Lignans and Related Phenols. Part 18.[1] The Synthesis of Quinones from Podophyllotoxin and its Analogues

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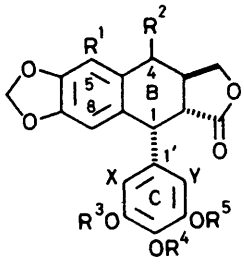
The preparation of quinones from podophyllotoxin and peltatins of the aryltetrahydronaphthalene class by oxidative demethylation is described. The derivation of 2′-substituted *ortho*-quinones from these products by the reductive addition of azide, bromide, and chloride and subsequent oxidation by periodate is reported. Acid-catalysed reactions of *ortho*-quinones with alcohols are described including an unusual example of reductive methylation.

Podophyllotoxin (**1a**) and other closely related aryltetrahydronaphthalene lignans are of interest owing to their powerful antimitotic activity, and to the ability of derived epiglucosides to inhibit DNA synthesis. This has led to the development of drugs such as etoposide (**1b**) and teniposide (**1c**) which have been widely used for the treatment of cancers.[2]

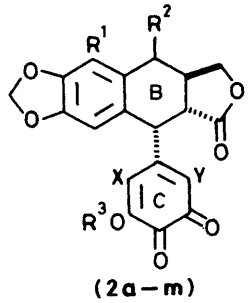
Recently the *in vivo* oxidative demethylation of these glucosides (**1b** and **c**) has been shown [3] to yield the corresponding ring C *ortho*-quinones (**2a** and **b**). These compounds have also been synthesized [4] *in vitro* from the parent drugs and found to be of comparable activity to them but to be appreciably more soluble in water–a property which is an aid to their administration.

The corresponding *ortho*-quinone (**2c**) derived from podophyllotoxin was first prepared by Ayres and Harris [5] by the oxidation of 4′-de-*O*-methylpodophyllotoxin with periodate and later from podophyllotoxin itself by oxidative demethylation using nitric acid.[1] We decided to prepare more quinones of this type for *in vivo* testing in view of their link [3] with the metabolism of the cancer inhibitors. 2′-Substituted quinones were made the first priority because insertion of substituents at this position stabilises the critical stereochemistry in ring C against epimerisation by alkali.[6] This change occurs so readily in the parent drugs that it may even occur at a pH which is attainable in the small intestine during oral administration.

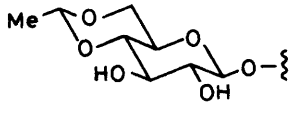
On re-preparation of the quinone (**2c**) it was found that the yield was optimal after 4 min reaction time in propionic acid solution at 0 °C, after which an inseparable mixture of products



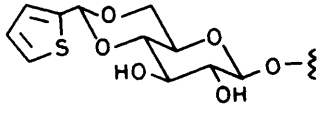
(1a–n)



(2a–m)



(A)



(B)

Structures of podophyllotoxins (**1**) and derived quinones (**2**)

	R¹	R²	R³	R⁴	R⁵	X	Y
(1) **a**;	H	α-OH	Me	Me	Me	H	H
b;	H	A	Me	H	Me	H	H
c;	H	B	Me	H	Me	H	H
d;	H	α-OH	Me	H	Me	H	H
e;	H	α-OAc	Me	Me	Me	H	H
f;	H	β-OH	Me	Me	Me	H	H
g;	H	H	Me	Me	Me	H	H
h;	H	β-OH	Me	H	H	Cl	H
i;	H	β-OH	Me	Me	Me	Cl	H
j;	H	H	Me	H	H	N_3	H
k;	H	β-OH	Et	H	H	Cl	H
l;	OH	H	Me	Me	Me	H	H
m;	OH	H	Me	H	Me	H	H
n;	OAc	H	Me	Me	Me	H	H

	R¹	R²	R³	X	Y
(2) **a**;	H	A	Me	H	H
b;	H	B	Me	H	H
c;	H	α-OH	Me	H	H
d;	H	α-OAc	Me	H	H
e;	H	β-OH	Me	H	H
f;	H	H	Me	H	H
g;	H	β-OH	Me	Cl	H
h;	H	H	Me	H	Br
i;	H	H	Me	N_3	H
j;	H	H	Et	H	H
k;	H	α-OH	Et	H	H
l;	OH	H	Me	H	H
m;	OAc	H	Me	H	H

was obtained. It was also found that, during chromatography, contact with surface-active media such as alumina and silica gel initiated further reactions and reduced the yield of the quinone. One of these products was identical with that[(**1d**)] obtained by reductive methanolysis.

In order to orientate substituents the ^{1}H n.m.r. spectrum of the starting quinone (**2c**) was studied using double-resonance techniques. Nuclear Overhauser enhancement (n.O.e.) difference experiments showed that irradiation of the C-5′-methoxy resonance at δ_H 3.76 produced a positive response at δ_H 6.48, confirming that this doublet could be assigned to the neighbouring 6′-H. The C-2′ proton gave rise to a quartet at δ_H 5.40 and decoupling showed that it was interacting with 6′-H (*J ca.* 2 Hz) and also with 1-H in ring B ($J < 1$ Hz). The C-6′ proton was coupled to 2-H and also to 1-H, which is to be expected since the pendent ring is no longer aromatic and allylic coupling occurs between ring C protons and 1-H. Another useful criterion is that the 1-H doublet is shielded relative to its position in podophyllotoxin (**1a**).

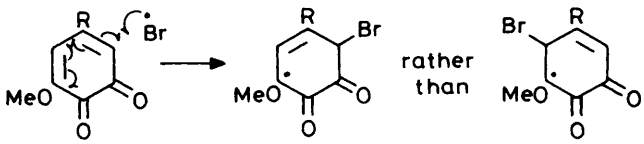
The nitric acid demethylation procedure was applied to 4-*O*-acetylpodophyllotoxin[7] (**1e**), epipodophyllotoxin[7] (**1f**), and 4-deoxypodophyllotoxin[8] (**1g**). The resulting 3′,4′-quinones (**2d**, **e**, and **f**) had the typical group of three peaks in the range 1 620—1 695 cm^{-1} in their i.r. spectra and the fine structure of the 2′- and 6′-H signals (outlined above) in the ^{1}H n.m.r. spectra. The quinone (**2f**) from 4-deoxypodophyllotoxin has been previously prepared and partially characterised.[9] We also found that the quinone system was unaffected on treatment of (**2c**) with acetic anhydride–pyridine, which afforded the 4-*O*-acetylquinone (**2d**) in good yield. This points the way to the synthesis of a range of 4-*O*-quinone derivatives including glycosides.

Hitherto ring C modification of podophyllotoxin[6] and other tetrahydronaphthalene lignans has been restricted to the use of electrophilic reagents, although quinones have been prepared from and used to orientate substituents in dibenzocyclooctadiene lignans.[10] There are only a few known examples of analogous monocyclic 3-alkoxy-1,2-benzoquinones and reports of their reactions with nucleophiles are rare. However, quinones in general react with a wide range of nucleophiles,[11] hence this approach offers many possibilities for the modification of these particular lignans.

The *ortho*-quinone (**2c**) was caused to react with hydrogen chloride gas at room temperature and, after hydrolysis of the 4-chloro group, 2′-chloro-4′,5′-dide-*O*-methylepipodophyllotoxin (**1h**) was obtained as the sole product. The ^{1}H n.m.r. spectrum established that the less reactive chloro substituent was located at the 2′-position of the pendent ring since, of the three aromatic protons, 5- and 8-H had shifts that were typical of 'epi' derivatives[12] and the third peak appeared at high-field close to the signal from the methylenedioxy ether group.[13] The doublet arising from 1-H was shifted downfield as a result of the restricted rotation of the C ring once a bulky substituent is placed at C-2′. On oxidation with periodate a red product was obtained and characterised as the 2′-chloro 4′,5′-quinone (**2g**). In its ^{1}H n.m.r. spectrum 6′-H resonated at δ_H 5.62 and the peak from the 3′-methoxy group was at δ_H 4.07. In an n.O.e. difference experiment the signal from the remaining ring C proton was unaffected on irradiation of the methoxy group, hence the chloro substituent had entered the position *ortho* to it.

The sequence of reactions was repeated with quinone (**2f**), using hydrogen bromide gas, to give a single yellow product which was converted into a red-brown quinone with characteristic i.r. absorption. In its ^{1}H n.m.r. spectrum irradiation of the methoxy protons (δ_H 3.55) gave a positive n.O.e. in the 6′-H peak and established the orientation as that shown (**2h**). Thus hydrogen bromide gave exclusive 1,6-addition in contrast to the 1,4-addition followed with hydrogen chloride.

We attempted to rationalise this apparent contradiction in terms of the 'hardness' of the two halides as nucleophiles. This view of the reaction is, however, unsatisfactory. A ^{13}C–^{1}H two-dimensional correlation spectrum showed that the site attacked by the softer bromide was hard (δ_C 123.29) relative to that (δ_C 112.40) *ortho* to the methoxy group which was unaffected. A more satisfactory explanation of the result may be that bromine addition follows a free-radical mechanism.* Attack at C-2′ would result in the formation of the allylically stabilised captodative radical (**3a**; Scheme 1) whereas attack at C-6′ would produce the less stable captodative radical (**3b**).



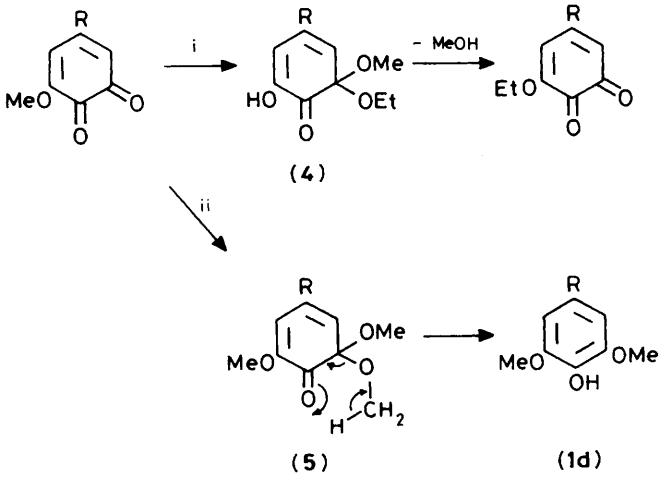
Scheme 1. Possible intermediates in bromination by a free-radical mechanism

The amination of ring C is a desirable modification but attempts at the preliminary nitration with sodium nitrate, nitronium tetrafluoroborate, and copper(II) nitrate–acetic anhydride were all unsuccessful. Since chloride addition has been demonstrated here, and there is an analogy between the reactions of quinones with azides and chloride,[14] we turned to this approach. It was borne out by the rapid formation of 2′-azido-4′,5′-dide-*O*-methyl-4-deoxyepipodophyllotoxin (**1j**) on treatment of the quinone (**2f**) with sodium azide–acetic acid. This compound was unstable both as a solid and in solution and could only be characterised by its i.r. and ^{1}H n.m.r. spectra. In the i.r. a strong absorption band lay at 2 118 cm^{-1} (azide) with the lactone carbonyl retained at 1 773 cm^{-1}. In the ^{1}H n.m.r. spectrum only one ring C proton appeared, at δ_H 6.09.

After a solution of the azide (**1j**) had been left for a few hours at room temperature, t.l.c. showed that several new products had been formed. The compound was readily oxidised and with periodate gave the red-purple 2′-azido 4′,5′-quinone (**2i**), typified by retention of the azide absorption (2 119 cm^{-1}) in the i.r. spectrum. An n.O.e. difference experiment showed that the orientation of this azide was the same as that of the 2′-chloro quinone (**2g**) and the ^{1}H n.m.r. spectra of the two compounds were also similar.

In the course of this work two observations prompted us to investigate further the reactions between these *ortho*-quinones and alcohols. The first was the modification mentioned above which occurred during chromatography on acidic media and the second was the isolation of a by-product from the reaction between the quinone (**2c**) and hydrogen chloride in reagent-grade chloroform. This substance was identified by ^{1}H n.m.r. spectroscopy and mass spectrometry as the 2′-chloro-3′-ethoxy homologue (**1k**). Its formation was ascribed to the acid-catalysed reaction of ethanol in the solvent (*ca.* 2% v/v). This was confirmed by the absence of the by-product when the reaction was conducted in ethanol-free chloroform and by the preparation of a similar homologue (**2j**) when the quinone (**2f**), from deoxypodophyllotoxin, reacted with ethanol present in AR chloroform on the addition of toluene-*p*-sulphonic acid (PTSA). This must follow a mechanism like that of ester exchange, in which a reversible nucleophilic addition gives the intermediate (**4**) (Scheme 2) and then proceeds to the right in the presence of an excess of ethanol.

* We acknowledge a helpful comment here from Dr. D. Crich.



Scheme 2. Acetal route to alkoxy exchange showing reductive methanolysis. *Reagents:* i, EtOH, H^+; ii, 2-MeOH, H^+

This reaction has potential for the preparation of analogues of existing drugs as was demonstrated by the synthesis of the ethoxy compound (**2k**) by treatment of the methoxyquinone (**2c**) with acidified ethanol.

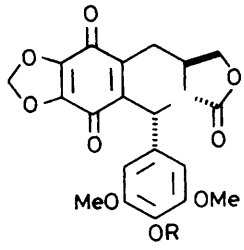
It has long been known that *ortho*-quinones undergo acid-catalysed reactions in methanol and ketonic hemiacetals have been proposed [15] as intermediates. On solution of the quinone (**2c**) in deuteriated methanol and recording the ^1H n.m.r. spectrum at 250 MHz it was immediately evident that several new peaks had appeared although those typical of the quinone were retained at a lower intensity. New signals assigned to 2′-H lay at δ_H 5.18 and 5.26 (normally δ_H 5.42) and those assigned to 6′-H fell at δ_H 5.89 and 5.91 (normally δ_H 6.42). The methanol was eliminated by evaporation under reduced pressure and the residue in deuterioacetone gave the normal spectrum of the quinone. These observations are supportive of the mechanism suggested (Scheme 2), and integration of ^1H n.m.r. signals pointed to the presence of the quinone and methanol adduct in about equal concentrations.

The acetalisation of these quinones was also shown by treatment in methanol with an acid with a weakly nucleophilic counterion, namely PTSA. Reduction of the quinone (**2c**) by the anion is now not possible and the reaction took another path which led to the isolation of 4′-de-*O*-methylpodophyllotoxin (**1d**). We are not aware of any precedent for this change but the nature of the product shows that a net reduction has occurred and we suggest that this follows the route shown *via* the C-3′ acetal (**5**) (Scheme 2). It would be difficult to detect formaldehyde generated in this way, because in the acidic conditions it would be expected to condense with oxyaromatic residues present in other lignan molecules. This would also account for the observed formation of a mixture of products.

It is significant that the formation of 4′-de-*O*-methylpodophyllotoxin only occurred following reaction with methanol, a reducing agent, and not with ethanol which exchanged alkoxy groups without changing the oxidation state. A useful application of the reductive methylation would be to incorporate a labelled methyl group into the 4′-demethoxy lignan.

α-Peltatin (**1m**) and β-peltatin (**1l**) resemble de-*O*-methylpodophyllotoxin and co-occur with podophyllotoxin in *Podophyllum peltatum*.[16] The respective yields are subject to seasonal variation but are more than sufficient for commercial development. Little attention has been given to the chemistry of the peltatins as compared with that paid to podophyllotoxin.

It has been shown [5] that, with the free phenolic OH group in ring A,β-peltatin (**1l**) can be oxidised with Fremy's salt to the *para*-quinone (**6a**). This reaction was selectively extended to α-peltatin which yielded the corresponding 4′-demethylated product (**6b**). However, in a useful variation the reaction with



(**6**) **a**; R = Me
b; R = H

periodate afforded the *ortho*-quinone (**2l**), whose i.r. spectrum showed that the strained lactone and 5-OH functions were retained. The ^1H n.m.r. spectrum included a group of peaks typical of those described for an *ortho*-quinone derived from ring C.

For commercial purposes the nitric acid route to lignan quinones is more cost effective. Although the methylenedioxy ether is not affected by nitric acid, the phenolic OH group in ring A of β-peltatin led to a mixture of products. The oxidation can be controlled if the phenol is protected by acetylation, when reaction is confined to ring C and gives the *ortho*-quinone (**2m**) in 69% yield.

Thus it has been shown that the properties of podophyllotoxins may be varied by the reaction of fused or pendent quinone components. It is significant that these provide a direct route to derivatives with a free C-4′ OH group which is necessary for activity in the topoisomerase–DNA complex.[17]

Experimental

Solvents were GPR grade except for chloroform and methanol (AR grade) and were purified by standard techniques and dried over molecular sieves (4 Å). T.l.c. was carried out on plastic-backed plates (Merck 5735). Preparative t.l.c. (p.l.c.) was conducted on glass plates coated with silica gel 60 (Merck 7739) (1 mm), whilst silica gel 7734 was employed for column chromatography. Detection on plastic plates was with phosphomolybdic acid (5% in ethanol) and/or by u.v. light. H.p.l.c. was carried out with a Spectra-Physics SP87000 system and an LC 871 u.v. detector, which ensured the homogeneity of analytical material.

M.p.s were measured on a hot stage and are uncorrected. I.r. spectra were employed using a Perkin-Elmer 298 spectrophotometer and mass spectra by Mr P. D. Cook using an AEI MS902 instrument. Proton magnetic resonance spectra were obtained by Mr G. Coumbarides using either a Bruker WP-80 or AM-250 spectrometer; chemical shifts are given as δ-values relative to tetramethylsilane as internal standard.

Sources of Precursors.—Podophyllotoxin was obtained by extraction of the roots of *Podophyllum emodi* and α- and β- peltatin from the resin of *Podophyllum peltatum* (Merck). 4-*O*-Acetylpodophyllotoxin, epipodophyllotoxin, and deoxypodophyllotoxin were derived by established procedures.[18]

Typical Procedure for Oxidative Demethylation.– Podophyllotoxin (**1a**) (1.00 g, 2.42 mmol) was dissolved in propionic acid (7.5 ml) and rapidly mixed with a solution of concentrated nitric acid (4.5 ml) in propionic acid (7.5 ml) at 0 °C. After exactly 4 min the dark red solution was poured into water (150

Table 1. ^{1}H N.m.r. signals of ring C *ortho*-quinones

Compound	5-H	6′-H	2′-H	4-H	1-H	3-CH_α	3-CH_β	2-H	3-H
(**2c**)[a]	7.17	6.48	5.40	4.78	4.45	4.65	4.24	3.30	3.10—2.75
(**2d**)	6.75	6.50	5.47	5.85		4.67—4.12		3.12	3.00—2.70
(**2e**)	6.83	6.52	5.20	4.83	4.28	4.50		3.49	3.05—2.70
(**2f**)[a]	6.75	6.48	5.33	3.20, 2.70	4.42	4.57	4.07		3.20—2.70
(**2g**)	6.80	5.62	(Cl)	4.84	5.12	4.45		3.59	3.10—2.60
(**2h**)	6.70	5.60	(Br)	3.13, 2.60	5.10	4.57	3.97		3.13—2.60
(**2i**)[a]	6.72	5.62	(N_3)	3.20, 2.60	4.90	4.53	4.07		3.20—2.60
(**2l**)[a]	(OH)	6.47	5.35	3.20, 2.60	4.36	4.58	4.07		3.30—2.60
(**2m**)	(Ac)	6.50	5.38	3.20, 2.60	4.30	4.63	4.05		3.20—2.60

[a] Solvent [$^2H_6$]acetone; all others in $CDCl_3$. 8-H Signals in the range δ_H 6.48—6.67 except for (**2l**), δ_H 6.31. Broad OH signals close to δ_H 2.20 except for (**2l**), δ_H 8.45. The spectra of (**2j**) and (**2k**) closely resemble those of (**2f**) and (**2c**), respectively. In (**2j**) the ethyl ether gave rise to a methyl peak at δ 1.39 (3 H), whilst the methylene signal was coincident with those of 3-H and 3-CH_α or 3-CH_β (4.22—3.70). In (**2k**) the corresponding peaks lay at δ 1.38 (3 H) and 3.80 (2 H).

Table 2. Other characteristics of ring *C ortho*-quinones[a]

Compound	M.p. (°C)	Yield (%)	M.s. (*m/z*) (required)	$\nu_{max.}$(cm^{-1}) (Quinone C=O)	Other
(**2c**)	190—192	75	*M*, 384.0845 (384.0845) $C_{20}H_{16}O_8$	1 698, 1 664, 1 628	3 460 (OH)
(**2d**)	218—220	75	(*M* + 2 H), 428.1121 (428.1107) $C_{22}H_{20}O_{11}$	1 695, 1 657, 1 619	1 725 (Ac)
(**2e**)	235—238	74	*M*, 384.0985 (384.0845) $C_{20}H_{16}O_8$	1 695, 1 660, 1 625	3 475 (OH)
(**2f**)[b]	207—210	70	*M*, 368.0903 (368.0896) $C_{20}H_{16}O_7$	1 696, 1 663, 1 624	
(**2g**)	217—220	80	(*M* + 2 H), 420.0626 (420.0612) $C_{20}H_{17}ClO_8$	1 685, 1 660 only	3 480 (OH)
(**2h**)	179—181	47	(*M* + 2 H), 448.0138* (448.0157) $C_{20}H_{17}BrO_7$	1 700, 1 676, 1 620	
(**2i**)	None	85	None	1 680, 1 655 only	2 119 (N_3)
(**2j**)	186—190	79	*M*, 382.1055 (382.1052) $C_{21}H_{18}O_7$	1 696, 1 660, 1 622	3 400 (OH)
(**2k**)	160—162	76	*M*, 398.1003 (398.1002) $C_{21}H_{18}O_8$	1 696, 1 660, 1 624	
(**2l**)	201—204	83	(*M* + 2 H), 386.1003 (386.1002) $C_{20}H_{18}O_8$	1 700, 1 661, 1 626	3 360 (OH)
(**2m**)	196—198	69	*M*, 426.0966 (426.0954) $C_{22}H_{18}O_9$	1 696, 1 661, 1 624	1 771 (AC)

[a] Compounds of the podophyllotoxin group are structurally similar to Dianins' compound[19] and like this substance they form a range of stable solvates which may be characterised by *X*-ray analysis (T. J. Petcher, H. P. Weber, M. Kuhn, and A. von Wartburg, *J. Chem. Soc., Perkin Trans. 2*, 1973, 288). For this reason it is often difficult to prepare a sample in a fit state for elemental analysis since removal of superficial solvent may be attended by only partial removal of interstitial solvent. *ortho*-Quinones of the type described tend to be modified on prolonging the drying procedure and therefore we have in the main depended on accurate mass measurements, n.m.r. spectra, and h.p.l.c. purity checks for characterisation of this group of interrelated compounds. [b] (**2f**) (Found: C, 62.2; H, 4.6. $C_{20}H_{16}O{\cdot}H_2O$ requires C, 62.2; H, 4.7%).

ml) and extracted with chloroform (4 × 25 ml). The combined extracts were washed with water (2 × 20 ml), dried ($MgSO_4$), and evaporated to low volume under reduced pressure. The residual solution was added dropwise to stirred, ice-cold light petroleum (b.p. 40—60 °C; 250 ml). After the mixture had been kept for 30 min, the precipitated product was filtered off and dried *in vacuo* to give 3′,4′-*didemethoxy*-3′,4′-*dihydro*-3′,4′-*dioxopodophyllotoxin* (**2c**) (0.78 g, 1.82 mmol, 75%, m.p. 192 °C,

benzene); δ_C 123.3 (C-2′), 112.4 (C-6′), 108.1 (C-8), 105.7 (C-5), 100.6 (OCH_2), 70.7 (C-4), 70.5 (C-3a), 54.3 (OCH_3), 44.2 (C-1), 43.0 (C-2), and 40.1 (C-3); other details of the characterisation are shown in the comparative Tables 1 and 2.

4-O-*Acetyl*-3′,4′-*didemethoxy*-3′,4′-*dihydro*-3′,4′-*dioxopodophyllotoxin* (**2d**) via (**1e**), 3′,4′-*didemethoxy*-3′,4′-*dihydro*-3′,4′-*dioxoepipodophyllotoxin* (**2e**) via (**1f**), 3′,4′-*didemethoxy*-4-*deoxy*-3′,4′-*dihydro*-3′,4′-*dioxopodophyllotoxin* (**2f**) via (**1g**), *and* 5-*acetoxy*-3′,4′-*didemethoxy*-4-*deoxy*-3,4′-*dihydro*-3′,4′-*dioxopodophyllotoxin* (**2m**) via (**1n**)[18] were all obtained by the above procedure on a scale in the range of 0.30—0.72 mmol. The only significant variations in procedure were: for (**2d**) the reaction time at 0 °C was extended to 7 min, and the product was recrystallised from ethyl acetate–light petroleum (b.p. 60—80 °C). For (**2f**) the recrystallisation solvent was propan-2-ol. For (**2m**) the reaction time was extended to 7 min. The characteristics of these compounds are given in Tables 1 and 2.

Acetylation of 3′,4′-*Didemethoxy*-3′,4′-*dihydro*-3′,4′-*dioxopodophyllotoxin* (**2c**).—The quinone (0.104 g, 0.272 mmol) was dissolved in acetic anhydride (2 ml) containing pyridine (2 drops) and the solution was stirred overnight at 40 °C. The product (0.0943 g, 81%) which separated on stirring the mixture in water (20 ml) was identical with that (**2d**) obtained above from oxidative demethylation of 4-*O*-acetylpodophyllotoxin (**1e**).

2′-*Chloro*-4′,5′-*dide*-O-*methylepipodophyllotoxin* (**1h**).—The quinone (**2c**) was dissolved in dichloromethane (25 ml) at 0 °C and a stream of hydrogen chloride was passed through it for 15 min. On evaporation the amorphous solid obtained was stirred with calcium carbonate (0.3 g) in acetone (10 ml)–water (2 ml) at 50 °C for 2 h, the mixture was filtered, and the product extracted into chloroform (3 × 20 ml). The dried ($MgSO_4$) extract was purified by column chromatography (silica gel; chloroform–methanol 100:2) to give 2′-chloro-4′,5′-dide-*O*-methylepipodophyllotoxin (**1h**) (0.10 g, 0.24 mmol, 46%), m.p. 206—208 °C; $\nu_{max.}$ 3 390 (OH), 1 755 (lactone C=O), and 1 608 (aromatic); δ_H([$^2H_6$]acetone) 7.88 (2 H, br s, OH), 6.90 (1 H, s, 5-H), 6.30 (1 H, s, 8-H), 6.10 (1 H, s, 6′-H), 5.98 (2 H, s, OCH_2O), 5.06 (1 H, d, $J_{1,2}$ 6 Hz, 1-H), 4.92 (1 H, d, 4-H), 4.32 (2 H, m, 3-CH_2O), 3.83 (3 H, s, OMe), 3.44 (1 H, q, 2-H), 3.30—2.90 (1 H, m, 3-H), and 2.84 (1 H, br s, OH); *m/z* 420 (M^+).

Typical Procedure for Periodate Oxidation.—The catechol (**1h**) (0.100 g, 0.238 mmol) was dissolved in methanol (10 ml)–water (4 ml) and the solution was stirred with a solution of sodium metaperiodate (0.052 g, 0.238 mmol) in water (1 ml) for 10 min; t.l.c. (chloroform–methanol 100:4) then showed that the reaction was complete and that a single red product had been formed. The solution was diluted with water (100 ml), and extracted with chloroform (2 × 20 ml); the extract was dried ($MgSO_4$), and evaporated under reduced pressure, to give 2′-*chloro*-4′,5′-*didemethoxy*-4′,5′-*dihydro*-4′,5′-*dioxoepipodophyllotoxin* (**2g**) (0.08 g, 0.192 mmol, 80%), whose characteristics are given in Tables 1 and 2.

2′-*Bromo*-3′,4′-*didemethoxy*-4-*deoxy*-3′,4′-*dihydro*-3′,4′-*dioxopodophyllotoxin* (**2h**).—The quinone (**2f**) was treated with hydrogen bromide in the same way as for the preparation of compound (**1h**) above. However, the catechol was not purified but was immediately treated with periodate and the crude 2′-*bromoquinone* (**2h**) was recrystallised from ethyl acetate–light petroleum (b.p. 60—80 °C) to give a 47% yield (0.0284 g, 0.064 mmol) of the title compound; for n.m.r. data see Tables 1 and 2).

2′-*Azido*-4′,5′-*dide*-O-*methyl*-4-*deoxypodophyllotoxin* (**1j**).—A solution of sodium azide (0.100 g, 1.54 mmol) in water (2 ml)–acetic acid (3 ml) at 0 °C was quickly added to a solution of the quinone (**2f**) (0.100 g, 0.272 mmol) in chilled acetic acid (5 ml), when the red colour rapidly faded to give a yellow-green solution. On dilution in cold water a pale yellow precipitate of the 2′-azido derivative was obtained (0.071 g, 0.173 mmol, 64%); $\nu_{max.}$ 3 395, 3 350 (OH), 2 118 (N_3), 1 773 (lactone C=O), and 1 608 cm^{-1} (aromatic); δ_H([$^2H_6$]acetone) 6.74 (1 H, s, 5-H), 6.33 (1 H, s, 8-H), 6.07 (1 H, s, 6′-H), 5.95 (2 H, s, OCH_2O), 4.95 (1 H, d, 1-H), 4.47 (1 H, m, HO), 4.00 (1 H, m, HO), 3.95 (3 H, s, OMe), and 3.12—2.63 (4 H, m, 2-, 3-, and 4-H).

2′-*Azido*-4′,5′-*didemethoxy*-4-*deoxy*-4′,5′-*dihydro*-4′,5′-*dioxopodophyllotoxin* (**2i**).—The 2′-azidocatechol (**1j**) was treated with periodate as described above and the 2′-azidoquinone (**2i**) was obtained as a red-purple solid (0.0424 g, 0.104 mmol, 85%), characterised by n.m.r. and i.r. spectroscopy (Tables 1 and 2).

Acid-catalysed Reactions between Quinones and Alcohols.—The quinone (**2c**) (0.104 g, 0.242 mmol) was treated with hydrogen chloride as above but in ethanol-stabilised chloroform (25 ml), when a product mixture was obtained (t.l.c.) which was separated by semi-preparative h.p.l.c. (reverse phase; 5 μ Hypersil; MeOH–water 1:1, flow 4 ml min^{-1}). This yielded the product (**1h**) (R_t 8.0 min) (17.4 mg, 0.04 mmol, 15%) previously described, and the product of alkoxy exchange, 2′-chloro-3′,4′,5′-tridemethyl-3′-*O*-ethylpodophyllotoxin (R_t 12.0 min) (10.0 mg, 0.023 mmol, 9%), m.p. 203—206 °C; $\nu_{max.}$ 3 395 (OH), 1 755 (lactone C=O), and 1 610 cm^{-1} (phenyl); δ_H([$^2H_6$]acetone) 7.67 (2 H, br s, 4′- and 5′-OH), 6.93 (1 H, s, 5-H), 6.33 (1 H, s, 8-H), 6.11 (1 H, s, 6′-H), 5.98 (2 H, s, OCH_2O), 5.08 (1 H, d, *J* 6 Hz, 1-H), 4.95 (1 H, d, 3 Hz, 4-H), 4.33 (2 H, m, 3-CH_2O), 4.09 (2 H, t, *J* 7 Hz, OCH_2Me), 3.48 (1 H, q, 2-H), 3.3—3.05 (1 H, m, 3-H), 2.80 (1 H, br s, 4-OH), and 1.39 (3 H, t, *J* 7 Hz, OCH_2Me); *m/z* 434 (M^+).

The quinone (**2f**) (0.031 g, 0.083 mmol) and one crystal of PTSA were dissolved in ethanol-stabilised chloroform. After the mixture had been kept overnight the residue obtained on evaporation of the solvent was crystallised from propan-2-ol to afford 3′,4′,5′-*tridemethoxy*-4-*deoxy*-3′-*ethoxy*-4′,5′-*dihydro*-4′,5′-*dioxopodophyllotoxin* (**2j**) (see Tables 1 and 2).

The analogous reaction of the quinone (**2c**) (0.60 g, 0.156 mmol) was complete on solution in ethanol in 7 h and gave 3′,4′,5′-*tridemethoxy*-3′-*ethoxy*-4′,5′-*dihydro*-4′,5′-*dioxopodophyllotoxin* (**2k**) (see Tables 1 and 2).

The quinone (**2c**) (0.100 g, 0.260 mmol) after similar treatment in methanol (10 ml) for 24 h gave a solution shown by t.l.c. ($CHCl_3$–MeOH 100:2) to contain one major and several minor products. P.l.c. under the same conditions led to the isolation of 4′-de-*O*-methylpodophyllotoxin (**1d**) (0.037 g, 0.093 mmol, 36%); m.p. 252—255 °C (lit.,[19] 250—252 °C), with i.r. and ^{1}H n.m.r. spectra identical with those of a reference sample; *m/z* 400.1147 (M^+. Calc. for $C_{21}H_{20}O_8$: *M*, 400.1158).

4′-*De*-O-*methyl*-4-*deoxy*-5,8-*dihydro*-5,8-*dioxopodophyllotoxin* (**6b**).—A solution of Fremy's salt[20] (potassium nitrosodisulphonate) (0.154 g, 0.574 mmol) in potassium dihydrogen phosphate buffer (0.166 mol; 15 ml) was added dropwise to a stirred solution of α-peltatin (**1m**) (0.100 g, 0.25 mmol) in acetone (3 ml) at 0 °C. After 30 min the mixture was diluted with water (100 ml), then extracted with chloroform (2 × 25 ml), and the extract was dried ($MgSO_4$), and evaporated under reduced pressure, to give the 5,8-para-*quinone* (**6b**) (0.066 g, 0.159 mmol, 64%); m.p. 242—244 °C; $\nu_{max.}$ 3 450 (OH), 1 771 (lactone C=O), and 1 663 (quinone C=O); δ_H[$(CD_3)_2SO$] 8.23 (1 H, s, 4′-OH), 6.46 (2 H, s, 2′- and 6′-H), 6.18 (2 H, q, OCH_2O), 4.41 (1 H, m, 3-$CH_\alpha H_\beta O$), 3.97 (1 H, m, 3-$CH_\alpha H_\beta O$), 3.94 (1 H, d, 1-H), 3.72 (6 H, s, 2 × OMe), and 2.90—

2.45 (4 H, m, 2- and 3-H and 4-H_2); *m/z* 416 (M + 2 H), 414.0951 (M^+) ($C_{21}H_{18}O_9$ requires M, 414.0951).

3′,4′-*Didemethoxy*-4-*deoxy*-3′,4′-*dihydro*-5-*hydroxy*-3′,4′-*dioxopodophyllotoxin* (**2l**).—A solution of α-peltatin (**1m**) (0.100 g, 0.25 mmol) in chloroform (15 ml) was shaken with periodic acid (0.057 g, 1 mmol equiv.) in water (100 ml) for 30 min. The sole product, isolated from the dried ($MgSO_4$) chloroform extract, was the 3′,4′-*quinone* (**2l**) (0.080 g, 0.21 mmol, 83%) (see Tables 1 and 2).

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