light petroleum to give 13 (113 mg), m.p. 137–140°. Two more recrystallizations from the same solvent mixture gave an analytical sample as long prisms, m.p. 144–145°; λ_{max}^{KBr} 2·85, 5·75–5·80, and 13·05 μ. (Found: C, 50·55; H, 5·71; Br, 19·75. Calc. for $C_{17}H_{23}O_6Br$: C, 50·60; H, 5·75; Br, 19·81%).

The bromohydrin ester 13 was also formed as a minor product when the bromo lactonic acid 3 was esterified with diazomethane in ether–methane (*vide supra*).

Lactonization of 13

Formation of 4. The bromohydrin ester 13 (25 mg) was heated for 5 hr in dry benzene (10 ml) containing a trace of *p*-toluenesulfonic acid. The benzene soln was diluted to 40 ml, washed with water, dried, and evaporated. The light yellow gum remaining was crystallized from ether to give 4 (15·5 mg), m.p. 177–178°, undepressed on admixture with an authentic sample of 4; the IR spectra of the two samples were identical.

Reaction of 3 *with zinc and acetic acid*

*Formation of anhydroshellolic acid** (17). Activated Zn[19] (400 mg) was added in portions to a hot soln of the hydrated 3 (100 mg) in glacial AcOH (10 ml). After the mixture had been heated for 3 hr, the excess Zn was filtered off and the AcOH was removed by freeze-drying. A white powder (60 mg) was precipitated from the residue on addition of water (5 ml). Addition of dil HCl (1:4) afforded 17 (16 mg) m.p. 195–200°. Recrystallization from acetone gave an analytical sample, m.p. 200·5–201·5°; λ_{max}^{KBr} 3–4 and 5·7–5·8 μ. (Found: C, 64·46; H, 6·58. Calc. for $C_{15}H_{18}O_5$: C, 64·73; H, 6·52%).

Dimethyl anhydroshellolate (18)

The ester 4 (400 mg) was reduced with activated Zn (800 mg) in glacial AcOH acid (15 ml) as in the case of 3 above. The residue obtained after evaporation of the AcOH was dissolved in water and extracted with EtOAc (75 ml) and $CHCl_3$ (3 × 25 ml). Evaporation of the solvents from the combined extracts gave

* See footnote on p. 3168.

a gum (331 mg), which on standing in light petroleum–benzene gave **19** (63 mg), m.p. 140–145°. A further 71 mg was obtained on reheating the remaining gum with activated Zn and AcOH and extracting the residue with $NaHCO_3$ aq. Recrystallization from light petroleum–benzene gave **19**, m.p. 147·5–148·5°; λ_{max}^{KBr} 3–4, 5·78, 5·85, and 13·9 μ. This was treated with diazomethane in ether to give **18**. Recrystallizations from light petroleum gave an analytical sample, m.p. 65–66°; λ_{max}^{KBr} 5·73–5·77, 6·14, and 13·95 μ. (Found: C, 66·50; H, 7·29. Calc. for $C_{17}H_{22}O_5$: C, 66·65; H, 7·24%).

The ester **18** was also obtained by esterification of **17** with diazomethane.

Reaction of **3** *with potassium carbonate*

Formation of keto acid **20**. The hydrate of **3** (300 mg) was heated with anhyd K_2CO_3 (210 mg) and water (1·0 ml) for 1·5 hr. The mixture was cooled to room temp and acidified with conc HCl. The acid **20** (120 mg, 55%), m.p. 232–234°, crystallized on standing. Recrystallization from acetone–benzene and from EtOAc gave an analytical sample, m.p. 237–238·5°; λ_{max}^{KBr} 3–4 and 5·8–5·9 (3 peaks); no high intensity UV maximum > 220 mμ. (Found: C, 61·02; H, 6·14. Calc. for $C_{15}H_{18}O_6$: C, 61·21; H, 6·17%).

Concentration of the mother liquors from which **20** separated afforded a crop (59 mg, 22%) of another crystalline material, m.p. 199–203°. The same product was obtained, although in lower yield, when the acidified reaction mixture was immediately extracted with EtOAc. In this case the second crop clearly consisted of two different crystalline substances. Individual crystals, m.p. 200–204° and 230–234°, could be separated by hand. When the mixture was treated with water the higher melting compound was leached out. The residue had m.p. 203–205°; λ_{max}^{KBr} 3–3·4, 5·68, 5·74, 5·90, and 6·15. (Found: C, 61·16; H, 6·29. Calc. for $C_{15}H_{18}O_6$: C, 61·21; H, 6·17%).

Keto dimethyl ester **16**

(i) *Esterification of keto acid* **20**. Treatment of the acid **20**, m.p. 230–233°, with diazomethane in ether–MeOH gave a gum from which **16**, m.p. 120–122·5°, was obtained by chromatography on Florisil. This was shown by a mixture m.p. and IR spectral comparison to be identical with the product obtained by mild oxidation of dimethyl shellolate (*vide infra*). (Found: C, 63·29; H, 6·80. Calc. for $C_{17}H_{22}O_6$: C, 63·34; H, 6·88%).

(ii) *Mild oxidation of dimethyl shellolate.* Dimethyl shellolate (0·45 g) was stirred for 67 hr with activated MnO_2[20] (5·0 g) in CH_2Cl_2. The MnO_2 was filtered through filter-cel and the filter cake was washed with CH_2Cl_2. Evaporation of the solvent gave a gum (0·32 g). A further quantity (0·13 g) of gum was obtained on washing the filter cake with 95% EtOH. The two fractions were combined and chromatographed on Florisil; elution with 30% ether in benzene and recrystallization from acetone–hexane gave **16**, m.p. 123–124°; $\lambda_{max}^{CHCl_3}$ 5·78 μ (br).*

Epishellolic acid (**23**)

Dimethyl epishellolate (280 mg) was hydrolyzed by treatment for 3 hr with boiling 1N NaOH under reflux. The exact equivalent of ca. 1 N HCl was added, and the soln was allowed to stand overnight. Epishellolic acid (213 mg), m.p. 220–223°, separated and was filtered, and the filtrate was concentrated to about half its volume. A second crop (20 mg; total 91%) of epishellolic acid, m.p. 219–223°, was thereby obtained. Repeated recrystallization from dil aqueous EtOH gave an analytical sample, m.p. 257–258°; λ_{max}^{KBr} 2·90, 3–4, 5·85–5·96, 6·10 (sh), and 6·20 μ. (Found: C, 60·63; H, 6·84. Calc. for $C_{15}H_{20}O_6$: C, 60·80; H, 6·80%).

When epishellolic acid (30 mg) was esterified with diazomethane in ether–MeOH a yellowish gum was obtained. Two recrystallizations from benzene gave dimethyl epishellolate (ca. 10 mg), m.p. 152–154°, undepressed on admixture with an authentic sample; the IR spectra of the two samples were identical.

Dimethyl eipishellolate diacetate

Dimethyl epishellolate (100 mg) was allowed to stand at room temp for 40 hr in a mixture of pyridine (1 ml) and Ac_2O (1 ml). $CHCl_3$ (25 ml) was added, and the soln was washed with 1 N HCl (3 × 10 ml), sat $NaHCO_3$ aq (10 ml), and distilled water (10 ml). The organic layer was dried and evaporated. Trituration of the residue with cyclohexane gave a gum (101 mg) from which the diacetate (69 mg), m.p. 112–113°, crystallized on standing in cyclohexane. Recrystallization from cyclohexane gave an analytical sample, m.p. 113–114°; $\lambda_{max}^{CCl_4}$ 5·75, 5·80, and 8–8·3 μ. (Found: C, 61·79; H, 6·86; $COCH_3$, 20·86. Calc. for $C_{21}H_{28}O_8$: C, 61·75; H, 6·91; $COCH_3$, 21·95%).

* This reaction appears to be very sensitive to the activity of the manganese dioxide, since with the batch of manganese dioxide used here it could not be effected in chloroform, as had previously been possible.[1] The oxidation was also carried out with chromium trioxide-pyridine.[1]

Epimerization of dimethyl shellolate

Formation of dimethyl epishellolate. Dimethyl shellolate (1·00 g) was heated for 6 hr in boiling dil methanolic NaOMe (0·50 g of Na per 100 ml MeOH; 10 ml) under reflux. The soln was cooled to room temp and neutralized with methanolic HCl. The MeOH was evaporated, and the residue was taken up in $CHCl_3$ (30 ml). The precipitated NaCl was filtered off and the soln was washed with $NaHCO_3$ aq and water, and dried. Evaporation of the solvent left a gum (850 mg), which was chromatographed on acid-washed alumina (Woelm, grade I). Dimethyl epishellolate (**24**) (134 mg, 13%) was eluted with 20% ether in benzene. Recrystallization from benzene gave pure **24**, m.p. 154–155°, undepressed on admixture with a sample of authentic dimethyl epishellolate but depressed to 129–140° on admixture with dimethyl shellolate; its IR spectrum was identical to that of authentic dimethyl epishellolate.

No dimethyl shellolate was isolated from the reaction mixture, nor was any detectible in the IR spectra of the chromatographed eluates. The major product, eluted with benzene as a gum, showed in its IR spectrum a sharp band at 5·78 μ and a reduced intensity OH band at 2·80 μ. Attempts to crystallize this product, which is considered to be **25**, were not successful.

The same yield of dimethyl epishellolate was obtained from a second experiment in which dimethyl shellolate was treated for 2 days with methanolic NaOMe under reflux.

Keto dimethyl ester **27**

(i) *Mild oxidation of dimethyl epishellolate.* Dimethyl epishellolate (108 mg) was stirred at room temp for 30 hr with a suspension of freshly prepared activated MnO_2[20] (1·00 g) in $CHCl_3$ (10 ml). The MnO_2 was filtered off and the filter-cake was washed with CH_2Cl_2 (2 × 20 ml). Evaporation of the solvents gave **27** (82 mg, 76%). Recrystallization from light petroleum containing a little acetone gave an analytical sample as long needles, m.p. 151–152°; $\lambda_{max}^{CCl_4}$ 5·76 and 5·80 μ. (Found: C, 63·65; H, 7·06. Calc. for $C_{17}H_{22}O_6$: C, 63·34; H, 6·68%).

(ii) *Epimerization of keto dimethyl ester* **16**. The ester **16** (10 mg) was heated with dil methanolic NaOMe (0·24 g of Na per 100 ml MeOH; 5 ml) under reflux at 45° for 18 hr and then at 60° for 3 hr. Work-up as described for the epimerization of dimethyl shellolate (*vide supra*) gave a gum (89·5 mg), which on standing in light petroleum–acetone gave crystalline **27** (27 mg), m.p. 143–146°. Recrystallization from the same solvent mixture gave pure **27**, m.p. 150–151·5°, undepressed on admixture with the product obtained by oxidation of dimethyl epishellolate with MnO_2; the IR spectra of the two samples were identical.

Bromination of epishellolic acid

Formation of bromohydrin **28**. Bromine vapour was passed into a soln of epishellolic acid (100 mg) and $NaHCO_3$ (200 mg) in water (2 ml) until a permanent yellow colour remained when the mixture was shaken. The soln was allowed to stand overnight and then acidified with dil HCl. The bromohydrin **28** (102 mg, 80%), m.p. 117–127°, separated from the soln after a few min. Repeated recrystallization from water gave an analytical sample, m.p. 115–125° (water of crystallization); λ_{max}^{KBr} 2·80, 2·90, 3–4·5, 5·8–5·9, and 6·25 μ. (Found: C, 45·88; H, 5·44; Br, 20·54. Calc. for $C_{15}H_{19}O_6Br$: C, 45·82; H, 5·38; Br, 20·32%).

When **28** was heated at 130° for 1 hr there was considerable decomposition but the IR spectrum of the product showed no indication of γ-lactone formation.

Bromohydrin dimethyl ester (**29**)

(i) *Methylation of bromohydrin* **28**. The bromohydrin **28** was esterified with diazomethane in ether–MeOH. The product was recrystallized from MeOH to give **29** as platelets, m.p. 175–177°; λ_{max}^{KBr} 2·80, 5·75, and 5·82 μ. (Found: C, 50·61; H, 5·79; Br, 20·11. Calc. for $C_{17}H_{23}O_6Br$: C, 50·60; H, 5·75; Br, 19·81%).

(ii) *Bromination of dimethyl epishellolate.* Bromination of **24** with liquid Br_2, as described for the preparation of **4** from (**5**) (*vide supra*), also gave **29**.

Acetate of the bromohydrin **28**

The bromohydrin **28** was acetylated with Ac_2O and pyridine as in the case of the preparation of dimethyl epishellolate diacetate (*vide supra*) to give after recrystallization from light petroleum–acetone the corresponding acetate, m.p. 177–179°; $\lambda_{max}^{CCl_4}$ 5·74 and 8–8·5 μ. (Found: C, 51·35; H, 5·73; Br, 18·4. Calc. for $C_{19}H_{25}O_7Br$: C, 51·24; H, 5·66; Br, 17·95%).

Attempted lactonization of epishellolic acid and its derivatives

Attempts to form a γ-lactone by heating a soln of dimethyl epishellolate in boiling dry benzene under reflux in the presence of a catalytic amount of *p*-toluenesulfonic acid were unsuccessful.

An attempted lactonization of a derivative of the acid was carried out as follows. The bromohydrin **28** (25 mg) was heated in boiling xylene (25 ml) under reflux for 2 hr, some of the solvent being distilled to remove any water formed. When the soln was cooled to room temp a product separated as a white powder; $\lambda_{max}^{CHCl_3}$ 3·4·3, 5·69, 5·86 μ. Recrystallization from water gave a small amount of crystalline material as platelets, m.p. 115–119°; this on esterification with diazomethane in ether–MeOH gave a yellowish solid that showed a single band at 5·82 μ in its IR spectrum.

Similar experiments with benzene as solvent were carried out with epishellolic acid and the bromohydrin ester **29**. In each case there was no γ-lactone formation, as indicated by the IR spectra of the products.

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