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LAC—I

THE STRUCTURE OF SHELLOLIC ACID[1]

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Abstract—Shellolic acid, a component of the hydrolysate from lac resin, is shown to be 2,3,4,7,8a-hexahydro-4-hydroxy-8-(hydroxy-methyl)-8-methyl-1H-3a,7-methanoazulene-3,6-dicarboxylic acid (**41**).

LAC is produced by the insect *Laccifer lacca* (Coccidae), which infests certain species of trees in India, Burma and the Moluccas.[2] The insects, whose life-span of 4 to 6 months has been described as "brief and rather miserable,"[3] exude a secretion that covers themselves and the twigs on which they reside; this exudate hardens to a dark red, tough coating known as lac. The name lac is said to derive from *lakh,* the Sanskrit word for one hundred thousand, and to refer to the fact that very large numbers of insects are involved in the production of appreciable amounts of the product.

The crude lac, known as *sticklac,* is purified by being ground and soaked under water; this permits removal of extraneous matter, including twigs and insect bodies, which floats to the surface and is skimmed off. The particles are then soaked in dilute aqueous sodium carbonate, which completes removal of water-soluble components and also removes one of the major colouring matters—the red laccaic acid.[4] The resulting granules, which retain a second major colouring matter—the yellow erythrolaccin,[5] are dried and then constitute *seedlac.* Further treatment by melting and filtration, or by solution in ethanol, filtration, and evaporation, provides *shellac.*

The major component of lac is a resin, which on mild hydrolysis with base gives a complex mixture of hydroxy acids and is considered to consist of polyesters derived from these hydroxy acids. The hydroxy acids have been found to be of two types—aliphatic and alicyclic. The composition of the hydrolysate is dependent on the lac source and the time of collection, but in general it has been found possible to isolate ca. 50% of aliphatic acids and 5–10% of alicyclic acids from the hydrolysate. The major component of the aliphatic fraction is aleuritic acid, 9,10,16-trihydroxypalmitic acid, which constitutes up to ca. 40% of the hydrolysate; it is accompanied by a large number of related acids.[6] The major component of the alicyclic fraction is *shellolic acid,* which usually constitutes 5–8% of the hydrolysate.[7, 8]

Relationship of the functional groups of shellolic acid

Earlier work by Harries and Nagel,[7] and Nagel and Mertens[8] established that shellolic acid has the molecular formula $C_{15}H_{20}O_6$. The presence of two carboxylic acid groups was established by titration and by conversion of shellolic acid to a dimethyl ester, dimethyl shellolate, and a dihydrazide. The remaining oxygen atoms

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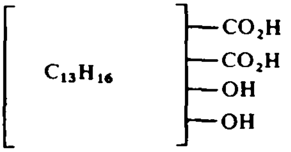
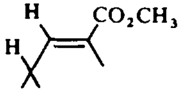
were shown to be present as hydroxyl groups by the formation of a diacetate from shellolic acid and a diphenylurethane from dimethyl shellolate. The presence of an ethylenic double bond was indicated by the formation of dihydroshellolic acid on catalytic hydrogenation of shellolic acid.[9] Thus at the inception of the present work, shellolic acid could be formulated as 1, and could tentatively be assigned a tricyclic structure. Earlier work had also resulted in the characterization of certain bromination and oxidation products of shellolic acid, but their formation was not interpreted in structural terms, and earlier structural proposals[7, 8] reflected the fact that no information was then available concerning the skeleton of shellolic acid.



$$\left[\;C_{13}H_{16}\;\right]\begin{matrix}-CO_2H\\-CO_2H\\-OH\\-OH\end{matrix}$$

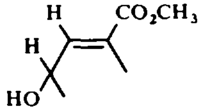
1



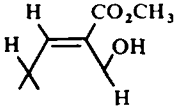
2

The IR spectrum of dimethyl shellolate has a broad carbonyl-stretching band at 5·8–5·9 μ, suggesting that one of the carboxylic ester groups is conjugated with the ethylenic double bond; a band at 6·11 μ can be assigned to the stretching vibration of the latter. The conjugation of an ester group with the ethylenic double bond is also vouchsafed by a maximum at 231 mμ (ε 6200) in the UV spectrum of dimethyl shellolate. The PMR spectrum of dimethyl shellolate shows a one-proton doublet (J 3 Hz) in the vinylic proton region at δ 6·50, indicating the presence of a single, β-*cis*-vinylic proton and a single proton on the γ carbon atom (cf. 2).*†

Oxidation of dimethyl shellolate with "activated" manganese dioxide in chloroform or with chromium trioxide and pyridine gave a dehydro product, $C_{17}H_{22}O_6$. The formation of such a product on oxidation with manganese dioxide suggested the presence of an allylic alcohol function[10] and led to the expansion of the part-structure 2 for dimethyl shellolate to either 3a or 3b. However, the spectroscopic properties of the dehydro product showed that it possessed neither of the part structures 4a or 4b, which would be expected to arise on simple oxidation of the groupings 3a and 3b, respectively. Thus it showed a single broad band in the CO-stretching region of its IR spectrum at 5·78 μ and no high intensity maximum in its UV spectrum above 220 mμ, patently excluding the presence of the α,β-unsaturated



3a



3b

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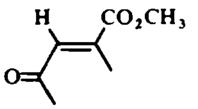
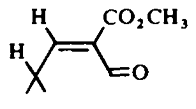
* It cannot be excluded at this stage that a second proton is attached to the γ carbon atom but is not significantly coupled with the vinylic proton; this possibility is excluded, however, by data presented subsequently.

† A bond in 2 and other part-structures whose terminus is unspecified signifies bonding to carbon or oxygen, but not to hydrogen.

ketone systems of **4a** and **4b**. Furthermore, the IR spectrum of the dehydro compound showed the absence of any band attributable to a OH-stretching vibration, although a simple oxidation of one of the OH groups of dimethyl shellolate would have given

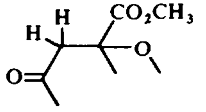


4a

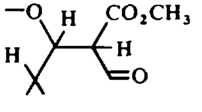


4b

a product retaining a OH group. This feature of the IR spectrum suggested that the dehydro product was formed by oxidation of the allylic alcohol system to give **4a** or **4b** followed by Michael-type addition of the other OH group to the β-carbon of the α,β-unsaturated ketonic grouping to give either **5a** or **5b**. Analogy for such an addition

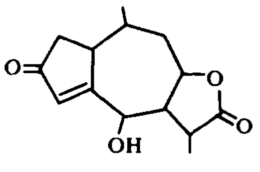


5a

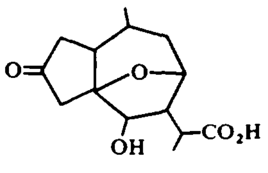


5b

reaction can be found, for example, in the conversion of geigerin (**6**) to *allo*-geigeric acid (**7**) on treatment with dilute base.[11]



6



7

A choice between the two part-structures **5a** and **5b** can be made on the basis of the properties of the product obtained when the dehydro product was subjected to further oxidation with selenium dioxide. This gave a yellow product, $C_{17}H_{20}O_7$, whose electronic spectrum [λ_{max}^{EtOH} 290 (ε 40), 430 mμ (ε 12)] clearly showed it to be an α-diketone [cf. 3,3,6,6-tetramethyl-1,2-cyclohexanedione; λ_{max} 297·5 (ε 29), 380 mμ (ε 11)[12]]. Addition of base to an ethanolic solution of this product failed to lead to the appearance of any high intensity maximum in its UV spectrum above 230 mμ, indicating that the α-diketone function is unable to enolize.[13] Thus part-structure **5b** for the dehydro compound can be eliminated, since this would give rise to a readily enolizable α-diketone, and part-structures **5a** and **3a** can be assigned to the dehydro product and to dimethyl shellolate, respectively. Further, the α-diketone can be represented by the part-structure **7**, because of its failure to enolize,* leading to the elaboration of the part-structure of dimethyl shellolate to **8**. A modification of part-structure 7 can be envisaged in which C-4 bears one H atom, the lack of enolization

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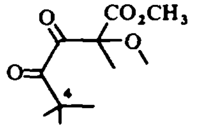
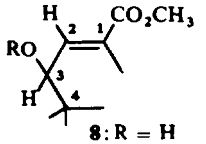
* The possibility that the α-diketone arises by oxidation of a CH_2 group on the other side of the ketonic carbonyl group in **5a** can be excluded, since the diketone would then be enolizable.

being then attributed to the situation of this C atom at the bridgehead of a small atom-bridged system or in some other steric environment in which such enolization is inhibited. However, the signal at δ 5·64 in the PMR spectrum of the diacetate of dimethyl shellolate (*vide infra*), which can be assigned to the proton at C-3 in part-structure **9** corresponding to part-structure **8** for dimethyl shellolate, appears as a doublet (J 3 Hz) due to coupling with the vinylic proton at C-2 (δ 6·39, d, J 3 Hz); the absence of further splitting suggests that C-4 bears no H atom and again favours the assignment of part-structure **8**.

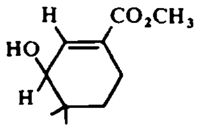


7

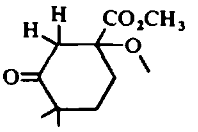


8: R = H
9: R = CH_3CO

The diacetate of dimethyl shellolate was prepared by treatment of the latter with acetic anhydride and pyridine. Ozonolysis followed by treatment with hydrogen peroxide and base gave an acidic product, which on treatment with diazomethane afforded an ester, $C_{15}H_{18}O_6$. The IR spectrum of the ester showed bands at 5·66 and 5·80 μ with the lower wavelength band considerably stronger than the other band, indicating the presence of two γ-lactone groups and a single ester group. Such a product can be accommodated in terms of the environment of the double bond in part-structure **9** if it is considered that the α-keto ester function formed at the C-1 terminus of the double bond by ozonolysis undergoes oxidative cleavage with the resulting loss of one of the C atoms of shellolic acid to give a C_{14} dihydroxy tricarboxylic acid after basic hydrolysis. The formation of such a C_{14} product requires that the ethylenic double bond of shellolic acid be incorporated into a ring. That this ring is 6-membered was indicated by the fact that fusion of dimethyl shellolate with potassium hydroxide at 300° gave, as one of two products isolated, *m*-hydroxybenzoic acid. The relationship of this product to part-structure **8** led to the tentative expansion of the part-structure of dimethyl shellolate to **10**, and that of the dehydro product to **11**.

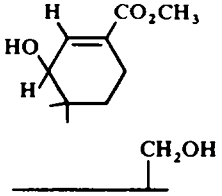


10

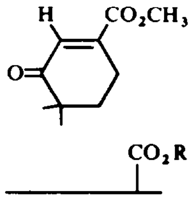


11

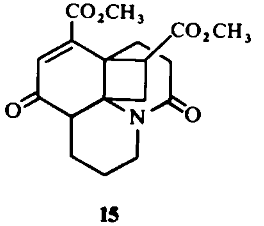
Information concerning the nature and environment of the second hydroxyl group in dimethyl shellolate, that giving rise to the ether linkage in **11**, was obtained by oxidation of dimethyl shellolate with chromium trioxide in aqueous acetic acid—sulfuric acid. Oxidation proceeded rapidly to give an acidic product; attempted purification of this by crystallization led to the appearance of a new band in its IR spectrum at 5·65 μ, indicating that lactone formation was occurring. The crude product was therefore treated with *p*-toluenesulfonic acid in boiling benzene to effect complete conversion to the lactone. There was thus obtained a product, $C_{17}H_{20}O_7$, that showed bands at 5·65 and 5·78 μ in its IR spectrum and no band in the OH-stretching region; its UV spectrum showed no high intensity maximum above 220 mμ. Methylation of the original oxidation product with methyl iodide and potassium carbonate in acetone gave a product, $C_{18}H_{22}O_7$, with bands at 5·78, 5·93, and 6·10 μ in its IR spectrum, and a maximum in its UV spectrum at 240 mμ (ε 8700). These observations can readily be interpreted in terms of the presence of a primary alcoholic group in dimethyl shellolate. The original oxidation product would then be formed by oxidation of this primary alcoholic group to a carboxylic acid group and also of the secondary alcoholic group in part-structure **10** to a ketonic group, the latter oxidation being analogous to that earlier postulated as occurring under milder oxidizing conditions. The part-structures **12**, **13**, and **14** can then be assigned to dimethyl shellolate, the product formed on oxidation with chromic acid and sulfuric acid, and the methylation product from the latter, respectively. The IR and UV spectra of the methylation product are in good accord with the presence of the α,β-unsaturated ketone system in **14**; it may be noted that the position of the ketonic CO-stretching band at 5·93 μ confirms that the α,β-unsaturated ketone system is not located in a 5-membered ring. The UV maximum may be compared with that of **15** in the annotinine series [λ_{max} 242 mμ (ε 8000)].[14] The presence of a primary alcoholic function in dimethyl shellolate is corroborated by the appearance of signals in the δ 3–4 region of its PMR spectrum and in the PMR spectra of its derivatives (*vide infra*).



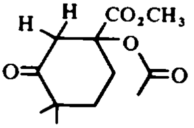
12



13: R = H
14: R = CH_3



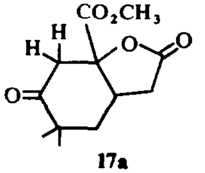
15



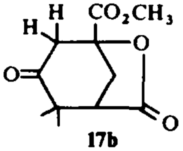
16

The ready formation of a lactone from the oxidation product can be accounted for in terms of part-structure **13** by postulating the addition of the carboxylic acid grouping to the β position of the α,β-unsaturated CO system in a manner entirely analogous to that proposed previously to account for the formation of the dehydro product with part-structure **11**. The resulting part-structure, **16**, is in accord with the disappearance of the α,β-unsaturated ketonic system of **13** on formation of the lactone, as revealed by the spectra of the latter. The IR spectrum also shows that the lactone ring is 5-membered since the CO-stretching band due to this function appears at 5·65 μ. The part-structure **16** for the lactone can then be elaborated to either **17a** or **17b**.

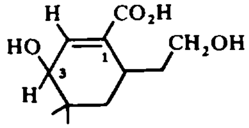
Choice between these part-structures can be made on the basis of the reaction of shellolic acid with sodium acetate and acetic anhydride. This gives rise to shellolic acid dilactone, $C_{15}H_{16}O_4$, with IR bands at 5·65 (sh) and 5·74 μ and strong end absorption in its UV spectrum. That no rearrangement occurs during its formation is indicated by its reconversion to shellolic acid on treatment with aqueous sodium bicarbonate followed by acidification. On treatment of the dilactone with water one of the lactone rings is opened to give shellolic acid monolactone, $C_{15}H_{18}O_5$, with IR bands at 2·83, 3–4, 5·59, 5·85, and 6·20 μ and an UV maximum at 227 mμ (ε 5500). The part-structures for shellolic acid that correspond to **17a** and **17b** are **18a** and **18b**, respectively. It is clear that steric factors preclude lactone formation between the carboxylic acid group at C-1 and the hydroxyl group at C-3 in either structure; lactone formation must therefore occur between this carboxylic acid group and the primary alcohol group, and the dilactone can be formulated as either **19a** or **19b** in terms of **18a** and **18b**, respectively. However, it is most unlikely that the highly strained system of **19b** would be formed under these conditions[15] and preference can be given to part-structure **19a** for the dilactone and thus to **18a** for shellolic acid.*



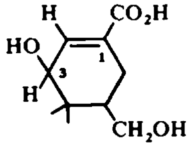
17a



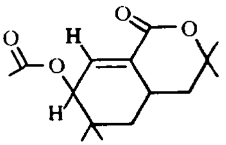
17b



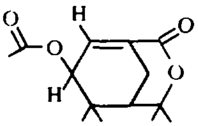
18a



18b



19a



19b

The IR spectrum of shellolic acid dilactone [5·65 (sh), 5·74 μ] shows that one of the

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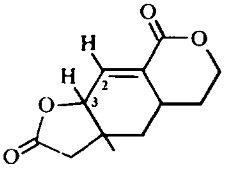
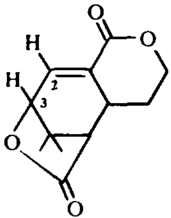
* The recent syntheses of bicyclo[3.3.1]non-1-ene[16] might be considered to cast doubt on this conclusion; it may be noted, however, that the presence of the lactone grouping in **19b** would be expected to make this system considerably more strained than the corresponding hydrocarbon.

lactone rings is 5-membered while the other is 6-membered. With the 6-membered lactone assigned as in **19a**, the size of the other lactone ring is defined, leading to the two alternative part-structures **20a** and **20b** for the dilactone. Although the corresponding structures based on **19b** have been rejected, because of the very high strain anticipated for the 6-membered lactone in that part-structure, nevertheless one of the lactone rings of the dilactone is subject to unusually facile hydrolysis and the IR spectroscopic data show that this is the 6-membered ring. The instability of the 6-membered lactone ring is associated with the presence of the ethylenic double bond, for dimethyl dihydroshellolate, the hydrogenation product from dimethyl shellolate, gives on treatment with *p*-toluenesulfonic acid in boiling benzene the corresponding dihydroshellolic acid dilactone (λ_{max} 5·63, 5·72 μ), which is not hydrolyzed by hot water. We shall return to discuss the origin of the lability of the 6-membered lactone ring in shellolic acid dilactone when the full structure of shellolic acid has been developed.



20a



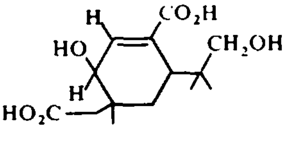
20b

In the low-field region of its PMR spectrum shellolic acid dilactone shows a one-proton doublet (*J* 2 Hz) at δ 6·56 and a broad one-proton singlet at δ 5·27, that are assigned to the protons at C-2 and C-3 respectively, in either **20a** or **20b**. In addition a two-proton singlet appears at δ 4·17, which can be assigned to the two protons of the methylene group adjacent to the annular O atom of the 6-membered lactone ring in either **20a** or **20b**, the fact that these give rise to a singlet must be due to accidental degeneracy. A similar signal appears at δ 4·43 in the spectrum of dihydroshellolic acid dilactone, where it is superimposed on a multiplet assignable to the proton at C-3; as anticipated, no vinyl proton signal appears in this spectrum. Dimethyl shellolate itself shows in its PMR spectrum a two-proton singlet at δ 3·30 that can be assigned to the protons of the methylene group of the primary alcohol function. The fact that these methylene proton signals appear in the spectra of these three compounds as singlets establishes that the C atom adjacent to the methylene group bears no hydrogen atoms. In the case of the diacetate of dimethyl shellolate, the corresponding methylene protons give rise to a multiplet which falls under, and is partially obscured by, the two singlet signals at δ 3·58 and 3·68 due to the OMe protons of the ester groups. The appearance of the $—CH_2—O—$ signal as a multiplet in this case can be attributed to its occurrence as a "non-equivalence quartet" due to the situation of the $—CH_2O—$ group near an asymmetric centre.[17]

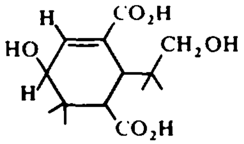
Thus the relationship among the functional groups in shellolic acid is represented by either part-structure **21a** or **21b**, based on **20a** or **20b** for shellolic acid dilactone and the PMR spectral evidence regarding the environment of the primary alcohol group.

Carbon skeleton of shellolic acid

In addition to the information concerning the carbon skeleton culled in establishing the relationship among the functional groups of shellolic acid, one further feature was readily deducible from the PMR spectra of dimethyl shellolate and other derivatives



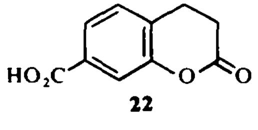
21a



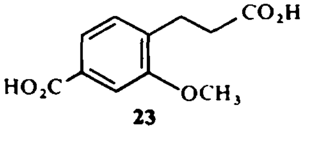
21b

of shellolic acid; a 3-proton singlet in the δ 1·2–1·25 region showed the presence of a Me group attached to a quaternary C atom. The presence of a $C—CH_3$ group was also demonstrable by Kuhn–Roth oxidation.

Of decisive importance in establishing the full carbon skeleton of shellolic acid was the major product obtained on fusing dimethyl shellolate with potassium hydroxide. This product, formed together with *m*-hydroxybenzoic acid, has the formula $C_{15}H_{16}O_6$, i.e., it retains all of the C atoms of shellolic acid. Its IR spectrum shows bands at 3–4, 5·63, 5·88 and 6·31 μ and maxima in its UV spectrum appear at 237 (ε 10,000), 282 (ε 1900), and 290 mμ (ε 1800). On treatment with diazomethane it gave a dimethyl ester, $C_{17}H_{20}O_6$, with bands in its IR spectrum at 5·67, 5·80, 6·20, and 6·37 μ. These data indicate that it is an aromatic carboxylic acid containing a lactone ring. On treatment with dimethyl sulfate and 1 N NaOH it gave a product, $C_{16}H_{20}O_7$, that contained one OMe group, titrated as a tribasic acid, and showed bands in its IR spectrum at 3–4, 5·8–5·9, and 6·33 μ and in its UV spectrum at 246 (ε 11,300) and 296 mμ (ε 3900). This methylation product can thus be written as $C_{12}H_{14}(OCH_3)(CO_2H)_3$ and it may be surmized that the C_{15} base fusion product is a phenolic lactone that is hydrolyzed prior to methylation. The lactone ring is indicated to be 6-membered by the position of its CO-stretching band at 5·63 μ. Its orientation with respect to the aromatic carboxylic acid group is suggested to be as shown in part-structure **22** by the concurrent formation of *m*-hydroxybenzoic acid in the base fusion reaction and by the fact that in both part-structures **21a** and **21b** the ethylenic C atom that is considered to correspond to C-2 of *m*-hydroxybenzoic acid bears a H atom. The corresponding part-structure for the product obtained on treatment with dimethyl sulfate



22



23

and base is then **23**; the relationship between the UV spectra of this product and the C_{15} base fusion product itself is in good accord with these structural assignments.*

The presence of the dihydrocoumarin system of **22** was confirmed by dehydrogenation of the C_{15} base fusion product under mild conditions. Treatment with Pd-C at

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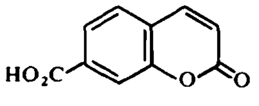
* For the incorporation of the phenolic oxygen atom into a lactone group in the latter suppresses its interaction with the aromatic ring.[18]

200° gave a crude oily product, which afforded a crystalline dimethyl ester on treatment with diazomethane; this ester was obtained in an overall yield of 65% from the base fusion product. Its formula, $C_{17}H_{18}O_6$, demonstrated that two H atoms had been lost in the dehydrogenation process, as anticipated for the formation from **22** of the coumarin system **24**. The IR spectrum of the ester showed a single, broad band in the CO-stretching region at 5·80 μ. Its UV spectrum is complex with maxima at 275 (sh, ε 13,300), 284 (ε 18,200), 296 (ε 16,200), 315 (sh, ε 7700), 324 (ε 8300), and 336 mμ (sh, ε 5300). These spectral data are in excellent accord with the assignment of part-structure **24** to the dehydrogenation product.[19]



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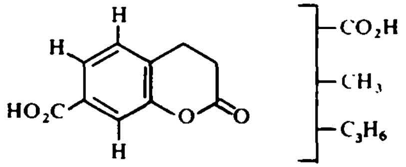
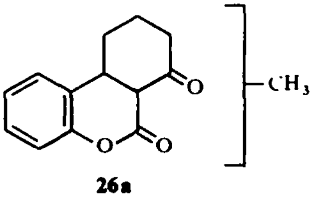


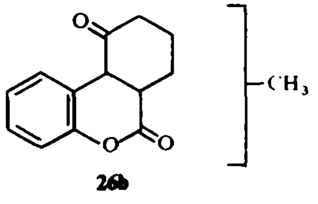
25

The PMR spectrum of the dimethyl ester of the C_{15} base fusion product confirmed the assignment of the part-structure **22** to the latter and permitted the elaboration of the part-structure to **25**. Thus the presence of a $C(sp^3)$—CH_3 group is shown by a 3-proton signal at δ 1·17; this appears as a doublet (*J* 7 Hz), establishing that the carbon to which the Me group is attached bears a single H atom. Two of the aromatic protons give rise to an AB pattern with a doublet at δ 7·40 and a broadened doublet at 7·80 (*J* 6 Hz); the third gives a broad singlet at δ 7·75. The orientation of the aromatic carboxylic acid group and the lactone ring is thus confirmed, and the absence of further substituents on the aromatic ring is established.

Treatment of the C_{15} base fusion product with copper powder in quinoline at reflux gave a neutral product, $C_{14}H_{14}O_3$, showing bands in its IR spectrum at 5·71 and 5·80 μ and no absorption in the 2·8–3·2-μ region. Its UV spectrum with maxima at 260 (ε 920) and 273 mμ (ε 930), is characteristic of a substituted benzene ring with little conjugative interaction between the substituents and the aromatic system.[20] This revealed that the carbon atom lost in the reaction must be that of the aromatic carboxylic group. The formula of the product indicates that its formation involves, in addition to decarboxylation, the loss of the elements of water. The band at 5·71 μ in its IR spectrum suggests that the lactone ring is intact, while the band at 5·80 μ can most simply be interpreted in terms of the presence of a ketonic group that is not conjugated with the aromatic ring. This in turn suggests that the dehydration process is an internal acylation reaction involving the carboxylic acid group not attached to the aromatic ring. The IR band at 5·80 μ indicates that the new ring formed by this process is 6-membered and that the three C atoms of the C_3H_6 group in **25** must form an unbranched

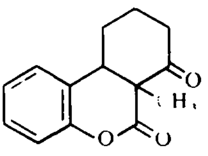


26a



26b

chain. Two part-structures are then possible for the C_{14} product, **26a** and **26b**. Of these, **26a** can be given preference on the basis of the fact that the ketonic carbonyl-stretching band of the product is at somewhat lower wavelength than normal for a cyclohexanone, which can be attributed to dipolar interaction with the adjacent lactone CO group in **26a**. Further, internal acylation at a methylene group adjacent to a CO group[21] may be counted as more likely than at a benzylic methylene group. Since the C_{14} product gives no ferric chloride test nor is its UV spectrum markedly changed in basic solution, it cannot be an enolizable β-dicarbonyl compound and structure **26a** can be elaborated to the full structure **27**, corresponding to structure **28** for the C_{15} base fusion product itself. The correctness of this structural assignment was established by an independent synthesis of the dehydrogenation product of compound **28**.



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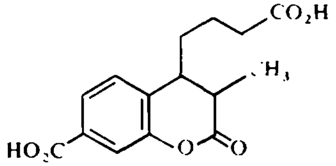
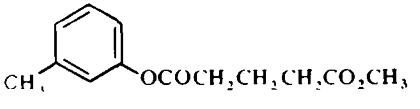


28

The most direct approach to the synthesis of this compound appeared to be via the preparation of a phenolic ester of *m*-hydroxybenzoic acid and subjection of this to a Fries rearrangement. However, the Fries rearrangement of *m*-acetoxybenzoic acid has been reported to fail[22] and we also were not able to effect rearrangement of esters of *m*-hydroxybenzoic acid. We therefore turned to the rearrangement of an ester of *m*-cresol in the expectation that it would be possible to transform the Me group to a carboxylic acid group at a subsequent stage. The ester **29** was formed from *m*-cresol and 4-carbomethoxybutyryl chloride and treated with aluminium chloride in tetrachloroethane at 130–140° to give the hydroxy keto acid **30**, which was converted by dimethyl sulfate and potassium carbonate to the methoxy keto ester **31**. The fact that, as expected,[23] the rearrangement product is an *o*-hydroxy ketone rather than the



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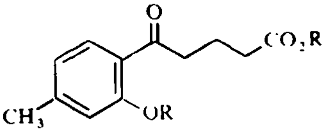

30: R = H
31: R = CH_3

corresponding *p*-hydroxy compound is evidenced by the long wavelength (6·10 μ) of the ketonic CO-stretching band in its IR spectrum[24] and by subsequent reactions involving ring closure. That the rearrangement product has, again as expected,[23] the 1,2,4 orientation of the aromatic substituents rather than the 1,2,3 orientation is shown by the pattern of the aromatic proton signals in the PMR spectrum of its methylation product **31**.*

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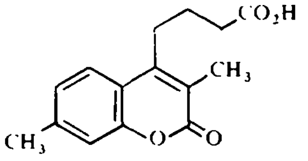
* Compound 31 was converted via the coumarin 32 to the lactone 33 (see Experimental), but this could not be converted to 28 by oxidation with chromic acid,[25] nor could the aromatic methyl group be brominated with N-bromosuccinimide.

Treatment of the ester **31** with N-bromosuccinimide and azobisisobutyronitrile gave a crude product whose PMR spectrum clearly indicated that the aromatic Me group had been converted to a CH_2Br group. The bromide was not purified, but was hydrolyzed with silver nitrate in aqueous acetonitrile to give the corresponding hydroxymethyl compound, and this, again without purification, was oxidized with chromic acid. The resulting acidic product was esterified with methanol and hydrogen chloride to give **34**, which was purified and fully characterized. Reaction of **34** with methyl α-bromopropionate and zinc followed by treatment with hydrobromic acid in acetic acid gave the coumarin **35**; this showed bands in its IR spectrum at 3–4, 5·8–5·9, and 6·21 μ and a complex UV spectrum with maxima at 284 (ε 17,600), 296 (ε 15,400), 315 (sh, ε 7500), 323 (ε 8000), and 335 mμ (sh, ε 5100). Esterification of **35** with diazomethane gave the dimethyl ester **36**, which was shown to be identical with the dimethyl ester of the compound obtained on dehydrogenation of the C_{15} base fusion product.



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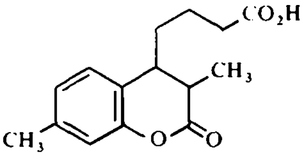

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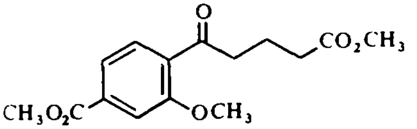

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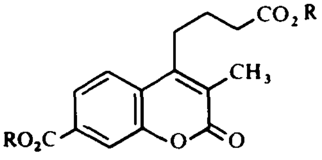
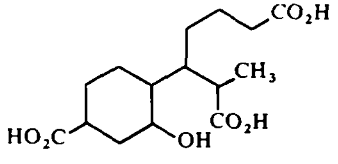


35: R = H
36: R = CH_3

The gross structure of this base fusion product is thus established as **28**. Its stereochemistry has not been investigated. This has no relevance, however, to the stereochemistry of shellolic acid, for epimerization can occur at each of the asymmetric carbon atoms of **28** under the vigorous reaction conditions, as demonstrated by the fact that this product is obtained as a racemate.

Structure of shellolic acid and its transformation products

The carbon skeleton and positioning of the oxygen-containing functions in the base fusion product **28** from dimethyl shellolate can be represented as in **37**. The presence of three carboxylic acid groups and one secondary OH group shows that in the course of the base fusion, the primary alcohol function of shellolic acid has been converted to a carboxylic acid grouping. Such a process finds ample analogy, for example, in the almost quantitative conversion of lauryl alcohol to lauric acid under similar conditions,[26] and the conversion of terranaphthol (**38**) to terranaphthoic acid (**39**).[27] Comparison of **37** with the alternative part-structures **21a** and **21b** previously deduced for shellolic acid shows that only the former is admissible, and that the carboxylic acid group attached to the 6-membered ring in **37** must correspond to the similarly placed carboxylic acid group in **21a**, and cannot therefore correspond to the primary alcohol group in shellolic acid. These considerations permit the elaboration of **37** to



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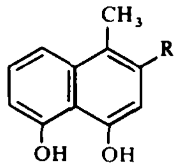
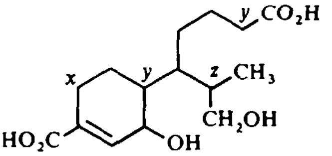
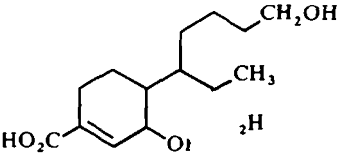


38: R = CH_2OH
39: R = CO_2H

40a or **40b**, in which one or the other of the two remaining carboxylic acid groups in **37** represents the site of the primary alcohol group. Structures **40a** and **40b** require the placement of two additional C-C bonds to provide the tricyclic structure of shellolic acid. Detailed comparison of part-structure **21a** with **40a** and **40b** shows that

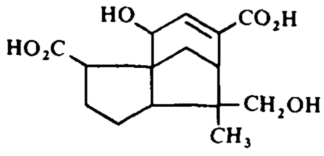


40a



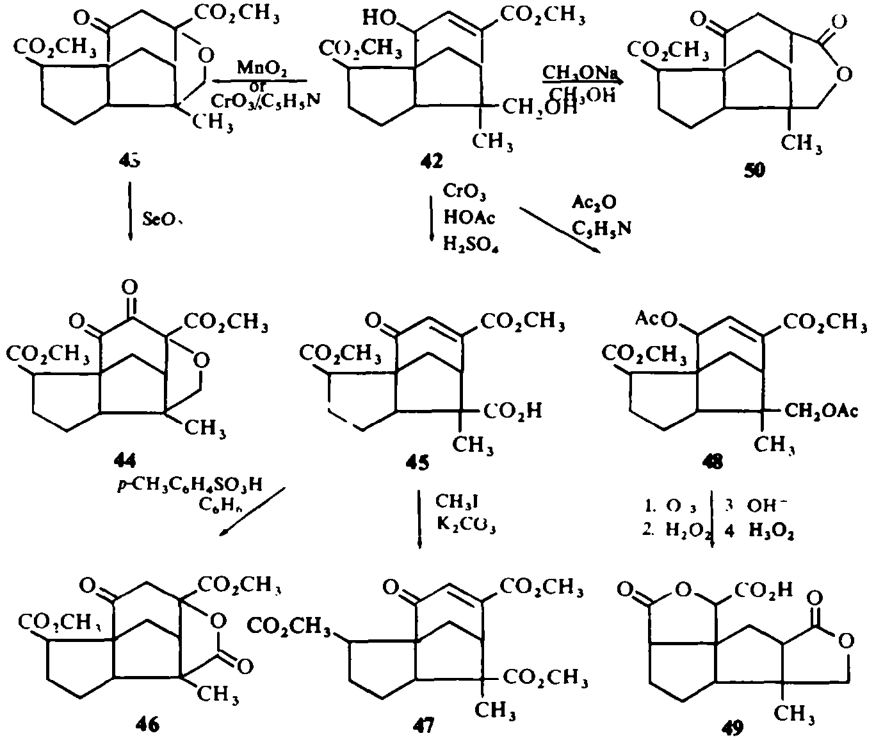
40b

there is a unique fashion in which two C—C bonds can be introduced into **40a** such that the resulting structure is compatible with **21a**, and no way in which **40b** can be reconciled with **21a**. The elaboration of **40a** requires the placement of one bond between the C atoms marked x and the other between the C atoms marked y, and leads to structure **41** for shellolic acid.



41

The structures for the transformation products of dimethyl shellolate (**42**) discussed previously can now be drawn in full and are given in Chart 1. The dehydro product obtained on treatment with manganese dioxide or chromium trioxide is formulated as **43**, and the diketone formed on its oxidation with selenium dioxide as **44**. The unstable acidic product formed on oxidation with chromium trioxide and sulfuric acid is formulated as **45**, its dehydration product as the lactone **46**, and its esterification product as **47**. The product formed on ozonolysis of **48**, the diacetate of dimethyl shellolate, followed by oxidative work-up, basic hydrolysis, and acidification is formulated as the dilactone **49**. In addition to these reactions, the reaction of dimethyl shellolate with methanolic sodium methoxide was investigated; it was anticipated that the γ-hydroxy α,β-unsaturated ester system of **42** would be isomerized to the corresponding γ-keto ester.* A product was obtained in low yield whose elemental composition showed that its formation had involved the loss of the elements of methanol. Its UV spectrum showed no high intensity absorption above 220 mμ and its IR spectrum showed no band in the 6-μ region, indicating that the desired isomerization of the allylic alcohol system had taken place. The absence of any hydroxyl-stretching band in the latter spectrum further indicated that the loss of methanol had resulted from lactone formation involving the other OH group, and the product is formulated as **50**.



The lactones from shellolic acid (**41**) and dimethyl dihydroshellolate (**51**) can now be fully formulated as in Chart 2. The dilactone formed on treatment of shellolic acid with acetic anhydride and sodium acetate is assigned structure **52**. The monolactone formed on treatment of this with water is then **53**, and the very facile hydrolysis of the 6-membered lactone ring of **52** can be interpreted as being due to the situation of the ethylenic double bond in this compound at the bridgehead of a relatively small atom-bridged system. Further, the geometry of the system precludes coplanarity between the double bond and the adjacent CO group, thus accounting for the fact

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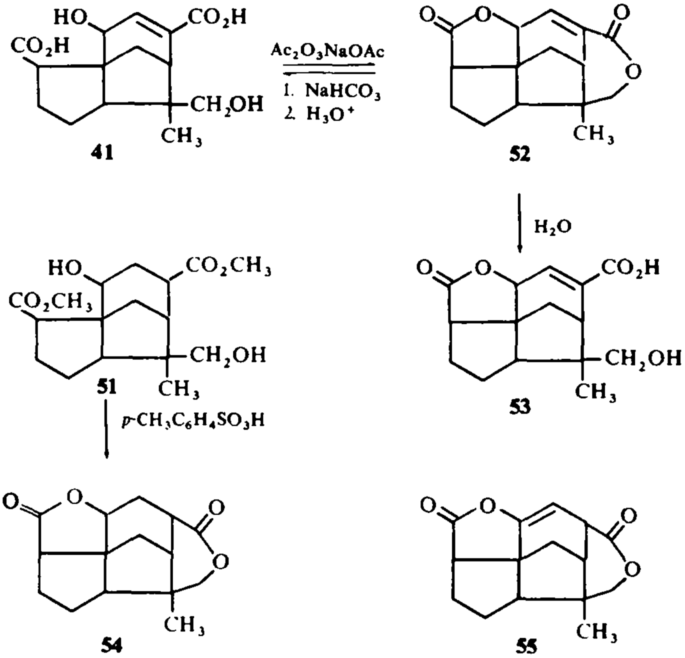
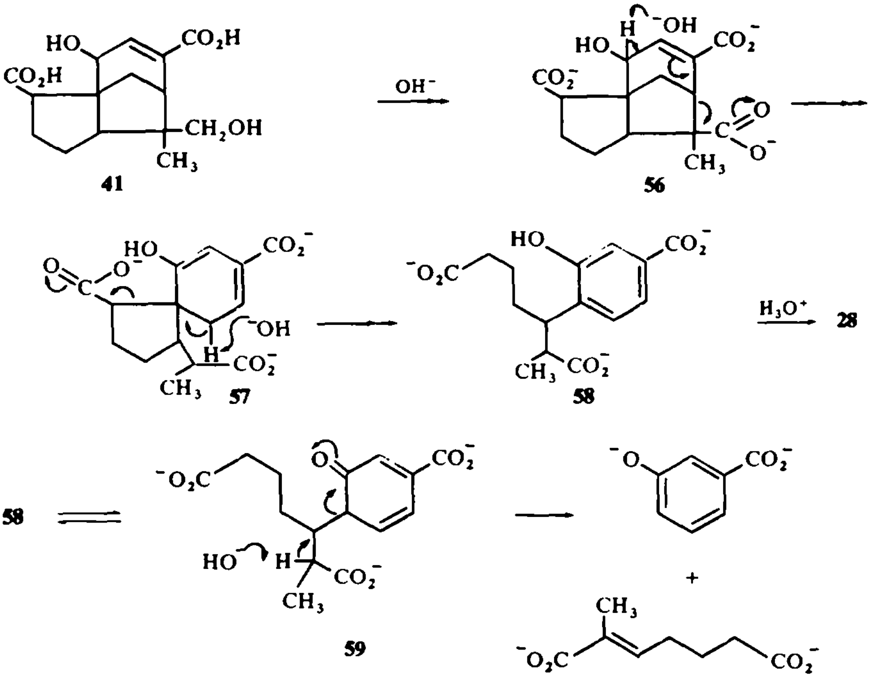
* Cf. the analogous reaction in the case of a transformation product of annotinine.[14]

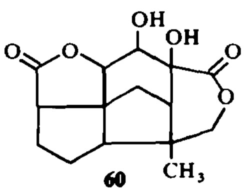
that, while the monolactone **53** shows an UV maximum at 227 mμ (ε 5500), the dilactone shows no high intensity UV absorption above 220 mμ. The view that the facile hydrolysis of **52** to **53** is associated with the strained position of the ethylenic double bond is corroborated by the fact that dihydroshellolic acid dilactone, now formulable as **54**, does not undergo such ready hydrolysis. Treatment of shellolic acid with copper and quinoline gave a product isomeric with shellolic acid dilactone. Its IR spectrum showed bands at 5·53, 5·78, and 5·97 μ, and it is considered to be the dilactone **55** in which double bond migration has occurred.



We return now to the base fusion of dimethyl shellolate and discuss the origin of the products in terms of structure **41** for shellolic acid. A proposed reaction sequence is given in Chart 3. Conversion of the primary alcohol group to a carboxylic acid group is considered to occur at an early stage to give the tricarboxylate ion **56**. This is postulated to undergo C—C bond cleavage as shown in **56** to give **57**.[28] A second such bond cleavage is then considered to occur leading to aromatization of the 6-membered ring and formation of **58**, which on acid work up gives the major product, **28**. Bond cleavage in a tautomer of **58**, as shown in **59**, accounts for its further fragmentation to give *m*-hydroxybenzoic acid.

It remains to consider the transformation products of shellolic acid obtained by earlier workers and to show that their formation can be interpreted in terms of the structure here assigned to shellolic acid. Nagel and Mertens[29] obtained a compound $C_{15}H_{18}O_6 \cdot H_2O$ when shellolic acid was oxidized with a limited amount of potassium permanganate and base. This is a dilactone and forms a monoacetyl derivative on treatment with acetic anhydride and pyridine. It can be formulated as the hydrate of the diol **60**; the formation of a monoacetyl derivative can be attributed to the fact that one of the hydroxyl groups is tertiary. Oxidation of this dilactone with neutral potassium permanganate was reported to give a monocarboxylic acid, $C_{14}H_{16}O_6$, m.p. 248°, which formed a monomethyl ester, m.p. 154°, with diazomethane. This acid corresponds in elemental composition and melting point to the acid obtained in the present work by ozonolysis of the diacetate of dimethyl shellolate followed by treatment with alkaline hydrogen peroxide; the melting points of the methyl esters are also very similar. The ozonolysis product has been assigned structure **49**, and the relationship between this structure and **60** is in excellent accord with the assignment of structure **49** also to the further oxidation product from **60**. Nagels and Mertens[29] reported that the acid contained two active H atoms; if the present structural assignment is correct, this observation must be discounted. Oxidation of shellolic acid with twelve equivalents of potassium permanganate in acid medium was found[29] to give a





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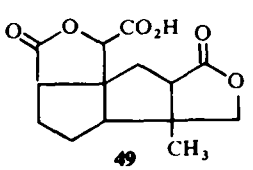
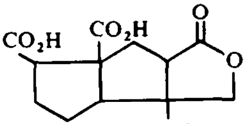


49

dibasic acid, $C_{13}H_{16}O_6 \cdot 2H_2O$. This may readily be formulated as **61**, but again the earlier active hydrogen determination must be discounted, since its methyl ester is reported to contain one active hydrogen atom; it may be noted, however, that the product was recrystallized from aqueous methanol.

Bromination of shellolic acid in aqueous sodium bicarbonate gave a compound, $C_{15}H_{17}O_5Br \cdot H_2O$.[8, 29] This can now be formulated as **62**, although it is reported to have two active H atoms.[29] In this case, our own investigation[30] of the product has established its structure as **62**, as has an X-ray crystallographic study by Gabe.[31]* This latter study has thus confirmed the gross structure assigned to shellolic acid as a result of the present work; it has also confirmed the stereochemistry assigned to shellolic acid,[1] which is discussed in detail in the following paper.[30]



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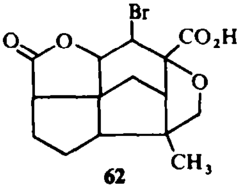

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Cookson[32] and Gunstone[33] *et al.* have investigated the chemistry of shellolic acid and have obtained results complementing those reported here that they have interpreted in terms of structure **41** for shellolic acid. Cookson *et al.* have also investigated the stereochemistry of shellolic acid, and we shall refer in more detail to their work in our own discussion of the stereochemistry of shellolic acid.[30]

EXPERIMENTAL

M.ps were determined on a Fisher–Johns micro hot-stage unless otherwise specified and are not corrected. Solns in organic solvents were dried over Na_2SO_4 unless otherwise specified.

Isolation of dimethyl shellolate (42)

Dimethyl shellolate was isolated first by a procedure patterned after that of Kirk *et al.*[9] Kusmi seedlac (550 g) was treated with EtOH (1 l.). The mixture, after standing for several days, was filtered with the use of Supercel, and the filter-cake was washed with EtOH to give a total of 1·7 l. of soln. NaOH (210 g) was added, and the mixture was allowed to stand at room temp for one week. The EtOH was then distilled under reduced press with the addition of water until 1·5 l. of aqueous soln was obtained. The soln, after being brought to pH 8–9 with CO_2, was concentrated under reduced press with a rotary evaporator, and the gummy, purple residue was extracted with hot EtOH (1·75 l.). The ethanolic extract was concentrated under reduced press, and the residue was taken up in water to give 7·5 l. of soln. To this soln was added with stirring 0·35 *M* $ZnSO_4$ aq (970 ml), and the brick red ppt (196 g) was filtered off. The filtrate was treated with more 0·35 *M* $ZnSO_4$ aq (1·43 l.) and the pH was adjusted to 7 with NaOH. The mixture was allowed to stand overnight, and the tan ppt (135 g) was filtered off. The filtrate was made basic with excess solid Na_2CO_3, the basic Zn salts were filtered off, and the filtrate was taken to dryness under reduced press. The residue was extracted with EtOH (1 l.), and the hot extract was mixed with a hot soln of lead acetate (124 g) in EtOH (2 l.). A gummy ppt was formed, which solidified when the mixture was cooled overnight. This solid (90 g), was dried and covered with methanolic 5% HCl (700 ml), and the mixture was left to stand for 4 days. The $PbCl_2$ was filtered, and the filtrate was neutralized with methanolic NaOH. The precipitated NaCl was filtered off, and the filtrate was concentrated under reduced press. The residue was taken up in $CHCl_3$ and, after the insoluble material had been filtered off, the soln was washed with

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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[1] had appeared.

10% Na_2CO_3 aq; formation of emulsions gave considerable trouble during this washing. The $CHCl_3$ soln was dried and concentrated to leave a yellow oil (21 g), which on standing overnight with ether deposited a white solid (7·2 g). Two recrystallizations from EtOAc gave crude dimethyl shellolate (4·6 g), m.p. 150–153°. An analytical sample obtained by further recrystallization from EtOAc had m.p. 153 154·5°; $\lambda_{max}^{CHCl_3}$ 2·90, 5·8–5·9, and 6·11 μ; λ_{max}^{EtOH} 231 mμ (ε 6200). (Found: C, 62·76; H, 7·33; C—CH_3, 3·38. Calc. for $C_{17}H_{24}O_6$: C, 62·96; H, 7·46; C—CH_3, 4·63%).

This procedure, which requires the concentration of large volumes of aqueous soln and some very tedious filtrations, is not convenient. An extraction procedure using buffers was then investigated.[*] Kusmi seedlac (500 g) was dissolved in a warm KOH aq (145 g) in water (500 ml). The resulting purple soln was allowed to stand for 3 days to 2 weeks. The very viscous soln was diluted with water (250 ml) and filtered with the use of Supercel to remove debris. An aliquot of this soln of K salts (25 ml), the buffer described below (25 ml), and 85% H_3PO_4 (1·2 ml) were combined and extracted with 25% EtOAc in ether (50 ml). The aqueous phase was acidified with H_3PO_4 and extracted with EtOAc (3 × 25 ml). The two organic phases were dried and stripped of solvent. The first extract contained 6·1 g of material with $E^1\% = 56$ at ca. 230 mμ; the second contained 3·3 g of material with $E^1\% = 154$ at this wavelength. Therefore, some concentration of shellolic acid and related substances into the aqueous buffer had occurred. Although the separation did not appear to be very efficient, the lack of efficiency[†] was compensated by the simplicity of the procedure, which gives reliable, if small, yields of dimethyl shellolate.

A buffer soln was made from $NaH_2PO_4 \cdot H_2O$, (250 g) and K_2HPO_4 (100 g) in water (1 l.). The basic soln of shellac-derived salts described above, the buffer (500 ml), 85% H_3PO_4 (60–75 ml), ether (1·3 l.), EtOAc (500 ml), and t-BuOH (200 ml) were combined. The phases were equilibrated and separated. The aqueous phase which had pH 6 was emulsified with EtOAc (700 ml) and treated with 85% H_3PO_4 (150 ml), and the phases were separated after equilibration. This separation was sometimes impeded by a small amount of black tar which gathered at the interface. The aqueous phase was re-extracted with EtOAc (2 × 500 ml). The crude acids with greater water solubility were obtained as a red tar (200–250 g) when the combined, dried EtOAc extracts were concentrated under reduced press. The red tar was dissolved in anhyd MeOH (3–3·5 l.) containing anhyd HCl (70–110 g). After this soln had stood at room temp for 3–5 days, the HCl was neutralized with methanolic NaOH. The ppt was filtered off, and the filtrate was concentrated under reduced press to a gum which was taken up in $CHCl_3$ (600–700 ml). The residual NaCl was filtered off, and the $CHCl_3$ soln was passed through a column of Florisil (100–150 g), which was then eluted with $CHCl_3$ (500 ml). The combined $CHCl_3$ eluates were stripped of solvent under reduced press to leave 200–230 g of resinous material, which was taken up in ether (ca. 200 ml). The soln was allowed to crystallize at ca. 4° for approximately 6 days. The crude solid esters (14–30 g) were filtered off, taken up in benzene containing 1% MeOH (150 ml), and chromatographed on Florisil or acid-washed alumina (Merck) (150 g). Elution with 1–2% MeOH in benzene gave dimethyl shellolate (11–15 g), m.p. 152–155°, after crystallization from EtOAc or acetone.

Shellolic acid (41)

Dimethyl shellolate (2·00 g) was hydrolyzed with boiling 1N NaOH (30 ml) under reflux for 3 hr. The exact amount of dil H_2SO_4 required to neutralize the NaOH used was added to the cooled soln. The soln was concentrated under reduced press to ca. 40 ml, giving crystalline shellolic acid (1·64 g), m.p. 204–207° (lit[9] m.p. 206°); λ_{max}^{KBr} 2·90, 3–4, 5·81, and 6·16 μ.

Mild oxidation of dimethyl shellolate—Formation of dimethyl dehydroshellolate (43)

(i) *With manganese dioxide.* Dimethyl shellolate (0·914 g) and freshly prepared "activated" MnO_2[34] (10 g) were stirred together in $CHCl_3$ (50 ml) for 20 hr at room temp. The MnO_2 was filtered off and washed with $CHCl_3$ (75 ml). Evaporation of the $CHCl_3$ left a residue (0·75 g) which was dissolved in benzene (ca. 20 ml) and chromatographed on Florisil (1·8 × 17 cm). Elution with 0·25 to 0·5% MeOH in benzene and crystallization from acetone–light petroleum gave a crude product (200 mg) which on further crystallization from acetone–hexane gave 43 (182 mg, 19%), m.p. 119–122° (cap). Repeated recrystallization from isopropanol and cyclohexane gave an analytical sample, m.p. 124·5–125·2°; $\lambda_{max}^{CHCl_3}$ 5·78 μ (br); no high intensity UV maxima > 220 mμ. (Found: C, 63·28; H, 6·55. Calc. for $C_{17}H_{22}O_6$: C, 63·34; H, 6·88%).

(ii) *With chromium trioxide-pyridine.* Dimethyl shellolate (1·00 g) was treated with the complex made

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[*] We thank Dr. D. Rosenthal for suggesting a separation based on this principle.

[†] A more efficient procedure might be developed if the conditions of the hydrolysis were changed such that most of the potassium aleuritate precipitated; indeed, if this could be accomplished the concentration with buffers of substances absorbing in the UV might become unnecessary.

from CrO_3 (0·45 g) in pyridine (20 ml). The slurry was kept in the steam cabinet at ca. 45° for 24 hr. The resulting brown mixture was decomposed with solid $NaHSO_3$ and 10% H_2SO_4aq (70 ml). The blue-green aqueous soln was extracted with benzene (4 × 25 ml), and the extracts were washed with 2N H_2SO_4 (30 ml) and brine (30 ml). Evaporation of the dried benzene soln left a residue (760 mg), which was dissolved in benzene and chromatographed on Florisil (1·8 × 26 cm). Elution with $CHCl_3$ and 0·5% MeOH in $CHCl_3$, and crystallization from ether gave 258 mg (26%) of **43**, m.p. 120–125°. An analytical sample prepared by 4 recrystallizations from isopropanol had m.p. 122–124° and spectra identical with those of the sample above. (Found: C, 63·18; H, 6·87. Calc. for $C_{17}H_{22}O_6$: C, 63·34; H, 6·88%).

Oxidation of **43** *with selenium dioxide*

Formation of **44**. Compound **43** (16 mg) was fused with freshly prepared SeO_2 (3 mg) at ca. 150° for 10 hr. The reaction mixture was cooled and taken up in $CHCl_3$. The $CHCl_3$ soln was filtered to remove Se and evaporated to leave 17 mg of yellow crystalline residue. Recrystallization from isopropanol gave yellow needles, m.p. 199–202°. An analytical sample, prepared by 3 recrystallizations from isopropanol, had m.p. 200–203·5°; $\lambda_{max}^{CHCl_3}$ 5·77 (br) μ; λ_{max}^{EtOH} 430 (ε 12) and 290 mμ (ε 40), no high intensity maxima > 230 mμ in basic ethanolic soln. (Found: C, 61·05; H, 6·02. Calc. for $C_{17}H_{20}O_7$: C, 60·71; H, 5·99%).

Diacetate of dimethyl shellolate (**48**)

Dimethyl shellolate (2·00 g) was dissolved in a mixture of pyridine (15 ml) and Ac_2O (15 ml), and the soln was allowed to stand at room temp for 20 hr. It was then concentrated to ca. 25 ml under reduced press at ca. 60°. $CHCl_3$ (50 ml) was added, and the soln was washed with 1N H_2SO_4 (3 × 25 ml) and sat $NaHCO_3$ aq (25 ml). Filtration through anhyd Na_2SO_4 and removal of the solvent followed by trituration of the residue with light petroleum gave the crude diacetate (2·20 g). Crystallization from cyclohexane gave 1·90 g (75%) of the diacetate, m.p. 125·5–126·7°. An analytical sample, m.p. 126–127·5°, was prepared by repeated recrystallization from cyclohexane and from MeOH; $\lambda_{max}^{CHCl_3}$ 5·76 (br) and 6·09 μ; λ_{max}^{EtOH} 223 mμ (ε 8500). (Found: C, 61·41; 61·39; H, 6·94, 6·91; $COCH_3$, 20·57. Calc. for $C_{21}H_{28}O_8$: C, 61·75; H, 6·91; $COCH_3$, 21·18%).

Ozonolysis of the diacetate of dimethyl shellolate

Formation of the methyl ester of **49**. The diacetate of dimethyl shellolate (1·90 g) was dissolved in MeOH (75 ml) and treated with a stream of ozonized O_2 at −78°. After 0·5 hr the soln was blue, and excess O_3 was swept out with a stream of N_2. H_2O_2 (30%, 5 ml) and 1N NaOH (5 ml) were added. More 1N NaOH (30 ml) was added until the soln remained basic. After the soln had stood overnight a further 10 ml of 1N NaOH was added, and the soln was boiled under refluxed for 1 hr. It was cooled, neutralized with dil H_2SO_4 and concentrated to ca. 40 ml at 40° under reduced press. The concentrate was extracted with EtOAc (ca. 70 ml in 6 portions). The extracts were dried over $MgSO_4$ and yielded 1·55 g of semicrystalline residue on removal of solvent. Repeated recrystallization of this material gave a sample of the acid, m.p. 248–255°. This was converted to the methyl ester with diazomethane in MeOH–ether, and the ester was recrystallized 6 times from MeOH to give an analytical sample, m.p. 158·5–159·5°; $\lambda_{max}^{CHCl_3}$ 5·66 and 5·80 μ. (Found: C, 61·08; H, 6·18. Calc. for $C_{15}H_{18}O_6$: C, 61·21; H, 6·17%).

Oxidation of dimethyl shellolate with chromium trioxide in acetic acid

(i) *Formation of* **46**. Dimethyl shellolate (1·00 g) dissolved in glacial AcOH (20 ml) was treated with a soln of CrO_3 (632 mg) in AcOH (75 ml) and 50% (v/v) H_2SO_4 aq (1 ml). The reaction mixture became warm, and the yellow colour of the oxidizing agent disappeared in ca. 5 min. After standing for 15 min the soln was concentrated under reduced press, and the residue was taken up in water (25 ml) and EtOAc (150 ml). The phases were separated and the organic layer was washed with water (25 ml) and sat $NaHCO_3$ aq (3 × 25 ml). The combined bicarbonate extracts were washed with EtOAc (25 ml). Brine (10 ml) was added to the bicarbonate soln, which was then made strongly acid with 50% H_2SO_4 (6 ml) and extracted with EtOAc (3 × 25 ml). The EtOAc soln was dried over $MgSO_4$, and the solvent was removed to leave a yellowish resin (0·53 g). Crystals (365 mg) of **45** were deposited when this product was allowed to stand overnight with water (5 ml); $\lambda_{max}^{CHCl_3}$ 3–4, 5·82, 5·94, and 6·24 (w) μ. Attempted recrystallization from aqueous EtOH led to partial conversion of **45** to **46**. The resulting mixture was treated with *p*-toluenesulfonic acid monohydrate (29 mg) in boiling benzene (25 ml) under reflux for 2 hr. The benzene soln was cooled, washed with sat $NaHCO_3$aq (10 ml) and brine (10 ml), and filtered through anhyd Na_2SO_4. Removal of the benzene left 230 mg of oil which gave **46** (160 mg, 15%), m.p. 147·5–151·5°, on crystallization from MeOH. Two recrystallizations from MeOH and sublimation in high vacuum gave an analytical sample, m.p. 145–147·5°; $\lambda_{max}^{CHCl_3}$ 5·56 and 5·80 μ; no high intensity UV maximum > 220 mμ. (Found: C, 60·56; H, 6·28. Calc. for $C_{17}H_{20}O_7$: C, 60·71; H, 5·99%).

(ii) *Formation of* **47**. Dimethyl shellolate (2·00 g) in AcOH (40 ml) was treated with a soln of CrO_3 (1·24 g) in a mixture of AcOH (140 ml) and 50% H_2SO_4 (1 ml). After 15 min the remaining CrO_3 was destroyed with MeOH (1 ml), and the soln was evaporated to dryness under reduced press at 70°. The residue was taken up in water (3 ml) and EtOAc (150 ml). The EtOAc layer was separated, washed with water (25 ml) and brine, dried over $MgSO_4$, and evaporated to leave 2·00 g of yellow-green oil. The oil was treated with MeI (10 ml) and anhyd K_2CO_3 (7·0 g) in refluxing acetone (100 ml) for 8·5 hr. More MeI (10 ml) was added in two portions during this time. The K_2CO_3 was filtered off, and the solvent was removed under reduced press. The residue was taken up in EtOAc (75 ml), and the soln was washed with $NaHCO_3$ aq (25 ml) and brine (25 ml), and dried over $MgSO_4$. Removal of the solvent left 1·73 g of yellow paste. This was dissolved in benzene (4 ml) and chromatographed on alumina (Woelm III, neutral, 40 g). The material eluted with benzene was crystallized from ether–light petroleum to give **47** (1·03 g, 48%), m.p. 98–99·5°. Three recrystallizations from ether–light petroleum gave an analytical sample, m.p. 99·5–100·2°; $\lambda_{max}^{CHCl_3}$ 5·78, 5·93, and 6·10 μ; λ_{max}^{EtOH} 240 mμ (ε 8700). (Found: C, 61·51; H, 6·46. Calc. for $C_{18}H_{22}O_7$: C, 61·70; H, 6·33%).

Reaction of dimethyl shellolate with methanolic sodium methoxide

Formation of **50**. Dimethyl shellolate (5·00 g) was added to a soln of Na (1·90 g) in anhyd MeOH (ca. 50 ml), and the soln was boiled under reflux for 9·5 hr. The soln quickly became red, and subsequently the colour gradually deepened. The final, deep purple soln was allowed to stand for 12 hr and then made slightly acidic with methanolic HCl, when its colour changed to yellow. The soln was concentrated under reduced press to ca. 10 ml, diluted with EtOAc (50 ml), and washed with half-saturated brine (40 ml), water (2 × 10 ml), half-saturated brine (20 ml), and saturated brine (10 ml). Removal of solvent from the EtOAc soln gave a yellow gum (3·60 g). Treatment of this with benzene–ether precipitated a solid (0·30 g) which, when recrystallized from EtOH, gave yellow needles, m.p. 296–298·5°. The remaining gum was dissolved in benzene (50 ml) and chromatographed on silica gel (Davison 923, 60 g). The material (0·90 g) eluted with 30% ether in benzene was rechromatographed on silica gel (60 g). The material (240 mg) eluted with 20% ether in benzene was recrystallized twice from MeOH to afford slightly yellow needles of **50** (0·10 g), m.p. 155–156°. Three further recrystallizations from MeOH gave an analytical sample as colourless needles, m.p. 155–155·5°, $\lambda_{max}^{CHCl_3}$: 5·8 μ (br); no high intensity ultraviolet maximum > 220 mμ. (Found: C, 65·42; H, 6·98. Calc. for $C_{16}H_{20}O_5$: C, 65·74; H, 6·90%).

Shellolic acid dilactone (**52**)

Shellolic acid (3·50 g) was treated with anhyd NaOAc (1·50 g) and Ac_2O (15 ml) in boiling benzene (400 ml) under reflux for 2 hr. The cooled soln was filtered through Na_2CO_3 (3·00 g) and concentrated to a yellowish oil. Trituration with light petroleum (ca. 25 ml) gave a semi-solid residue, which was crystallized from benzene–ligroin to give the dilactone (1·67 g, 54%), m.p. 160–165° (sintering at 156°). Four recrystallizations from isopropanol and sublimation in high vacuum gave an analytical sample, m.p. 147–151°; $\lambda_{max}^{CHCl_3}$ 5·65 (sh) and 5·74 μ; its UV spectrum showed only end absorption. (Found: C, 69·55; H, 6·34. Calc. for $C_{15}H_{16}O_4$: C, 69·21; H, 6·20%).

Hydrolysis of **52**

Reconversion to shellolic acid. The dilactone **52** (18 mg) was warmed with 1N NaOH (1 ml) until it dissolved. After standing for a few min, the soln was acidified with dil H_2SO_4. The resulting soln on standing deposited shellolic acid (10 mg), identified by its IR spectrum and m.p. Shellolic acid was also formed when the dilactone was warmed with $NaHCO_3$ aq for 1 hr.

Partial hydrolysis of **52**

Formation of shellolic acid monolactone (**53**). The dilactone **52** (200 mg) was heated with boiling water (5 ml) under reflux for 0·5 hr. Soln was not complete so more water (5 ml) was added. Reflux was continued for a further 2·5 hr. The soln on cooling deposited crystals of **53** (90 mg), m.p. 227·5–228·5° dec (sintering at 224°). This was recrystallized 3 times from aqueous EtOH to give an analytical sample, m.p. 230–233° dec; λ_{max}^{KBr} 2·83, 3–4, 5·59, 5·85, and 6·20 μ; λ_{max}^{EtOH} 227 mμ (ε 5500). (Found: C, 64·61; H, 6·62. Calc. for $C_{15}H_{18}O_5$: C, 64·73; H, 6·52%).

Hydrogenation of dimethyl shellolate

Formation of dihydroshellolic acid dilactone (**54**). Dimethyl shellolate (1·00 g) was hydrogenated in ethanolic soln over prereduced 10% Pd-C (0·20 g) at room temp and atm press. After 25 hr 1·07 molar equiv of H_2 had been consumed. The catalyst was filtered off with the use of Supercel, and the solvent was removed under reduced press. The residue was taken up in benzene (50 ml), and the soln was boiled under reflux for 2 hr with a trace of *p*-toluenesulfonic acid. The cooled soln was washed with sat $NaHCO_3$aq (25 ml) and brine (25 ml). It was then filtered through anhyd Na_2SO_4 and stripped of solvent. The residue solidified when triturated with light petroleum. Crystallization from a small amount of ether gave 574 mg (74%) of **54**, m.p. 153–157°. An analytical sample, prepared by recrystallization from isopropanol and benzene–light petroleum, was obtained as stubby prisms, m.p. 154–155·5°; $\lambda_{max}^{CHCl_3}$ 5·63 and 5·72 μ; no UV maxima > 220 mμ. (Found: C, 68·91; H, 7·01. Calc. for $C_{15}H_{18}O_4$: C, 68·68; H, 6·92%).

Fusion of dimethyl shellolate with potassium hydroxide

(i) *Isolation of the dihydrocoumarin* **28**. Dimethyl shellolate (2·00 g) was fused with KOH (20·0 g) in a nickel crucible for 50 min at 290–320°. This reaction was repeated and the two dark brown melts were cooled and together dissolved in a minimal amount of water. The soln was acidified with 50% (v/v) H_2SO_4, and the ppt of inorganic salts was filtered off and washed with water and EtOAc. The original aqueous soln was extracted with EtOAc (175 ml, including the EtOAc used to wash the ppt, in 3 portions). The organic extracts were stripped of solvent to leave a tarry residue (3·40 g). This was boiled with water (20 ml) and conc HCl (2·0 ml) for 2·3 hr. The soln deposited a dark tar on cooling. This material was extracted with EtOAc (4 × 25 ml). Drying of the EtOAc extract over $MgSO_4$ and concentration left a residue which on standing for 4 days at room temp with benzene–$CHCl_3$ gave a dark tan solid (1·00 g). Two recrystallizations from dil aqueous EtOH gave **28** as a yellow solid (286 mg), m.p. 190–195°. More material could be obtained by chromatography of the contents of the mother liquors on silica gel and elution with 3% MeOH in benzene. For analysis a sample was recrystallized 3 times from water with charcoal treatment and then 4 times from EtOAc–cyclohexane (1:1); the product had m.p. 199·5–201·5°; λ_{max}^{KBr} 3–4, 5·63, 5·88, and 6·31 μ; λ_{max}^{EtOH} 237 (ε 10,000), 282 (ε 1900), and 290 mμ (ε 1800). (Found: C, 61·48; H, 5·55. Calc. for $C_{15}H_{16}O_6$: C, 61·64; H, 5·52%).

(ii) *Isolation of* m-*hydroxybenzoic acid*. Dimethyl shellolate (2·50 g) was ground with KOH (20·0 g). The mixture was placed in a nickel crucible in a Wood's metal bath preheated to 305°. It foamed vigorously for ca. 20 min. Heating was continued at 300–320° for an additional 1 hr. The melt was cooled and dissolved in water (80 ml); the soln was acidified with 50% H_2SO_4 (18 ml. The ppt of inorganic salts was filtered off and washed with EtOAc (75 ml). The aqueous filtrate was extracted with EtOAc (5 × 50 ml). The combined organic extracts were dried and stripped of solvent to leave a tan foam (2·19 g). Chromatography of a soln in 1:1 EtOAc–benzene (10 ml; a further 10 ml of the solvent mixture was used to wash the soln onto the column) on silica (Davison 923. 1·7 × 45 cm) with initial elution with benzene resolved the mixture into 4 fractions. The material (60 mg) eluted with 20% EtOAc in benzene was recrystallized twice from ether light petroleum sublimed. and crystallized again from ether light petroleum to give *m*-hydroxybenzoic acid (24 mg), m.p. 199–200°, undepressed on admixture with authentic *m*-hydroxybenzoic acid. The IR spectra of the two samples were identical.

The second fraction (0·30 g), eluted with 25% EtOAc in benzene, was the dihydrocoumarin **28**. Recrystallization twice from aqueous EtOH and twice from acetone–light petroleum gave a small amount of material, m.p. 196–199·5°.

The third fraction (0·50 g), eluted with 35% EtOAc in benzene, yielded, after being washed with cold ether and twice crystallized from water, an off-white solid (93 mg), m.p. 169–174° with resolidification and remelting at 199–203°.*

The fourth fraction was eluted with 50% EtOAc in benzene. It could not be induced to crystallize and was not examined further.

Dimethyl ester of **28**

The dihydrocoumarin **28** (0·10 g) in MeOH was treated with excess ethereal diazomethane to give the dimethyl ester. Two crystallizations from ether light petroleum gave 0·030 g of the ester, m.p. 59·5–61°. Three further recrystallizations from this solvent mixture gave an analytical sample, m.p. 61–62°; $\lambda_{max}^{CCl_4}$ 5·67, 5·80, 6·20, and 6·37 μ. (Found: C, 63·64; H, 6·13. Calc. for $C_{17}H_{20}O_6$: C, 63·72; H, 6·29%).

Reaction of **28** *with dimethyl sulfate and sodium hydroxide*

The dihydrocoumarin **28** (579 mg) was dissolved in 1N NaOH (6 ml). Me_2SO_4 (freshly distilled, 1·15 ml) was added. More 1N NaOH (10 ml) was added in portions to the stirred soln over the course of 1 hr.

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* This is considered to be the parent phenolic tricarboxylic acid of the lactone **28**.

while the pH of the soln was allowed to drop frequently to 5. After standing for 40 hr at room temp, the mixture deposited no solid. More 1N NaOH (5 ml) was added, and the mixture was boiled reflux for 5 hr. The soln was saturated with $(NH_4)_2SO_4$, acidified with 50% H_2SO_4, and extracted with EtOAc. The dried extract was stripped of solvent to leave a residue that on being washed with cold EtOAc ether, and crystallized from dil aqueous EtOH gave crystals, m.p. 202–209·5°. Recrystallization from dil aqueous EtOH 3 times, chromatography over silica, and 3 recrystallizations from water with charcoal treatment gave an analytical sample, m.p. 206·5–209·5°, λ_{max}^{KBr} 3–4, 5·8 5·9, 6·21, and 6·33 μ; λ_{max}^{EtOH} 296 (ε 3880) and 246 mμ (ε 11,300); optically inactive at 546, 589, and 486 mμ. (Found: C, 59·15; H, 6·43; OCH_3, 9·61; neut. equiv. 110. Calc. for $C_{15}H_{17}O_6(OCH_3)$: C, 59·25; H, 6·22; OCH_3, 9·55%).

Dehydrogenation of **28**

Formation of the coumarin **36**. The dihydrocoumarin **28** (200 mg) was mixed with 10% Pd-C (200 mg), and the mixture was heated at 175–215° for 7·25 hr. It was then cooled and extracted with hot MeOH (10 ml), and the MeOH was distilled to leave 137 mg of yellow oil which was esterified with ethereal diazomethane in MeOH–ether. Recrystallization from ether gave **36** as needles (130 mg, 65%), m.p. 114·5–116·5°. This was treated with charcoal in MeOH and recrystallized from MeOH to give an analytical sample, m.p. 115–116·5°, undepressed on admixture with the synthetic sample of coumarin **36** (*vide infra*); $\lambda_{max}^{CHCl_3}$ 5·7–5·90 and 6·20 μ; λ_{max}^{EtOH} 336 (sh, ε 5300), 324 (ε 8300), 315 (sh, ε 7700), 296 (ε 16,200), 284 (ε 18,200), and 275 mμ (sh, ε 13,300). (Found: C, 64·21; H, 5·74. Calc. for $C_{17}H_{18}O_6$: C, 64·14; H, 5·70%).

Treatment of **28** *with copper and quinoline*

Formation of **27**. The dihydrocoumarin **28** (100 mg) and copper bronze (washed with ether, 100 mg) were heated in boiling quinoline (Eastman Kodak synthetic, redistilled) under reflux for 9 hr. The mixture was cooled and extracted with ether, and the copper was filtered. The quinoline was removed by extraction with dil HCl, and the acidic material was removed by extraction with $NaHCO_3$ aq. The ether was distilled to leave the neutral material (38 mg). Distillation at 150–165° at the water aspirator gave an oil (32 mg), which slowly deposited crystalline material (9 mg) from a mixture of water, MeOH, and ether. This material together with 10 mg from a similar experiment were recrystallized 4 times from cyclohexane and sublimed to give an analytical sample, m.p. 102·5–104°; $\lambda_{max}^{CHCl_3}$ 5·70, 5·80, 6·18, and 6·28 μ; λ_{max}^{EtOH} 274 (ε 930), 226 mμ (ε 920), and strong end absorption. (Found: C, 72·75; H, 6·10. Calc. for $C_{14}H_{14}O_3$: C, 73·20; H, 6·13%).

4-(2-*Hydroxy-4-methylbenzoyl*)*butyric acid* (**30**)

γ-Carbomethoxybutyryl chloride (139·7 g, 0·85 mole) (**35**) was mixed with *m*-cresol [purified via *m*-cresyl benzoate (**36**); 91·5 g, 0·84 mole], and the mixture was allowed to stand at room temp for 2 hr. It was then heated on a steam bath until HCl evolution was slow (1 hr). Tetrachloroethane (500 g) and $AlCl_3$ (267 g, 2·00 mole) were added in portions. There was copious evolution of HCl, and the solvent refluxed. After the reaction had subsided, the mixture was heated at 130–140° for 1·5 hr, allowed to cool slightly, and treated with dil HCl (1 l.). Most of the tetrachloroethane was steam distilled (2 hr). The remaining mixture was cooled on ice, and the brown solid (ca. 197 g) that separated was collected and washed with water (300 ml). This material was extracted with hot EtOH (500 ml), and the residue was washed with more EtOH (200 ml). A tan powder (24 g), m.p. 180–185°, $\lambda_{max}^{CHCl_3}$ 3–4, 6·10, and 6·35 μ, remained. Charcoal (10 g) was added to the combined hot ethanolic extract and washings; the mixture was filtered, and the charcoal was washed with MeOH (200 ml). Water (0·8 l.) was added to the combined alcoholic filtrate and washings. The ppt that deposited when the mixture was cooled was crystallized from benzene to give the crude keto acid **30** (52 g, 28%), m.p. 138–145°. Five recrystallizations gave an analytical sample, m.p. 140–141·5°; $\lambda_{max}^{CHCl_3}$ 3–4, 5·83, and 6·10 μ; λ_{max}^{EtOH} 325 (ε 4370) and 263 mμ (ε 13,400). (Found: C, 64·84; H, 6·35. Calc. for $C_{12}H_{14}O_4$: C. 64·85: H. 6·35%).

Methyl 4-(2-*methoxy-4-methylbenzoyl*)*butyrate* (**31**)

The acid **30** (1·00 g) was treated in boiling acetone (50 ml) under reflux with K_2CO_3 3·0 g) and Me_2SO_4 (1·5 ml) with stirring for 15 hr. The K_2CO_3 was filtered, and the filtrate was concentrated to a yellow oil (1·2 g), which was taken up in ether (40 ml). The ethereal soln was washed with saturated $NaHCO_3$ aq (10 ml), water (10 ml), and brine (10 ml), and dried over $MgSO_4$. The solvent was distilled and the residue was crystallized from ether light petroleum in an ice–salt bath to give **31** (875 mg, 78%). m.p. 37·5–38·5°. An analytical sample, prepared by 3 recrystallizations from ether light petroleum, had m.p. 38·5–39·2°; $\lambda_{max}^{CHCl_3}$ 5·74, 5·98, and 6·22 μ; λ_{max}^{EtOH} 307 (ε 4360), 255 (ε 10,200), and 215 mμ (ε 18,700). (Found: C, 67·26; H, 7·32. Calc. for $C_{14}H_{18}O_4$: C, 67·18; 7·25%).

4-(3-Carboxypropyl) 3,7-dimethylcoumarin (32)

Zn (2·50 g) was washed with dil HCl, water, acetone, and ether and dried briefly. It was added to a soln of **31** (4·00 g) and ethyl α-bromopropionate (4·0 ml) in benzene (50 ml). The mixture was refluxed for 23 hr during which time further ethyl α-bromopropionate (4·0 ml) and Zn (1·00 g) were added in portions. The reaction mixture was acidified with glacial AcOH, washed with water (4 × 25 ml), and extracted with 5% $NaHCO_3$aq (2 × 25 ml). Acidification of the bicarbonate extract, extraction with EtOAc (4 × 25 ml), drying over $MgSO_4$, and removal of solvent gave a yellow oil (4·66 g). Treatment of 4·20 g of this oil with a boiling mixture of glacial AcOH (15 ml) and 48% HBr (15 ml) under reflux for 1 hr gave a dark green soln, which was partitioned between water (100 ml) and ether (100 ml). The aqueous phase was washed with ether (50 ml), and the combined ethereal extracts were washed with water (4 × 50 ml). Drying with $MgSO_4$, removal of solvent and crystallization from EtOAc gave the coumarin **32** (1·10 g, 26%), m.p. 160·5–161·5°. Three recrystallizations from EtOAc gave an analytical sample· m.p. 160·5–161·5°; $\lambda_{max}^{CHCl_3}$ 3–4, 5·84, and 6·20 μ; λ_{max}^{EtOH} 315 (br, ε 10,200), 288 (ε 10,600), and 281 mμ (ε 10,400). (Found: C, 69·36; H, 6·16. Calc. for $C_{15}H_{16}O_4$: C, 69·21; H, 6·20%).

Hydrogenation of 32

Preparation of 4-(*3-carboxypropyl-3,4-dihydro-3,7-dimethylcoumarin* (33). Hydrogenation of the coumarin **32** (0·50 g) in glacial AcOH (20 ml) over a prereduced PtO_2 catalyst (133 mg) at atm press and temp proceeded without any break in the hydrogenation curve after the uptake of one molar equiv of H_2.* The product mixture which had taken up ca. 2 molar equivs of H_2, was dissolved in benzene and chromatographed on silica (Davison 923, 2 × 16·5 cm). Elution with 1% MeOH in benzene and crystallization from ether–light petroleum gave **32**, m.p. 120·5–121·5°, in low yield. Recrystallizations from EtOAc–cyclohexane gave an analytical sample, m.p. 121–121·5°; $\lambda_{max}^{CHCl_3}$ 3–4, 5·70, 5·84, 6·16, and 6·33 μ; λ_{max}^{EtOH} 277 (ε 800), 268 (ε 760), and 263 mμ (ε 595). (Found: C, 68·40: H, 6·85. Calc. for $C_{15}H_{18}O_4$· C, 68·68: H, 6·92%).

Methyl 4-(4-carbomethoxy-2-methoxybenzoyl)butyrate (34)

The ester **31** (1·79 g) was treated in boiling CCl_4 (50 ml) under reflux with N-bromosuccinimide (84 mg) and azobisisobutyronitrile (12 mg) for 0·5 hr. The reaction mixture was cooled, and the succinimide was filtered. Removal of the solvent left a yellow oil (1·80 g), which was taken up in cold MeCN $AgNO_3$ (1·00 g) in water (15 ml) was added to the MeCN soln and the mixture was heated on the steam bath for 0·5 hr. The Ag ions remaining in soln were precipitated with NaCl aq, and the silver halides were filtered and washed with acetone. The combined filtrate and washings were concentrated under reduced press, and the yellow oil that separated was extracted with ether (4 × 10 ml). After being dried over $MgSO_4$ and stripped of solvent, the ethereal extract gave 1·33 g of oil. The oil (10·1 g) obtained from 10·0 g of **31** in a similar experiment was dissolved in AcOH (50 ml). A soln of CrO_3 (5·1 g) in water (10 ml), conc H_2SO_4 (4 ml), and AcOH (150 ml) was added slowly (0·5 hr) with stirring to the AcOH soln of the reaction product. After the soln had stood for a further 0·5 hr, MeOH (5 ml) was added. The ppt was filtered and washed with AcOH (20 ml). The EtOAc extract obtained by partitioning the filtrate and washings between EtOAc (1 l.) and water (200 ml) was washed with water (3 × 500 ml) and dried over $MgSO_4$. The dried soln was concentrated under reduced press until 24 g of yellow oil remained. This oil was dissolved in a mixture of anhyd MeOH (500 ml) and methanolic HCl (18 g HCl in 100 ml), and the soln was boiled under reflux for 3 hr. After being cooled the soln was neutralized with methanolic NaOH; the ppt was filtered, and the filtrate was concentrated under reduced press. The residue was taken up in ether, the remaining NaCl was filtered, and the ether was removed to leave a brown oil (8·7 g). A soln of this oil in benzene was filtered through a column of alumina (Merck acid-washed, 50 g). The eluate was stripped of solvent, and the residue was crystallized from ether–light petroleum to yield 2·00 g of crude product, which was recrystallized from MeOH to give **34** (1·79 g), m.p. 77·5–78·5°. Three recrystallizations from MeOH gave an analytical sample, m.p. 78–79°; $\lambda_{max}^{CHCl_3}$ 5·79, 5·96, and 6·36 μ; λ_{max}^{EtOH} 320 (ε 3900) and 254 mμ (ε 12,800). (Found: C, 61·14; H, 6·19. Calc. for $C_{15}H_{18}O_6$: C, 61·21; H, 6·17%).

7-Carboxy-4-(3-carboxypropyl)-3-methylcoumarin (35)

The diester **34** (500 mg), ethyl α-bromopropionate (0·50 ml), and Zn (30 mesh, washed with dil HCl, water, EtOH, and ether, and dried; 500 mg) were heated in boiling benzene (10 ml) and ether (5 ml) under reflux for 2 hr. There was an apparent induction period of ca. 0·5 hr; after ca. 1 hr a ppt formed. The reaction mixture was treated with 1M H_2SO_4 (15 ml) and extracted with ether (20 ml). The organic phase was

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* A Pd-C catalyst was ineffective, as was Pt in EtOH.

washed with water (10 ml) and brine (10 ml) and filtered through anhyd Na_2SO_4. Removal of the solvent left 728 mg of an oil, which was triturated with light petroleum to leave 570 mg of oil. This material was heated under reflux with boiling AcOH (5 ml) and 48% HBr (5 ml) for 3·5 hr. The course of the reaction was followed by measuring the UV spectrum of aliquots removed periodically. The reaction was very nearly completed after 3·5 hr, when the ratio of the height of the peak at 250 mμ due to the starting material to that of peak due to the product at 284 mμ had become nearly constant. The cherry red soln was cooled, and water (20 ml) and EtOAc (30 ml) were added. The phases were separated, and the aqueous phase was washed with EtOAc (10 ml). The combined EtOAc solns were washed with water (4 × 10 ml) and brine (10 ml) and dried over $MgSO_4$. Removal of the solvent left a residue (530 mg) that afforded 230 mg of greenish yellow powder on treatment with ether. Treatment of a methanolic soln of this material with charcoal and 5 recrystallizations from MeOH gave **35** (95 mg), m.p. 248–249·5°; λ_{max}^{KBr} 3–4, 5·8–5·9, and 6·21 μ; λ_{max}^{EtOH} 335 (sh, ε 5100), 323 (ε 8000), 315 (sh, ε 7500), 296 (ε 15,400), and 284 mμ (ε 17,600). (Found: C, 62·07; H, 4·86. Calc. for $C_{15}H_{14}O_6$: C, 62·06; H, 4·86%).

7-Carbomethoxy-4-[3-(carbomethoxy)propyl]-3-methylcoumarin (**36**)

The residues (ca. 0·40 g) from the recrystallization of the acid **35** were treated in MeOH with ethereal diazomethane at 0°. The solvents were removed, and the residue was taken up in $CHCl_3$ (35 ml). The soln was passed through a column of acid-washed alumina (Merck, 5 g). Removal of the solvent and crystallization from MeOH–ether afforded a yellow solid (142 mg). Five recrystallizations from MeOH with charcoal treatment gave **36** (97 mg), m.p. 115·5–116·2°; $\lambda_{max}^{CHCl_3}$ 5·7–5·90 and 6·20 μ; λ_{max}^{EtOH} 336 (sh, ε 5200), 324 (ε 8200), 315 (sh, ε 7800), 296 (ε 16,200), 284 (ε 18,000), 275 mμ (sh, ε 13,000). (Found: C, 64·18; H, 5·69. Calc. for $C_{17}H_{18}O_6$, C, 64·14; H, 5·70%).

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