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CHEMISTRY OF THE PODOCARPACEAE—XIV[1]

PER-ACID OXIDATION OF SOME DITERPENOID PHENOLS AND ETHERS

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Abstract—The per-acid oxidation of some phenols and their methyl ethers in the podocarpa-8,11,13-triene series has given both *p*-benzoquinones and 4-hydroxycyclohexa-2,5-dienones. When reaction mixtures were heterogenous, oxidation also occurred at a Me group remote from the phenolic ring.

THE readily available diterpenoid, podocarpic acid[2] (I), with its phenolic ring and tertiary carboxyl group, provides an attractive starting point for the synthesis of other terpenoid compounds. Previous work on podocarpic acid has been concerned primarily with the chemistry of the carboxyl group[3] and this has now been extended to an examination of the products of oxidation of the phenolic ring. Most studies on ring C in podocarpic acid have been concerned with its reduction[4] while other workers have studied the transposition of the oxygen function.[5] Oxidative reactions of ring C include its removal during ozonolysis[6] and the oxygenation of a derived αβ unsaturated ketone.[7]

In this paper we report the per-acid oxidation of some derivatives of podocarpic acid. The reaction of per-acids with phenols and their methyl ethers appears to involve electrophilic attack *ortho* or *para* to the oxygen function. Phenols in the benzene series with a free *para* position are oxidized to *p*-benzoquinones.[8] If the *para* position is blocked, attack may occur either at this position, to give a hydroxycyclohexadienone,[8c] or at a free *ortho* position. In the latter case ring cleavage then occurs to give a muconic acid.[9] Phenyl methyl ethers may undergo attack *para* to the MeO group giving a *p*-benzoquinone with displacement of the MeO group. If

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[1] Part XIII: C. R. Bennett and R. C. Cambie, *Phytochemistry*, in press.

[2] For bibliography, see S. G. Brooker, R. C. Cambie and M. A. James, *Trans. Roy. Soc. N.Z.* **1**, 205 (1966).

[3] C. R. Bennett and R. C. Cambie, *Tetrahedron* **23**, 927 (1966).

[4] R. H. Bible and R. R. Burtner, *J. Org. Chem.* **26**, 1174 (1961); H. L. Dryden, G. M. Webber, R. R. Burtner and J. A. Cella, *Ibid* **26**, 3237 (1961); F. Sondheimer and M. Gibson, *Bull. Res. Council Israel* **9A**, 204 (1960); N. N. Girotra and L. H. Zalkow, *Tetrahedron* **21**, 101 (1965)

[5] [a] R. Hodges and R. A. Raphael, *J. Chem. Soc.* 52 (1960); [b] K. Mori and M. Matsui, *Tetrahedron* **22**, 879 (1966)

[6] E. Wenkert and D. P. Strike, *J. Am. Chem. Soc.* **86**, 2044 (1964).

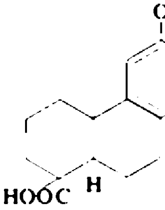
[7] K. Crowshaw, R. C. Newstead and N. A. J. Rogers, *Tetrahedron Letters* No. 33, 2307 (1964).

[8] [a] G. G. Henderson and R. Boyd, *J. Chem. Soc.* 1659 (1910); [b] C. Grundmann and H. Trischmann, *Ber. Dtsch. Chem. Ges.* **69**, 1755 (1936); [c] R. D. Chambers, P. Goggin and W. K. R. Musgrave, *J. Chem. Soc.* 1804 (1959); [d] D. Bryce-Smith and A. Gilbert, *Ibid.* 873 (1964).

[9] J. Böeseken and C. F. Metz, *Rec. Trav. Chim.* **54**, 345 (1935); J. A. Elvidge, R. P. Linstead and P. Sims, *J. Chem. Soc.* 3386 (1951)

positions 2 and 5 with respect to the ether function are unsubstituted, oxidation can occur to give a methoxy-*p*-benzoquinone.[10]

12-Hydroxypodocarpa-8,11,13-triene (II; R = H, R′ = Me)[5a] in acetic anhydride was added to peracetic acid, prepared *in situ* by the addition of 30% hydrogen peroxide to cold acetic anhydride containing a little sulphuric acid. The suspension rapidly became homogeneous and after 4 days at 20° yielded neutral and acidic fractions. The former gave 12-acetoxypodocarpa-8,11,13-triene (II; R = Ac, R′ = Me; ca. 10%) and a new compound identified as 8β-hydroxypodocarpa-9(11),13-dien-12-one (III, R = Me; ca. 19%). The compound showed IR absorption at 3390 (OH), 1672 (C=O), 1634 and 1613 cm^{-1} (C=C) and in the UV had λ_{max} 236 mμ (ε 14,800). This hydroxy dienone is presumably formed by direct hydroxylation *para* to the phenolic oxygen.



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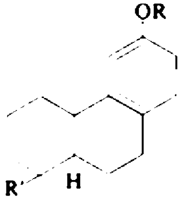
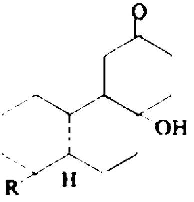


II



III

The stereochemistry at C_8 was assigned on the basis of the NMR and ORD spectra. In the former the signal assigned to the C_{17} Me group appeared at a lower field than in any related compounds (see Table). Introduction of an OH group in a 1,3-diaxial relationship to an angular Me group normally shifts the resonance of the latter downfield by about 0·2 ppm, whereas adjacent OH groups in different environments cause only small shifts.[11] Furthermore, the ORD curve of the hydroxy dienone was of the same shape and similar magnitude to that of cholesta-1,4-dien-3-one.

Zinc-acid reduction of the hydroxy dienone III (R = Me) gave the phenol II (R = H, R′ = Me) but attempted dienone-phenol rearrangements were unsuccessful. The dienone-phenol rearrangement might, in this case, proceed by two 1,2-migrations of carbon, through a spiran intermediate, or by a 1,2-migration of oxygen, probably as acetoxyl.[12] The former route is presumably prevented as it would involve eclipsing of two adjacent quaternary carbon atoms[13] while if the hindered tertiary OH group was not acetylated, migration of that function would be rendered less likely.

The monoperphthalic acid oxidation of the corresponding methyl ether II (R = R′ = Me) in ether was then investigated but found to proceed very slowly. After 3 months with 0·18M monoperphthalic acid, half of the diterpene ether was recovered unchanged, but two products of oxidation were found, each in about 25% yield.

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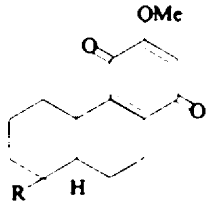
[10] S. L. Friess, A. H. Soloway, B. K. Morse and W. C. Ingersoll, *J. Am. Chem. Soc.* **74**, 1305 (1952); H. Davidge, A. G. Davies, J. Kenyon and R. F. Mason, *J. Chem. Soc.* 4569 (1958)

[11] R. F. Zurcher, *Helv. Chim. Acta* **46**, 2054 (1963); A. I. Cohen and S. Rock, *Steroids* **3**, 243 (1964).

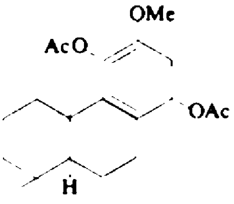
[12] A. M. Gold and E. Schwenk, *J. Am. Chem. Soc.* **80**, 5683 (1958); S. Goodwin and B. Witkop, *Ibid.* **79**, 179 (1957)

[13] B. R. Davis and T. G. Halsall, *J. Chem. Soc.* 1833 (1962)

The less polar compound formed needles, the yellow colour of which indicated a *p*-benzoquinone. This compound was identified as 12-methoxypodocarpa-8,12-diene-11,14-dione IV (R = Me) by its IR [ν_{max} 1680 (C=O), 1661 and 1610 cm^{-1} (C=C)], UV [λ_{max} 274 mμ (ε 20,800) and 372 mμ (ε 530)][14] and NMR spectra (see Table). Reductive acetylation gave a compound whose physical and chemical properties were in full accord with its assigned structure as the methoxy quinol diacetate V. The more polar oxidation product was identified as the hydroxy dienone III (R = Me).



IV



V

Oxidation of this same methyl ether II (R = R′ = Me) with peracetic acid prepared *in situ* proceeded more rapidly. The methyl ether was only partly soluble in the reagents at the start of the reaction but was all dissolved after 3 hr. Oxidation was continued, at 20°, for a further 16 hr giving 6 compounds in the neutral fraction. Apart from starting material, both the hydroxy dienone III (R = Me; 17%) and the methoxy quinone IV (R = Me; 7%) were isolated and identified. With these were obtained 4 products in which oxidation at the C_{16} Me group, a saturated centre, had occurred. These were (i) 12-methoxypodocarpa-8,11,13-trien-16-yl acetate II (R = Me, R′ = CH_2OAc; 6%) identified with an authentic sample prepared from the corresponding alcohol,[15] (ii) the aldehyde II (R = Me, R′ = CHO; 2%) identified with an authentic sample,[15] (iii) the acetoxy-hydroxy-dienone III (R = CH_2OAc; 1%) and (iv) the acetoxy-methoxyquinone IV (R = CH_2OAc; 0·3%). The two latter compounds were identified by their analytical and spectral data and were prepared independently by the peracetic acid oxidation of 12-methoxypodocarpa-8,11,13-trien-16-ol II (R = Me, R′ = CH_2OH)[15] in acetic anhydride. Oxidation of this compound gave a neutral oil, chromatography of which yielded the corresponding acetate II (R = Me, R′ = CH_2OAc) and the two products of oxidation in ring C—the hydroxy dienone III (R = CH_2OAc) and the quinone IV (R = CH_2OAc).

It appears that attack at the saturated carbon atom only occurs when the reaction mixture remains heterogeneous for some hours. This suggests that oxidation may be occurring on the surface of the crystals on the presumably exposed axial Me group. Oxidations of this type are rare, but not unknown. Fieser *et al.*[16] found that cholesterol in the solid state underwent oxidation to give small amounts of 25-hydroxycholesterol and Beckwith[17] found that treatment of crystalline cholesterol

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[14] O. E. Edwards, G. Feniak and M. Los, *Canad. J. Chem.* **40**, 1540 (1962) describe the properties of the 13-isopropyl derivative of this quinone.

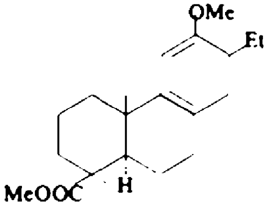
[15] R. H. Bible, *Tetrahedron* **11**, 22 (1960).

[16] L. F. Fieser, W. Y. Huang and B. K. Bhattacharyya, *J. Org. Chem.* **22**, 1380 (1957).

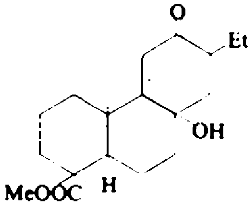
[17] A. L. J. Beckwith, *Proc. Chem. Soc.* 194 (1958)

with Fenton's reagent yielded products which had undergone oxidation at an allylic site, C_7, and also at a saturated carbon atom, C_{25}. No oxidation was observed in this case when 12-methoxypodocarpa-8,11,13-triene was treated with Fenton's reagent.

In order to determine whether an *ortho* hydroxydienone could be prepared, methyl 13-ethyl-12-methoxypodocarpa-8,11,13-trien-16-oate VI was submitted to peracetic acid oxidation. The only product isolated was the *para* hydroxydienone VII.



VI



VII

NMR Spectra

δ ppm FROM TMS

Compound	Methyl groups			OAc	OCH_3	Vinyl			Aromatic
	15	16	17			11	13	14	
III, R = Me	0·85	0·95	1·35	—		5·8		6·55[*]	
IV, R = Me	0·88	0·88	1·20		3·69		5·58		
V	0·92	0·92	1·25	2·26	3·68				6·48
III, R = CH_2OAc[d]	0·95	·	1·37	2·04	—	5·95		6·63[*]	
IV, R = CH_2OAc[e]	1·00	—	1·27	2·04	3·70	—	5·74	-	—
VII	1·06		1·22	—	3·70	6·02		6·42	—
III, R = CO_2Me[b•]	1·25	–	1·25		3·75	6·07		6·76[*]	
IV, R = CO_2Me[c•]	1·14	—	1·25		3·67 3·80		5·86		
VI	0·98		1·23	--	3·63 3·75				6·6, 6·7

[•] Prepared by Mr. W. B. Watkins in this laboratory.

[*] J 13, 14 = 9·5 c/s.

[b] m.p. 206–207°.

[c] m.p. 210–211·5°.

[d] C_{16} protons: 4·32, 3·95, J = 10 c/s.

[e] C_{16} protons: 4·28, 4·00, J = 11·5 c/s.

EXPERIMENTAL

For general experimental details, see Part XII.[3] Alumina for column chromatography was P. Spence Type H deactivated with 5% of 10% aq HOAc.

Demethylation of 12-*methoxypodocarpa*-8,11,13-*triene* (II, R = R′ = Me)

(a) 12-Methoxypodocarpa-8,11,13-triene (1·82 g) was added to pyridinium chloride [from pyridine (39 ml)] and the mixture heated under N_2 for 3 hr. Crystallization of the product from light petroleum gave needles of II (R = H, R′ = Me; 1·37 g, 80%), m.p. 139–141° (lit.[18], m.p. 140–141°).

(b) The ether (1 g) was reacted with BBr_3 (0·34 ml) in benzene (50 ml) at 80° for 24 hr to give the phenol (0·33 g, 35%) m.p. 138–140°.

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[18] W. P. Campbell and D. Todd, *J. Am. Chem. Soc.* **62**, 1287 (1940).

Peracetic acid oxidation of 12-*hydroxypodocarpa*-8,11,13-*triene* (II; R = H, R′ = Me)

12-Hydroxypodocarpa-8,11,13-triene (1·2 g) in Ac_2O (20 ml) was added to cold peracetic acid [from 100 vol H_2O_2 (20 ml), Ac_2O (46 ml) and conc H_2SO_4 (0·5 ml)]. The suspension became homogeneous within 15 min and the pale yellow soln was kept in the dark for 4 days at 20°. Working up gave neutral (0·486 g) and acidic (0·346 g) fractions. TLC of the neutral oil showed it to contain 6 compounds, but only 2 in any amount. These were isolated by alumina chromatography.

(a) Light petroleum eluate (0·115 g) recrystallized from aqueous MeOH to give needles of 12-*acetoxypodocarpa*-8,11,13-*triene* (II; R = Ac, R′ = Me), m.p. 75–76°, identical in all respects with a sample prepared by direct acetylation of the phenol. (Found: C, 79·45; H, 9·2; Ac, 14·9. $C_{19}H_{26}O_2$ requires: C, 79·7; H, 9·15; Ac, 15·0%.)

(b) Benzene–ether (1:1) eluate (0·25 g) recrystallized from aqueous acetone to give needles of 8β-*hydroxypodocarpa*-9(11),13-*dien*-12-*one* (III, R = Me), m.p. 149–151°. (Found: C, 77·85; H, 9·4; O, 12·55. $C_{17}H_{24}O_2$ requires: C, 78·4; H, 9·3; O, 12·3%.) ν_{max} 3390 (OH), 1672 (C=O), 1634 and 1613 cm^{-1} (C=C), λ_{max} 236 mμ (ε 14,800), ORD (c 0·065) $[\phi]_{589}$ −680°, $[\phi]_{500}$ −640°, $[\phi]_{400}$ −610°, $[\phi]_{350}$ −950°, $[\phi]_{284}$ −4310°.

Reduction of the hydroxydienone (III, R = Me)

Zn dust (0·2 g) was added to the hydroxydienone (50 mg) in HOAc (2 ml) and conc HCl (0·2 ml) and the mixture stood at 20° for 15 min. After removal of Zn dust, ether extraction yielded II (R = H, R′ = Me), m.p. and mixed m.p. 137–139° (lit.[5a], m.p. 140–141°), identical IR spectrum.

Attempted dienone-phenol rearrangements

(a) The hydroxydienone (55 mg) in HOAc (0·5 ml), Ac_2O (0·5 ml) and conc H_2SO_4 (0·05 ml) was stood at 20° for 24 hr. Working up gave only starting material.

(b) The hydroxydienone (50 mg) in HOAc (5 ml), water (0·5 ml) and conc HCl (1 ml) was heated under reflux for 3 hr. Working up gave only starting material.

Monoperphthalic acid oxidation of 12-*methoxypodocarpa*-8,11,13-*triene* (II, R = R′ = Me)

Monoperphthalic acid in ether (16·25 g in 500 ml by titration) was added to 12-methoxypodocarpa-8,11,13-triene (6·784 g) and kept at 0° for 3 months. At the end of this time, titration showed there to be 2·02 g of unreacted peracid. The ether soln was washed with 20% Na_2CO_3aq to yield a neutral yellow oil (6·6 g) which was chromatographed on alumina to yield 3 fractions.

(a) Light petroleum eluate (3·22 g) recrystallized from MeOH to yield unchanged 12-methoxypodocarpa-8,11,13-triene, m.p. and mixed m.p. 29–30° (lit.[5a], m.p. 30–31·5°).

(b) Benzene–light petroleum (1:4) eluate (1·46 g) recrystallized from aqueous MeOH to yield yellow needles of 12-*methoxypodocarpa*-8,12-*diene* 11,14-*dione* IV (R = Me), m.p. 171–172·5°. (Found: C, 75·0; H, 8·5; O, 17·0. $C_{18}H_{24}O_3$ requires: C, 75·0; H, 8·4; O, 16·6%.) ν_{max} 1680 (C=O), 1661 and 1610 (C=C), 1238 and 1020 (=C–O–C), and 850 cm^{-1} (C=C—H). λ_{max} 274 mμ (ε 20,800) and 372 mμ (ε 530), ORD (c 0·054) $[\phi]_{589}$ −425°, $[\phi]_{500}$ −212°, $[\phi]_{450}$ 0°, $[\phi]_{400}$ +2280°, $[\phi]_{350}$ +3380°, $[\phi]_{300}$ +12,150°, $[\phi]_{278}$ +20,900°.

Zn dust (0·2 g) was added to IV (R = Me; 50 mg) in HOAc (0·5 ml) and the mixture stood at 20° for 15 min. After removal of the Zn, ether yielded 11,14-*diacetoxy*-12-*methoxypodocarpa*-8,11,13-*triene* (V; 56 mg, 84%) as needles from MeOH, m.p. 125–127°. (Found: C, 70·3; H, 8·1. $C_{22}H_{30}O_5$ requires: C, 70·6; H, 8·1%.) ν_{max} 1775 (C=O), 1198 (C–O—C), 1240 and 1040 cm^{-1} (=C–O—C).

(c) Benzene–ether (1:1) eluate (1·27 g) recrystallized from aqueous acetone to give needles of 8β-hydroxypodocarpa-9(11),13-dien-12-one, m.p. and mixed m.p. 148–150°, identical IR spectrum.

Peracetic acid oxidation of 12-*methoxypodocarpa*-8,11,13-*triene* (II, R = R′ = Me)

12-Methoxypodocarpa-8,11,13-triene (10 g) partly dissolved in Ac_2O (10 ml) was slowly added to a cold soln of peracetic acid (340 ml, preparation described above). The suspension was stirred and slowly allowed to come to room temp. After 3 hr all the starting material had dissolved and the soln stood at 20°, in the dark, for 19 hr. The soln was poured into cold water (500 ml) and yielded neutral (8·29 g) and acidic (1·34 g) fractions. The neutral portion was chromatographed on alumina and the fractions identified as below, giving eluting solvent and weight of fraction.

(a) Light petroleum (2·33 g) 12-methoxypodocarpa-8,11,13-triene, identified by m.p., mixed m.p. and IR spectrum.

(b) Benzene–light petroleum (1:9) (0·66 g) recrystallized from MeOH to give needles of 12-*methoxy*-

podocarpa-8.11.13-*trien*-16-*yl acetate*, m.p. and mixed m.p. 72–73° with an authentic sample prepared by acetylation of the known 12-methoxypodocarpa-8,11,13-trien-16-ol.[15] (Found: C, 76·05; H, 8·6. $C_{20}H_{28}O_3$ requires: C, 75·9; H, 8·9%.)

(c) Benzene–light petroleum (1:4), (0·89 g) recrystallized from MeOH to give yellow needles of 12-methoxypodocarpa-8,12-diene-11, 14-dione, m.p. and mixed m.p. 171–172·5°.

(d) Benzene–light petroleum (2:3), (0·39 g) recrystallized from aqueous acetone to give 12-methoxypodocarpa-8,11,13-trien-16-al[15] (II; R = Me, R′ = CHO) identified by its m.p., mixed m.p. and IR spectrum.

(e) Benzene (0·13 g) recrystallized from aqueous MeOH to give yellow flakes of 16-*acetoxy*-12-*methoxypodocarpa*-8,12-*diene*-11,14-*dione*, m.p. 202–203°. (Found: C, 69·7; H, 7·9; O, 22·75. $C_{20}H_{26}O_5$ requires: C, 69·3; H, 7·5; O, 23·1%.) ν_{max} 1740 and 1680 (C=O), 1640 (C=C), 1220 (C—O—C), 1240 and 1040 cm^{-1} (=C—O—C), λ_{max} 277 mμ (ε 18,800) and 368 mμ (ε 550), ORD (*c* 0·105) $[\phi]_{589}$ −198°, $[\phi]_{500}$ −505°, $[\phi]_{450}$ +99°, $[\phi]_{400}$ +1190°, $[\phi]_{350}$ +4150°, $[\phi]_{300}$ +9750°, $[\phi]_{290}$ +12,430°.

(f) Benzene–ether (1:1), (1·59 g) recrystallized from aqueous acetone to give 8β-hydroxypodocarpa-9(11),13-dien-12-one, m.p. and mixed m.p. 149–150·5°, identical IR spectrum.

(g) Ether (0·23 g) recrystallized from MeOH to yield needles of 16-*acetoxy*-8β-*hydroxypodocarpa*-9(11),13-*dien*-12-*one* (III, R = CH_2OAc), m.p. 133–135°. (Found: C, 71·2; H, 8·05; O, 20·3. $C_{19}H_{26}O_4$ requires: C, 71·7; H, 8·2; O, 20·1%.) ν_{max} 3390 (OH), 1741 and 1672 (C=O), 1634 and 1613 (C=C) and 1225 cm^{-1} (C—O—C), λ_{max} 237 mμ (ε 18,550).

Acidic fraction TLC of the acid fraction showed it to consist of 2 compounds but neither was obtained pure.

Peracetic acid oxidation of 12-*methoxypodocarpa*-8,11,13-*trien*-16-*ol* (II; R = Me, R′ = CH_2OH)

12-Methoxypodocarpa-8,11,13-trien-16-ol (10 g) partly dissolved in Ac_2O (15 ml) was added to peracetic acid (330 ml). The suspension rapidly became homogeneous and the soln was stood at 20° for 22 hr. Chromatography of the neutral fraction (7·3 g) gave 3 compounds.

(a) Light petroleum–benzene (1:1) (2·6 g) 12-methoxypodocarpa-8,11,13-trien-16-yl acetate, m.p. and mixed m.p. 72–73°, identical IR spectrum.

(b) Benzene–ether (1:1), (2·9 g) 16-acetoxy-12-methoxypodocarpa-8,12-diene-11,14-dione as yellow flakes from MeOH, m.p. and mixed m.p. 202–203°, identical IR spectrum.

(c) Ether (1·2 g) 16-acetoxy-8β-hydroxypodocarpa-9(11),13-dien-12-one, needles from acetone, m.p. and mixed m.p. 133–135°, identical IR spectrum.

Preparation and oxidation of methyl 13-*ethyl*-12-*methoxypodocarpa*-8,11,13-*trien*-16-*oate* (VI)

Methyl 13-acetyl-12-methoxypodocarpa-8,11,13-trien-16-oate[18] (10 g) in EtOH (200 ml) was treated with amalgamated Zn (23 g) and conc HCl (50 ml). The mixture was refluxed for ½ hr, poured into water and extracted with ether to give the 13-*ethyl derivative* (VI) as needles from EtOH (7·8 g, 81%), m.p. 111–112·5°. (Found: C, 76·3; H, 9·15; O, 14·5. $C_{21}H_{30}O_3$ requires: C, 75·9; H, 9·2; O, 15·0%.) ν_{max} 1730 (C=O), 1060 (=C—O—C), 865 and 850 cm^{-1} (1,2,4,5-substituted aromatic ring).

The methoxy ester (10 g) was treated with peracetic acid [from 30% H_2O_2 (98 ml), Ac_2O (230 ml) and conc H_2SO_4 (2·5 ml)] and stirred at 20° for 24 hr. The solid neutral fraction (8·3 g) was chromatographed on alumina to yield both starting material (6·8 g) and *methyl* 13-*ethyl*-8-*hydroxypodocarpa*-9(11),13-*dien*-12-*on*-16-*oate* (VII; 0·9 g) as needles from acetone, m.p. 202–204°. (Found: C, 72·1; H, 8·65; O, 19·55. $C_{20}H_{28}O_4$ requires: C, 72·3; H, 8·5; O, 19·25%.) ν_{max} 3580 (OH), 1735 and 1675 (C=O), 1647 and 1623 cm^{-1} (C=C), λ_{max} 242 mμ (ε 12,350).

Acknowledgement—We thank Mr I. R. C. McDonald, Chemistry Division, N.Z. DSIR for generous gifts of podocarpic acid. G.F.B. is the holder of a N.Z. Universities Postgraduate Research Scholarship and a Duke of Edinburgh Scholarship.