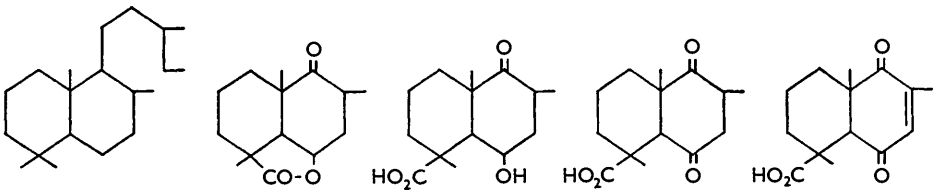
578. *Marrubiin. Part I.*[1] *Oxidation Products.*

By D. G. Hardy, W. Rigby, and (in part) D. P. Moody.

Conditions are defined for the degradation of marrubiin, through tetrahydromarrubiin, to the keto-lactone $C_{14}H_{20}O_3$: new by-products are reported, notably a derivative of tetrahydrofurylacetaldehyde. Reactions of the keto-lactone are shown to be consistent with its formulation as (II). The major product of oxidation of marrubic acid by alkaline permanganate is the hydroxy-acid $C_{17}H_{26}O_5$; the simultaneous production of formic acid is consistent with degradation of a furan ring. Oxidation of the known keto-acid $C_{17}H_{24}O_5$ gives a hydroxy-keto-lactonic acid $C_{17}H_{24}O_6$ which can be decarboxylated with alkali to yield two hydroxy-keto-lactones $C_{16}H_{24}O_4$: formulæ for these substances are discussed.

It has long been known that marrubiin is a lactone and a tertiary alcohol, and that the lactone group is derived from a secondary alcohol group. The only compounds of known structure which have been obtained by degradation of marrubiin are 1 : 2 : 5-trimethylnaphthalene,[2,3] acetone (in traces),[4] and perhaps acetaldehyde.[4] Lawson and Eustice,[2] and Hollis, Richards, and Robertson,[3] proposed the carbon skeleton (I) which is at present accepted, and Cocker, Cross, Duff, and Holley [5] suggested that the long side-chain carried a furan ring, accounting for the spectral properties and the loss of three carbon atoms on oxidation.

Analogy leads to the suggestion that the carboxyl group of marrubic acid will be derived from a *gem.*-dimethyl group. We have found [1] that marrubiin is a γ-lactone (absorption maximum at 1780 cm.$^{-1}$ in CS_2) (cf. Cocker *et al.*[6]).



(I) (II) (III) (IV) (V)

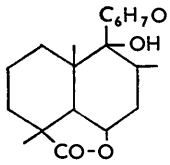
Tetrahydromarrubiin was prepared by Lawson and Eustice [2] and by Hollis, Richards, and Robertson [3] by hydrogenation of marrubiin. We find that the hydrogenation gives a 60% yield of a tetrahydromarrubiin of m. p. 123·5° (*ca.* 10° lower than reported before [2,3]); the remainder of the material is largely accounted for as two hexahydromarrubiins, m. p. 80° and 154°, respectively, which presumably arise by opening of the hydrofuran ring. We have oxidised tetrahydromarrubic acid to the corresponding keto-acid and have worked out satisfactory conditions for the conversion of tetrahydromarrubiin into anhydrotetrahydromarrubiin: anhydrotetrahydromarrubiin gives an epoxide, $C_{20}H_{30}O_4$, when oxidised with potassium permanganate in acetic acid.

By oxidising anhydromarrubiin Ghigi [7] obtained a compound $C_{14}H_{20}O_3$. As it seemed likely that the six carbon atoms lost in its formation represented the side chain, we have used this substance to investigate the ring system of marrubiin.[1] Anhydromarrubiin could only be prepared in moderate yield from marrubiin, and we find that the compound $C_{14}H_{20}O_3$ is best made by ozonolysis of anhydrotetrahydromarrubiin: the other product

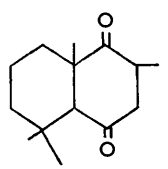
[1] Cf. Hardy and Rigby, *Chem. and Ind.*, 1953, 1150.
[2] Lawson and Eustice, *J.*, 1939, 587.
[3] Hollis, Richards, and Robertson, *Nature*, 1939, **143**, 604.
[4] Ghigi, *Gazzetta*, 1951, **81**, 336.
[5] Cocker, Cross, Duff, and Holley, *Chem. and Ind.*, 1952, 827.
[6] Cocker, Cross, Duff, Edward, and Holley, *J.*, 1953, 2540.
[7] Ghigi, *Gazzetta*, 1948, **78**, 856.

of the ozonolysis should be a tetrahydrofurylacetaldehyde, and a 2 : 4-dinitrophenylhydrazone of the appropriate empirical composition has been isolated. The compound $C_{14}H_{20}O_3$ has an ultraviolet absorption maximum at 2950 Å and infrared absorption maxima at 1782 and 1718 cm.$^{-1}$ (in CS_2), indicating that it is a keto-γ-lactone and suggesting its formulation as 8-hydroxy-1 : 6 : 10-trimethyl-5-oxodecalin-1-carboxylic lactone (II).[cf. 1, 6] In an attempt to confirm this formula, the lactone was hydrolysed to the acid (III), which was oxidised to 1 : 6 : 10-trimethyl-5 : 8-dioxodecalin-1-carboxylic acid (IV); this was dehydrogenated by selenium dioxide to a yellow compound 1 : 6 : 10-trimethyl-5 : 8-dioxo-Δ^6-octalin-1-carboxylic acid (V) which when reduced by zinc and acetic acid regenerated the diketo-acid (IV). Its absorption maximum at 2420 Å is consistent with the formulation of the enedione as (V); the enedione system cannot be fully transoid.[8] If it is assumed that no rearrangements occur during the conversion of marrubiin into the keto-lactone (II), the formula of marrubiin will be (VI).

When the diketo-acid (IV) was boiled with acetic anhydride, the mixed anhydride (VII) was formed. If sodium acetate was also present, the product was the lactol-acetate (VIII) together with some enol-lactone (IX); pyrolysis of the lactol acetate also gave the enol-lactone.



(VI)



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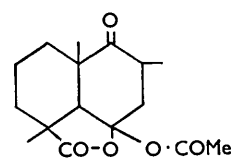

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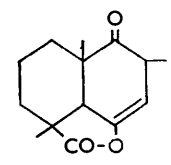
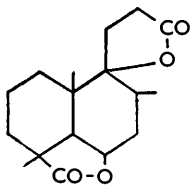
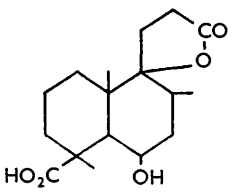


(IX)

By oxidising sodium marrubate with permanganate, Ghigi obtained an acid "$C_{17}H_{22}O_5$," and by oxidising marrubiin with chromic acid a lactone "$C_{17}H_{22}O_4$." We [1] (cf. Cocker *et al.*[6]) have shown that Ghigi had at different times [4, 7, 9] worked with two acids and had later confused them. When marrubic acid is oxidised with alkaline permanganate, formic acid is produced in considerable amount; this is consistent with the presence of a furan ring in the side-chain : the other main product of this oxidation is a hydroxy-acid $C_{17}H_{26}O_5$ (corresponding to Ghigi's [9] acid "$C_{13}H_{20}O_4$") which can be dehydrated to the lactone $C_{17}H_{24}O_4$ and has a methyl ester of m. p. 154°. Oxidation of the hydroxy-acid gives a keto-acid $C_{17}H_{24}O_5$ (corresponding to Ghigi's [9] acid "$C_{13}H_{18}O_4$") which has a methyl ester of m. p. 165·5°. At variance with Cocker *et al.*,[6] we find that the ultraviolet



(X)



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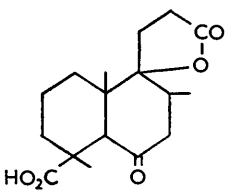

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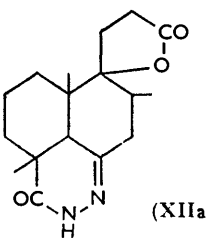


(XIIa)

absorption of this acid is normal ($\lambda_{max.}$ 2820 Å). The dilactone $C_{17}H_{24}O_4$ shows only one infrared absorption maximum in the carbonyl-stretching region (1778 cm.$^{-1}$ in CS_2) and so contains two γ-lactone groups. One of these is relatively difficult to open hydrolytically and the resulting acid is stable : it evidently corresponds to the original lactone group of marrubiin. The other readily comes into equilibrium with its acid in solution; this

[8] Campbell and Harris, *J. Amer. Chem. Soc.*, 1941, **63**, 2721; Barton, Fawcett, and Thomas, *J.*, 1951, 3147.

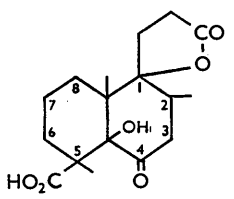
[9] Bernardi and Ghigi, *Ricerca sci.*, 1947, **17**, 937 (*Chem. Abs.*, 1949, **43**, 5011); Ghigi and Bernardi, *Farm. sci. e tec.* (*Pavia*), 1947, **2**, 397 (*Chem. Abs.*, 1948, **42**, 3140).

second lactone group will be derived from the long side-chain of marrubiin and the dilactone will thus be the dilactone (X). The acids $C_{17}H_{26}O_5$ and $C_{17}H_{24}O_5$ will be the γ-lactone (XI) derived from the same acid, and the γ-lactone (XII) from the corresponding keto-acid.

With hydrazine, under Wolff–Kishner conditions, the intermediate (XII) gave the cyclic hydrazone (XIIa).

By oxidation of her acid " $C_{17}H_{24}O_5$ " Ghigi obtained a lactone " $C_{14}H_{20}O_4$; " we have found that her product is a keto-dilactone $C_{17}H_{22}O_5$ and that it arises from oxidation of the keto-acid $C_{17}H_{24}O_5$ (XII) [the same substance can be obtained from the hydroxy-acid $C_{17}H_{26}O_5$ (XI), but in much smaller yield]. The primary product of the reaction is a lactonic hydroxy-keto-acid $C_{17}H_{24}O_6$ which readily lactonises in the presence of acid, and this accounts for Ghigi's failure to isolate it : the same findings have been made by Cocker *et al.*[10] The analytical data would fit either the C_{14} or the C_{17} formula for the lactone, but molecular-weight determinations exclude the former, and the C_{17} formula is confirmed when further reaction products are considered; the acetaldehyde observed by Ghigi [4] as being formed along with the lactone " $C_{14}H_{20}O_4$ " must arise in some other reaction—we have failed to detect it. By heating the keto-dilactone with alkali, Ghigi [4] obtained a lactone which was formulated as $C_{13}H_{22}O_3$; we have repeated the work and find that two isomeric substances $C_{16}H_{24}O_4$ are produced and that 1 mol. of carbon dioxide is formed during the reaction. One of these substances corresponds to Ghigi's product, and the other is converted into it by the action of alkali.

It might be expected that the compound $C_{17}H_{24}O_6$ would be the γ-lactone (XIII) or the corresponding 3-hydroxy-compound (XIV). The keto-acid $C_{17}H_{24}O_5$ (XII) gives an enol-lactone (XV) [10] (the infrared absorption maximum at 847 cm.$^{-1}$ and the absence of a maximum near 1800 cm.$^{-1}$ support the rejection by Cocker *et al.*[11] of the earlier conjectured formula [6] which had the double bond to the bridgehead), and this with osmium tetroxide gives the γ-lactone (XIV) which is not identical with the permanganate-oxidation product (a second substance $C_{17}H_{22}O_5$ is also produced in the osmium tetroxide reaction).



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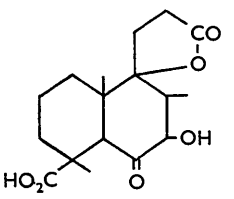

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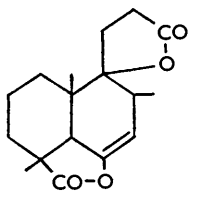
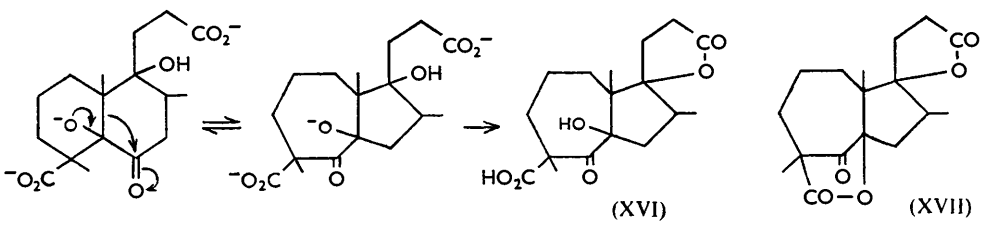


(XV)



(XVI) (XVII)

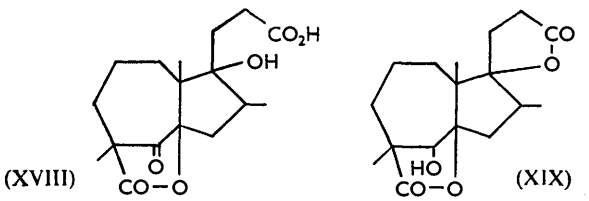
This seems to favour the formulation of the permanganate-oxidation product as (XIII); however, formula (XIII) does not allow for lactonisation of the acid, nor does it account for the decarboxylation by alkali to give the C_{16} lactone.

The transformations of the ketol system in certain steroids [11] suggested that a substance (XIII) might pass into the structure (XVI) under the conditions obtaining at its formation.

[10] Cocker, Edward, Holley, and Wheeler, *Chem. and Ind.*, 1955, 1484.
[11] Jones, Lewis, Shoppee, and Summers, *J.*, 1955, 2876; Turner, *J. Amer. Chem. Soc.*, 1953, **75**, 3484.

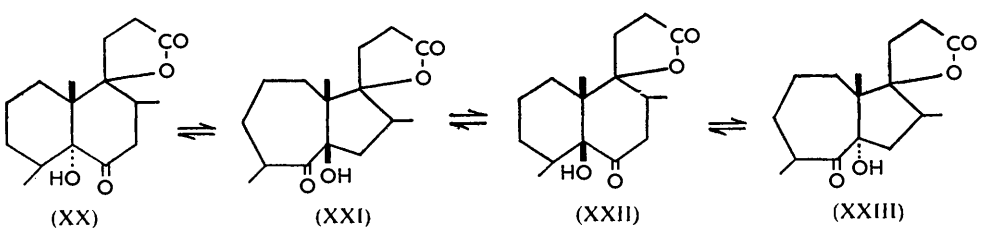
The accumulation of substituents might favour the transformation to the 7 : 5-ring system. The keto-dilactone would then be (XVII). Cocker *et al.*[10] have considered and accepted formulæ (XVI) and (XVII). However, a substance with the structure (XVI) might be expected to undergo thermal decarboxylation more readily than is observed: the acid is stable up to its m. p. (210°) and then decomposes entirely by lactonisation—there is no trace of decarboxylation. The spectral properties are also against formula (XVI). Accordingly the structure (XVIII) is proposed, which is free from these criticisms. The ring transformation will be favoured in that non-bonded repulsions involving one of the *gem.*-groups at position 5 in the structure (XIII) are replaced by chemical linkage of analogous points in structure (XVIII). Incorporation of the keto-group into the γ-lactone ring will increase the infrared absorption frequencies, and the observed maxima of 1794, 1743, and 1705 cm.$^{-1}$ will be due respectively to the exalted γ-lactone group, the exalted keto-group, and the carboxyl group (Na salt 1797 and 1754 cm.$^{-1}$). A formula with the ketone group in the *spiro*-lactone ring is excluded as the decarboxylation product fails to give the iodoform reaction. Catalytic reduction of the acid gives a hydroxy-dilactone (XIX) which has a normal γ-lactone frequency (1765 cm.$^{-1}$). The ultraviolet absorption maxima of the acid, its methyl ester, and the dilactone (all with $\lambda_{max.}$ ~2960 Å) are consistent with the large hydroxyl–carbonyl angle implicit in the formulæ. For lactonisation, the hydroxyl group and carboxyl group involved must be either both α or both β.

We find that decarboxylation of the acid is best effected by heating it (or the lactone) with alkali in 2-ethoxyethanol: strongly alkaline conditions are not needed. The two products are both keto-lactones $C_{16}H_{24}O_4$: one of these, (A), is Ghigi's compound "$C_{13}H_{22}O_3$"; it has m. p. 162°, an ultraviolet absorption maximum at 3020—3070 Å, and infrared maxima at 1778 and 1727 cm.$^{-1}$; it gives an oxime under the usual conditions and is



(XVIII) (XIX)

readily hydrogenated catalytically. The other, isomeric compound, (B), has its absorption maxima at 2820 Å and 1760 and 1710 cm.$^{-1}$, does not readily give an oxime, and does not take up hydrogen in the presence of Adams catalyst; when boiled with alkali it is converted into (A). Decarboxylation of the acid (XVIII) would be expected to give a mixture of sodium salts corresponding to (XX)—(XXIII). The labile isomer (B), which according to its ultraviolet spectrum will have a small hydroxyl–carbonyl angle, could be



(XX) (XXI) (XXII) (XXIII)

(XXI) or (XXII); the stable isomer (A) has an infrared band consistent with its having a keto-group in a six-membered ring [and the spectrum has a general similarity to that of the keto-lactone (II)], suggesting the structure (XX), and the ultraviolet absorption is consistent with this.

Catalytic reduction of the isomer (A) gave a dihydroxy-lactone [10] which was inert to periodic acid, but slowly reduced lead tetra-acetate; reduction with lithium aluminium

hydride gave the tetrol together with some of the same dihydroxy-lactone. The compound (A) was recovered after treatment with sodium triphenylmethyl, but with phenylmagnesium bromide or *tert.*-butylmagnesium chloride it gave, in low yield, a substance $C_{16}H_{24}O_4$.

With the object of correlating marrubiin with either abietic or podocarpic acid, marrubiin, the enedione (V), and the ozonide of the enol-lactone of (XII) were oxidised with nitric acid and with permanganate. The crystalline, optically inactive dimethyl-*cyclo*hexanetricarboxylic acid was not obtained, although parallel experiments carried out on abietic acid readily gave it. On this negative evidence we favour the β-configuration for the carboxyl group in marrubic acid (corresponding with that in podocarpic acid). Attempts to convert the oxidation product into the difficultly accessible methyl ester-anhydride derivable from agathenedicarboxylic acid [12] were unsuccessful; small amounts of two crystalline substances were obtained, but they could not be identified.

Experimental

Rotations were determined in B.P. chloroform and ultraviolet absorption spectra in ethanol solutions.

Hydrogenation of Marrubiin.—Marrubiin (50 g.) was hydrogenated in acetic acid (500 ml.) in the presence of 10% palladised charcoal and Adams catalyst; several grams of catalyst were needed if the reduction was to be completed in a few hours. The catalyst was removed, the solvent evaporated at reduced pressure, and a benzene solution of the residue was washed with water and transferred to a column of silica (800 g.). Elution with benzene (*ca.* 15 l.) containing 2% of alcohol gave a syrup *A* (39 g.) which crystallised, followed by a syrup *B*. Elution with benzene (3 l.) containing 10% of alcohol then gave a greenish syrup *C*. The product *A* was digested with ether (100 ml.) which removed the colour and left almost pure tetrahydromarrubiin (30 g.); after recrystallisation from ether, cineole, or ethyl acetate, the tetrahydromarrubiin had m. p. 123·5° (Lawson and Eustice [2] give m. p. 134°), $[\alpha]_D^{22}$ +31·8° (*c* 2·8) (Found: C, 70·7; H, 9·7. Calc. for $C_{20}H_{32}O_4$: C, 71·4; H, 9·6%). The products *B* and *C* crystallised very slowly under anhydrous ether at 0°. Product *B* recrystallised from ether as prisms of a *hexahydromarrubiin*, m. p. 79—80°, $[\alpha]_D^{21·5}$ +32·6° (*c* 2·7) (Found: C, 70·5; H, 10·1. $C_{20}H_{34}O_4$ requires C, 71·0; H, 10·1%). The ethereal liquor was filtered from product *C*, leaving colourless crystals (5·4 g.). Digestion of these with anhydrous ether (40 ml.) left a residue *D* (2·3 g.), m. p. 132—138°, and on concentration to 10 ml. the ethereal extract deposited crystals *E* (2·2 g.), m. p. 78—80°. Recrystallisation of material *D* from alcohol and washing with ether gave prisms of a *hexahydromarrubiin*, m. p. 153—154°, $[\alpha]_D^{21·5}$ +47·9° (*c* 2·6) (Found: C, 70·5; H, 10·2%). Recrystallisation of material *E* from ether gave more of the hexahydromarrubiin of m. p. 79—80°.

The Keto-acid $C_{20}H_{32}O_5$.—Tetrahydromarrubic acid [3] (0·333 g.) was kept at 30° with chromium trioxide (1·1 atom-equiv. of O) in 90% acetic acid (6 ml.), reaction being complete in 2 hr. The solution was evaporated, and a solution of the residue in chloroform was washed with dilute hydrochloric acid. The syrup left on evaporation of the chloroform was chromatographed on silica (30 g.) with benzene–alcohol. The benzene–4% alcohol eluate crystallised on evaporation, and recrystallisation from ethyl acetate–light petroleum gave the *keto-acid* as prisms, m. p. 159°, $\lambda_{max.}$ 2800 Å (ε 51·5) (Found: C, 68·1; H, 9·3. $C_{20}H_{32}O_5$ requires C, 68·15; H, 9·15%).

Anhydrotetrahydromarrubiin.—The following methods are based on those of Lawson and Eustice,[2] whose details we found inadequate.

(a) *Thionyl chloride method.* Tetrahydromarrubiin (5 g.) was boiled for 15 min. with pure thionyl chloride (12 ml.), the solution was at once evaporated in the cold, and a benzene solution of the residue was washed with ice-water and chromatographed on silica (80 g.). After sulphur-containing compounds had been removed by benzene, benzene containing 1% of alcohol eluted a brown band; this evaporated eluate on crystallisation from anhydrous ether gave anhydrotetrahydromarrubiin, needles, m. p. 125—126°, $[\alpha]_D^{16·5}$ +55·2° (*c* 0·9) (Found: C, 75·9; H, 9·9. Calc. for $C_{20}H_{30}O_3$: C, 75·4; H, 9·5%). The yield varied from 12 to 37%; with the

[12] Ruzicka and Bernold, *Helv. Chim. Acta*, 1941, **24**, 931.

higher yields no tetrahydromarrubiin was recovered, but up to 16% was recovered in other cases. When the reaction was carried out at 75—80°, 55% of starting material and 10% of product were obtained. (b) *Phosphorus trichloride method.* A 10% solution of phosphorus trichloride (0·44 ml.) in benzene was added to a boiling solution of tetrahydromarrubiin (2 g.) in benzene (40 ml.), and boiling was continued for 15 min. The cooled solution was washed with water and with aqueous sodium hydroxide and evaporated. When anhydrous ether was added to the residue, anhydrotetrahydromarrubiin crystallised (28—31%); if the reaction time was reduced to 5 min. some tetrahydromarrubiin was recovered. By either method of preparation the yield fell if more than 10 g. of tetrahydromarrubiin were used in an experiment.

Oxidation of Anhydrotetrahydromarrubiin.—(a) *Ozonolysis.* Anhydrotetrahydromarrubiin was ozonised at −30° in methylene dichloride, the solvent removed, and the residue decomposed with water and steam-distilled. The residual crystals were dissolved in benzene and washed with potassium hydrogen carbonate solution; evaporation of the benzene gave 8-hydroxy-1 : 6 : 10-trimethyl-5-oxodecalin-1-carboxylic lactone (II), prisms (from methanol or acetic acid) (74%), m. p. 196°, $[\alpha]_D$ +119° (*c* 1·02), $\lambda_{max.}$ 2950 Å (ε 28·4) (Found: C, 71·9; H, 8·3. Calc. for $C_{14}H_{20}O_3$: C, 71·2; H, 8·5%). The substance was brominated by bromine in acetic acid. The oxime [6] (prepared in pyridine) formed needles (from alcohol), m. p. 184—185·5° (Found: C, 67·1; H, 8·5; N, 5·8. Calc. for $C_{14}H_{21}O_3N$: C, 66·9; H, 8·4; N, 5·6%). The 2 : 4-*dinitrophenylhydrazone* (prepared in alcoholic phosphoric acid) formed needles (from ethyl acetate), m. p. 250—251·5° (Found: C, 57·55; H, 6·3; N, 13·8. $C_{20}H_{24}O_6N_4$ requires C, 57·7; H, 5·8; N, 13·5%).

The steam-distillate was extracted continuously with ether and the extracted oil gave the 2 : 4-*dinitrophenylhydrazone* of tetrahydrofurylacetaldehyde; this crystallised from alcohol in square plates, m. p. 144—145° (Found: C, 49·2; H, 4·9; N, 19·1. $C_{12}H_{14}O_5N_4$ requires C, 49·0; H, 4·8; N, 19·0%).

(b) *Oxidation with permanganate.* Oxidation of anhydrotetrahydromarrubiin with potassium permanganate in 66% acetic acid, and chromatography on silica with benzene containing 1% of alcohol gave an *oxide*, needles (from ether–light petroleum), m. p. 115°, inflexion at 2450 Å (Found: C, 70·7; H, 9·1. $C_{20}H_{30}O_4$ requires C, 71·8; H, 9·0%).

Anhydromarrubiin.—The method of Lawson and Eustice [2] was used, the heating time being restricted to 0·5 hr. The anhydromarrubiin crystallised as needles from a solution of the crude syrup in a little ethyl acetate (charcoal), in 27% yield. Recrystallised from methanol, it had m. p. 98°, $[\alpha]_D^{26}$ +34° (*c* 1·65), $\lambda_{max.}$ 2050 Å and a complex system 2550—2800 Å (log ε 3·64, 0·93).

Oxidation of Anhydromarrubiin.[1]—Crude anhydromarrubiin was oxidised by chromium trioxide in acetic acid by Ghigi's method.[7] The chloroform-soluble portion was chromatographed on silica, the keto-lactone $C_{14}H_{20}O_3$ (II) being eluted with 1 : 4-chloroform–benzene (yield 10% from marrubiin): this keto-lactone was better prepared from anhydrotetrahydromarrubiin (see above).

8-*Hydroxy*-1 : 6 : 10-*trimethyl*-5-*oxodecalin*-1-*carboxylic Acid* [1,6] (III).—The keto-lactone (II) (0·7 g.) was heated at 100° for 1 hr. with potassium hydroxide (0·3 g.) in 2-ethoxyethanol (3 ml.) containing a little water. The solution was acidified with hydrochloric acid and the precipitate was recrystallised from benzene, to give the keto-hydroxy-acid (0·7 g.) as prisms, m. p. 178°, $[\alpha]_D^{25}$ −43·4° (*c* 0·42), $\lambda_{max.}$ 2900—2930 Å (ε 30·5) (Found: C, 66·1; H, 8·6. Calc. for $C_{14}H_{22}O_4$: C, 66·1; H, 8·7%).

1 : 6 : 10-*Trimethyl*-5 : 8-*dioxodecalin*-1-*carboxylic Acid* (IV).—A solution of the keto-hydroxy-acid (0·68 g.) and chromium trioxide (0·18 g.) in 90% acetic acid (14 ml.) was kept at 25° overnight, the solvent was removed at low temperature and a chloroform solution of the residue was washed with dilute hydrochloric acid and with water. Evaporation of the chloroform gave an oil which crystallised (0·4 g.) from benzene, and more of the same *diketo-acid* (IV) was eluted by benzene containing 1% of alcohol when the mother-liquors were chromatographed on silica (12 g.). This acid (yield 83%) formed needles (from benzene), m. p. 109—110°, $[\alpha]_D^{25}$ +60° (*c* 0·95), $\lambda_{max.}$ 2900 Å (ε 58) (Found: C, 66·2; H, 7·8. $C_{14}H_{20}O_4$ requires C, 66·6; H, 8·0%).

Action of Acetic Anhydride on the Diketo-acid (IV).—The acid (0·2 g.) was boiled for ½ hr. with acetic anhydride (2 ml.) and again for ½ hr. after sodium acetate (0·025 g.) had been added. The solution was evaporated and a benzene solution of the residue was washed with aqueous sodium carbonate and evaporated: addition of ether to the residue caused crystallisation of 8-*acetoxy*-8-*hydroxy*-1 : 6 : 10-*trimethyl*-5-*oxodecalin*-1-*carboxylic lactone* (VIII), prisms, m. p.

163—164°, $[\alpha]_D^{20}$ +162°, $\lambda_{max.}$ 2190, 2950 Å (ε 162, 19) (Found: C, 65·9; H, 8·0. $C_{16}H_{22}O_5$ requires C, 65·3; H, 7·5%). When the residues were chromatographed on silica, benzene (in some experiments) eluted some keto enol-lactone (IX) (see below) and then more of the lactol acetate could be eluted by benzene containing 1—2% of alcohol. If the sodium acetate was omitted, the product was the mixed *anhydride* (VII), needles (from ether), m. p. 172—173°, $\lambda_{max.}$ 2150, 2920 Å (ε 160, 29·4) (Found: C, 65·6; H, 8·0. $C_{16}H_{22}O_5$ requires C, 65·3; H, 7·5%).

8-*Hydroxy*-1 : 6 : 10-*trimethyl*-5-*oxo*-Δ^7-*octalin*-1-*carboxylic Lactone* (IX).—The lactol acetate (VIII) was heated under nitrogen at 250° for 10 min.; acetic acid (*ca.* 0·75 mol.) was evolved. Addition of ether to the residue cause crystallisation of the *keto-enol-lactone* (IX), needles (from ether), m. p. 130—132°, $[\alpha]_D$ +28·7° (Found: C, 71·7; H, 8·1. $C_{14}H_{18}O_3$ requires C, 71·8; H, 7·7%).

1 : 6 : 10-*Trimethyl*-5 : 8-*dioxo*-Δ^6-*octalin*-1-*carboxylic Acid* (V).—The diketo-acid (IV) (0·94 g.) was boiled for 1½ hr. with selenium dioxide (0·4 g.) in purified dioxan (10 ml.) containing water (0·5 ml.). The filtered solution was evaporated, the residue, dissolved in benzene, was poured on silica (25 g.) and some impurities were eluted with benzene (400 ml.). On elution with benzene containing 1% of alcohol the *enedione-acid* (V) travelled as a yellow band (almost black in ultraviolet light); it formed pale yellow platelets (from benzene–light petroleum), m. p. 140·5°, $[\alpha]_D^{27}$ +139° (*c* 0·91), $\lambda_{max.}$ 2420 Å (log ε 4·01) (Found: C, 66·95; H, 7·5. $C_{14}H_{18}O_4$ requires C, 67·2; H, 7·25%). When smaller proportions of selenium dioxide were used for the oxidation some diketo-acid remained and was difficult to separate from the enedione-acid. Zinc and acetic acid in the cold rapidly reduced the enedione-acid to the diketo-acid, m. p. and mixed m. p. 110—111°. No identifiable products were obtained when the enedione-acid was oxidised with ozone, nitric acid, or potassium permanganate; but, while the quantities used would have allowed detection of the dimethyl*cyclo*hexanetricarboxylic acid derivable from abietic acid, they were inadequate to ensure detection of the isomer derivable from podocarpic acid.

Marrubic Acid.—Marrubiin was hydrolysed by boiling it for 15 min. with potassium hydroxide (2 mol.) in purified 2-ethoxyethanol containing a little water; hydrolysis with alcoholic potassium hydroxide takes many hours.

Oxidation of Sodium Marrubate with Potassium Permanganate.—A solution of potassium permanganate (12·6 g.) in water (250 ml.) was added, in one portion, to a solution of marrubic acid (7 g.) and sodium hydroxide (3·5 g.) in water (100 ml.); reaction was instantaneous and the temperature rose to 45°. Yields were greatly lowered if the permanganate was added gradually. Sulphur dioxide (6 g.) was added, followed by 20N-sulphuric acid (10 ml.). The precipitate *A* (3·8 g.) was removed and the filtrate was extracted with chloroform; evaporation of the chloroform solution yielded a syrup *B* (1·4 g.). The aqueous liquor was almost neutralised with sodium hydroxide and was evaporated to low bulk; a pale yellow syrup *C* (1·4 g.) separated. Material *A* was recrystallised from ethyl acetate, giving the hydroxy-acid $C_{17}H_{26}O_5$ (XI). The evaporated ethyl acetate liquors and syrups *B* and *C* were chromatographed together on silica (40 g.): benzene containing 2% of alcohol eluted successively the dilactone $C_{17}H_{24}O_4$ (X), a substance of m. p. 225° (decomp.), prisms from methyl alcohol (Found: C, 67·7; H, 7·8%), and the hydroxy-acid $C_{17}H_{26}O_5$ (XI). Yield of the hydroxy-acid 70—75%: large-scale experiments gave similar results, *e.g.*, 60 g. of marrubiin gave 53 g. of the hydroxy-acid (74·5%).

The aqueous liquor from which material *C* had separated was acidified to Congo-red with sulphuric acid, evaporated, and steam-distilled. The steam-distillate was refluxed to remove sulphur dioxide, neutralised, evaporated, acidified with sulphuric acid, and again refluxed. Residual sulphur dioxide was removed by the addition of 0·1N-potassium permanganate, and the solution was evaporated and steam-distilled. The steam-distillate was neutralised with N-sodium hydroxide (9·5 ml.) and evaporated to dryness and the residue was boiled with alcohol. Sodium formate, m. p. and mixed m. p. 253·5—254·5°, remained; the alcoholic extract contained a negligible amount of material and this was not sodium acetate.

γ-*Lactone of* β-(5-*Carboxy*-1 : 4-*dihydroxy*-2 : 5 : 9-*trimethyl*-1-*decalyl*)*propionic Acid* [1,6] (XI)—The lactonic hydroxy-acid, prepared as described above, was identical with material prepared by the hydrolysis of the dilactone (X), and formed needles (from benzene) or prisms (from ethyl acetate), m. p. 214—215° (decomp.) (heated rapidly from 210°), $[\alpha]_D^{22}$ −18·7° (*c* 6·1) (Found: C, 65·75; H, 8·3. Calc. for $C_{17}H_{26}O_5$: C, 65·8; H, 8·4%). The methyl ester (prepared by diazomethane) formed prisms (from benzene–*cyclo*hexane), m. p. 154° (Found: C,

66·8; H, 9·1. Calc. for $C_{18}H_{28}O_5$: C, 66·6; H, 8·7%). The acetate (prepared by acetic anhydride–pyridine) formed prisms (from ethyl acetate–*cyclo*hexane), m. p. 262—263° (decomp.) (lit.,[6] m. p. 246°) (Found: C, 64·4; H, 8·15. Calc. for $C_{19}H_{28}O_6$: C, 64·75; H, 8·0%).

Lactone of β-(5-*Carboxy*-1-*hydroxy*-2 : 5 : 9-*trimethyl*-4-*oxo*-1-*decalyl*)*propionic Acid* [1,6] (XII).—A solution of chromium trioxide (9 g.) in 90% acetic acid (150 ml.) was added to the hydroxy-acid (XI) (39 g.) in 90% acetic acid (150 ml.). Next morning the solution was evaporated to dryness and the residual lactonic keto-acid (XII) was crystallised from 80% methanol, forming prisms (34·5 g.), m. p. 222—223·5°, $[\alpha]_D^{25}$ +76·6° (*c* 3·9), $\lambda_{max.}$ 2820 Å (ε 33) (lit.,[6] 2580 Å) (Found: C, 66·4; H, 8·0. Calc. for $C_{17}H_{24}O_5$: C, 66·2; H, 7·85%). The Zimmermann test was negative. The oxime (prepared in pyridine at 100° during 1 hr.) formed prisms, m. p. 270—272° (decomp.) (from acetic acid) (Found: C, 62·9; H, 7·6; N, 4·3. Calc. for $C_{17}H_{25}O_5N$: C, 63·1; H, 7·8; N, 4·3%). The methyl ester (prepared by diazomethane) formed plates (from benzene–*cyclo*hexane), m. p. 165·5° (depressed by admixture with the methyl ester of the corresponding hydroxy-acid) (Found: C, 67·5; H, 8·3. Calc. for $C_{18}H_{26}O_5$: C, 67·1; H, 8·1%). The oxime of the methyl ester (prepared in pyridine at 100°) formed needles (from benzene–*cyclo*hexane), m. p. 195—196·5° (187—189° [6]) (Found: C, 64·0; H, 8·15; N, 4·3. Calc. for $C_{18}H_{27}O_5N$: C, 64·1; H, 8·1; N, 4·15%).

Bromination of the Lactonic Keto-acid $C_{17}H_{24}O_5$ (XII).—The acid (0·63 g.) in acetic acid (5 ml.) containing hydrobromic acid (2 drops of 60%) was left for 18 hr. with 0·2N-bromine in acetic acid (25 ml.), rather more than 1 mol. being absorbed. Sodium hydroxide was added, sufficient to neutralise the mineral acid, and the solution was evaporated under reduced pressure: the residue crystallised on addition of methyl alcohol and water. Recrystallisation from ethyl acetate–*cyclo*hexane or from cineole gave the *α-bromo-keto-acid* as prisms, m. p. 195—197° (decomp.), $\lambda_{max.}$ ~2900 Å (ε 126) (Found: C, 51·1; H, 6·0; Br, 22·1. $C_{17}H_{23}O_5Br$ requires C, 52·75; H, 6·0; Br, 20·6%). Chromatography of the residues on silica in benzene containing 1% of alcohol gave a small quantity of an *isomer*, prisms (from ethyl acetate), m. p. 220° (Found: C, 53·7; H, 6·4; Br, 19·2%). No characterised materials were isolated when the bromo-keto-acid was boiled with pyridine or quinoline.

Action of Hydrazine on the Lactonic Keto-acid $C_{17}H_{24}O_5$ (XII).—The acid (0·155 g.) was heated with sodium ethoxide (from 0·16 g. of sodium) and hydrazine hydrate (1 ml.) in diethylene glycol (4 ml.) for 4 hr. at 200°. Chloroform extraction of the acidified mixture gave the cyclic *hydrazone* (XIIa), prisms (from alcohol), m. p. 261—263° (Found: C, 67·1; H, 8·0; N, 9·0. $C_{17}H_{24}O_3N_2$ requires C, 67·1; H, 7·95; N, 9·2%). Chromatography of the residues on silica (10 g.) yielded more of the same material (eluted by benzene containing 2% of alcohol) but no reduction product was recognised. Clemmensen reduction of the keto-acid yielded no characterised products.

The Lactonic Hydroxy-keto-Acid, $C_{17}H_{24}O_6$.—A 5% solution (150 ml.) of potassium permanganate was added in 10 ml. portions, with cooling, to a solution of the lactonic keto-acid (XII) (5·2 g.) in 2·6% aqueous sodium hydroxide (100 ml.). The final solution remained green overnight. Sulphur dioxide (4 g.) was added and the cooled solution was acidified with hydrochloric acid. The precipitate was washed with water and recrystallised from alcohol (60 ml.) and then from methanol, the lactonic hydroxy-keto-acid (3·47 g.) forming needles, m. p. 210—210·5° (decomp.) (lit.,[10] 205°), $\lambda_{max.}$ 2960 Å (ε 36·1) [Found: C, 63·2; H, 7·7%; equiv. (at 0°), 164, 166. Calc. for $C_{17}H_{24}O_6$: C, 62·95; H, 7·5%; equiv., 162]. Titration or back-titration at room temperature gave spurious equivs. of 280—307. The mother-liquors yielded a further 0·48 g. (total yield 76%). Similar oxidation of the hydroxy-acid (XI) gave only a 30% yield. The acid was eluted from silica by benzene containing 2% of alcohol; it yielded sparingly soluble silver, lead, and calcium salts (all needles). It was readily converted into the corresponding dilactone by heat or by storage in acid solution; it gave a negative Zimmermann test and took up negligible amounts of bromine when exposed for 6 days to 0·1N-bromine in acetic acid. It was converted into the corresponding dilactone by periodic acid, and was recovered after the sodium salt had been exposed to sodium periodate for 200 hr. Acetic anhydride in pyridine converted it into its dilactone. Its methyl ester [10] (prepared by diazomethane) formed prisms (from methyl acetate–*cyclo*hexane) or platelets (from benzene–ether), m. p. 108—108·5°, $\lambda_{max.}$ 2940—2960 Å (ε 34) (Found: C, 64·0; H, 7·7. Calc. for $C_{18}H_{26}O_6$: C, 63·9; H, 7·7%), and gave an oxime (in pyridine, room temp., 36 hr.), needles (from alcohol), m. p. 279—281° (decomp.).

On hydrogenation (Adams catalyst) in acetic acid, the acid yielded the *hydroxy-dilactone*

(XIX), prisms (from alcohol), m. p. 156·5—158°, $[\alpha]_D^{22}$ −4·1° (*c* 1·7), max. at 3468 and 1765 cm.$^{-1}$ (Found : C, 66·2; H, 8·3. $C_{17}H_{24}O_5$ requires C, 66·2; H, 7·85%). The corresponding keto-dilactone was not readily hydrogenated.

The Keto-dilactone $C_{17}H_{22}O_5$ (XVII).—This was best made by heating the lactonic hydroxy-keto-acid to its m. p. under nitrogen : conversion was complete almost at once; water (1 mol.) was evolved, but no carbon dioxide. If during the preparation of the lactonic hydroxy-keto-acid the solution was allowed to become too acid or if acid solutions were not worked up at once the main product was often this dilactone; it may also be formed on recrystallisation of the acid if the solution is left too long. The dilactone sublimed readily at 180° under reduced pressure, and formed needles, m. p. 210—210·5° (lit.,[10] 214°), $\lambda_{max.}$ 2980 Å (ε 24) (from benzene) [Found : C, 66·6; H, 7·25%; *M* (ebullioscopic in C_6H_6), 302—335; equiv. (warm 0·1N-NaOH, back-titrated at 0°), 159, 157. Calc. for $C_{17}H_{22}O_5$: C, 66·65; H, 7·2%; *M*, 306]. The substance gave a negative Zimmermann test, absorbed negligible amounts of bromine (in acetic acid) in 6 days, and was unaffected by periodic acid, lead tetra-acetate, and sodium bismuthate. The *oxime* (prepared in pyridine; 100°, 1—2 hr.) crystallised from the hot pyridine, and from alcohol formed needles, m. p. 290—292° (decomp.) (heated from 285° : very dependent on the temp. of insertion) (lit.,[10] 265°) (Found : C, 63·7; H, 7·3; N, 4·6. $C_{17}H_{23}O_5N$ requires C, 63·5; H, 7·2; N, 4·4%).

The Hydroxy-keto-lactones A and B, $C_{16}H_{24}O_4$ (XX and XXI).—The lactonic hydroxy-keto-acid $C_{17}H_{24}O_6$ (3·04 g.) was boiled for 15 min. with solid 85% potassium hydroxide (2 g.) in purified 2-ethoxyethanol (10 ml.) containing water (3 drops). The diluted solution was acidified with 10N-hydrochloric acid (3·8 ml.), the crystalline product was dissolved in ethyl acetate, and the solution filtered. When the solvent was replaced by alcohol, rhombic plates crystallised; needle-shaped crystals also separated overnight but these were dissolved by cautious warming. The plate-like crystals were recrystallised, to give the *hydroxy-keto-lactone A* [10] (1·25 g.), m. p. 161—162°, $\lambda_{max.}$ 3020—3070 Å (ε 30·5) [Found : C, 68·6; H, 8·6%; equiv. (0·1N-sodium hydroxide at 100°; end-point permanent), 270; *M* (ebullioscopic in benzene), 311. $C_{16}H_{24}O_4$ requires C, 68·5; H, 8·6%; *M*, 280]. The Zimmermann test was negative; very little absorption of bromine took place from 0·1N-bromine in acetic acid in 6 days. The *oxime* (pyridine, 100°, 1 hr.) formed prisms (from aqueous alcohol or ethyl acetate), m. p. 219—220° (Found : C, 64·25; H, 8·55; N, 4·8. $C_{16}H_{25}O_4N$ requires C, 65·1; H, 8·5; N, 4·7%).

The alcoholic mother-liquors from the hydroxy-keto-lactone (A), on concentration, deposited needles of the *hydroxy-keto-lactone* (B) which recrystallised from ethyl acetate and then from ether as hexagonal prisms which changed into needles, m. p. 181—182°, $\lambda_{max.}$ 2800—2830 Å (ε 47) (Found : C, 68·3; H, 8·6. $C_{16}H_{24}O_4$ requires C, 68·5; H, 8·6%). This did not yield an oxime under the conditions used for (A); it was converted into (A) by boiling alcoholic potassium hydroxide. It was inert to catalytic hydrogenation.

The residues from the isolation of these products were chromatographed on acid-washed alumina (100 g.). Elution with light petroleum–benzene (3 : 1) yielded more of (B), followed shortly by (A).

Reduction of the Hydroxy-keto-lactone (A).—(*a*) Hydrogenation in acetic acid in the presence of Adams catalyst gave the dihydroxy-lactone $C_{16}H_{26}O_4$ [10] (see below), m. p. 197—199°. It was inert to periodic acid (1 month), but was slowly oxidised by lead tetra-acetate. (*b*) The hydroxy-keto-lactone (A) (0·523 g.) was added gradually (percolation from a thimble) to stirred ethereal lithium aluminium hydride (1·5 × theor.), and the mixture was boiled for 7 hr. and left overnight. Acidification and working up in the usual way gave a syrup which was chromatographed on silica (25 g.). Benzene containing 2% of alcohol eluted the dihydroxy-lactone which crystallised from ether as tetrahedra (15 mg.), m. p. and mixed m. p. 197—199° (Found : C, 68·3; H, 9·5. Calc. for $C_{16}H_{26}O_4$: C, 68·05; H, 9·3%). Benzene containing 5% of alcohol then eluted the *tetrol* which crystallised as prisms (0·1 g.), m. p. 146—147°, on concentration of an ethereal solution (Found : C, 67·1; H, 10·8. $C_{16}H_{30}O_4$ requires C, 67·1; H, 10·6%). 0·544 g. of the tetrol reduced *ca.* 80 ml. of 5·3% alkaline potassium permanganate at 65°, but only oxalic acid was isolated.

Action of Organometallic Compounds on the Hydroxy-keto-lactone A.—An ethereal solution of the lactone (0·075 g.), boiled for 2 hr. with 6—7 mol. of phenylmagnesium bromide, gave a *substance* (*ca.* 0·02 g.) which crystallised as needles (from ether), m. p. 212·5°, $\lambda_{max.}$ 2060, 2960 Å (log ε 3·69, 1·54) (Found : C, 68·5; H, 8·8. $C_{16}H_{24}O_4$ requires C, 68·5; H, 8·6%). The same

substance was obtained when *tert.*-butylmagnesium chloride was used in place of the phenylmagnesium bromide.

Oxidation of Marrubiin with Nitric Acid.—Marrubiin was oxidised by nitric acid according to the second procedure used by Levy [13, 14] for the oxidation of abietic acid. Subsequent chromatography (silica; benzene–alcohol) gave no crystalline product except succinic acid.

Oxidation of the Enol-lactone of (XII).—(*a*) The enol-lactone (0·1 g.) was ozonised at −20° in carbon tetrachloride. The ozonide [m. p. *ca.* 110° (decomp.)] separated: it was not readily decomposed by water. It was oxidised with nitric acid by the procedure used with marrubiin. The crude product, freed from nitric acid, was esterified with diazomethane, and the ester was kept at room temperature for varying periods (up to 4 days) in saturated aqueous hydrobromic acid. As sublimation of the product (cf. ref. 12) yielded only traces of crystalline material, it was boiled with acetic anhydride and chromatographed on silica: benzene eluted a small amount of a substance (needles), m. p. 110—115°, and benzene containing 5% of ether then eluted a small amount of a substance, needles (from dioxan), m. p. 240—245° (decomp.), $[\alpha]_D \sim +40°$ (in dioxan) (Found: C, 56·7; H, 5·8; OMe, ~0). (*b*) Hydrogen peroxide (0·88 ml.; 6%) was added dropwise to a solution of the enol-lactone (0·5 g.) in *tert.*-butyl alcohol (5 g.) containing 1% aqueous osmium tetroxide (15 drops). The residue left on evaporation was chromatographed on silica. Benzene containing 2% of alcohol eluted a *substance*, prisms (from alcohol–ether), m. p. 216—219° (Found: C, 66·6; H, 7·5. $C_{17}H_{22}O_5$ requires C, 66·65; H, 7·2%). Benzene containing 5% of alcohol then eluted the *γ-lactone* (XIV) of β-(5-carboxy-1 : 3-dihydroxy-2 : 5 : 9-trimethyl-4-oxo-1-decalyl)propionic acid, prisms (from alcohol), m. p. 211—215° (decomp.) (Found: C, 63·1; H, 7·6. $C_{17}H_{24}O_6$ requires C, 62·95; H, 7·5%). Its *methyl ester* (prepared by diazomethane) formed prisms, m. p. 199—200° (Found: C, 63·8; H, 7·8. $C_{18}H_{26}O_6$ requires C, 63·9; H, 7·7%). On pyrolysis the acid lost carbon dioxide (0·7 mol.) but no carbon monoxide, yielding a small amount of crystals, m. p. 208—210°, not identical with the first product.

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