Lignans and Related Phenols. Part XV.[1] Remote Substituent Effects on the Rates and Products of Some Reactions of Aryltetrahydronaphthalenes

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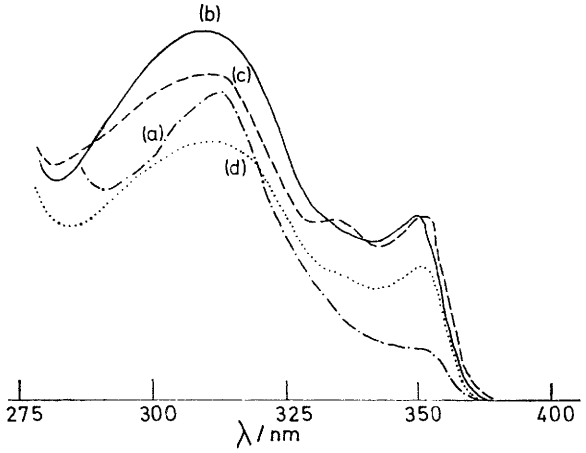
An unambiguous example of the steric acceleration of a simple solvolysis at an uncongested site by a remote substituent is given. Other evidence of remote control of product formation has been obtained and related to the design of cancer-inhibitory podophyllotoxins. The findings have been applied to the synthesis of a peltatin (VII) which is stable and physiologically active in both acid and alkaline media. Evidence of extreme compression, ready extrusion of substituents, and encagement of other molecules is presented.

In our preliminary communication [2] we reported the enhanced rates of solvolysis of 4-halogenodeoxypodophyllotoxins when a remote hindered substituent was inserted in the pendant ring (I; X = Br or Cl, Y = Cl). These results were correlated with physical evidence of strain in ring B and the lactone function; increases in the carbonyl stretching frequencies of the 2′-halogenopodophyllotoxones (I; X = halogen, Y = carbonyl) relative to the parent keto-lactone are evidence of this.

The 4α- and 4β-chloro-compounds † (I, X = H, Y = α- or β-Cl) are hydrolysed at a similar rate in 12% water–dioxan and the data given were evaluated for the initial stage of the reaction when t.l.c. showed that the only significant product was epipodophyllotoxin, the 4β-ol (I; X = H, Y = OH). Under the same conditions the solvolysis of the 2′,4β-dichloro-compound (I; X = Y = Cl) was too fast for convenient measurement and this precluded a direct comparison. The reaction of the 2′,4β-dichloro-compound was moderated satisfactorily by reducing the temperature of measurement from 40 to 30 °C by decreasing the polarity of the medium (3% water–dioxan); however direct comparison was still excluded as there was then negligible hydrolysis of the epimers (I; X = H) after 16 h. As the acidity of the medium increases so does the reversion of the 4β-ol to the carbocation and in the natural podophyllotoxins this hydroxy-group is re-established by solvation from the less-hindered side and elimination does not compete; introduction of the hindered 2′-substituent diverts the reaction to give new products [(I) ⟶ (II); X = Cl] with the irreversible aromatisation of ring B [(II) ⟶ (III)]. This new feature necessitates a shorter period for initial rate measurements than that used in the previous calculation [2] and we have consequently revised the half-life from 478 to 340 min. This rate in the less polar medium at 30 °C is similar to those of the epimeric pair (I; X = H) in the more polar medium at 40 °C and a fair estimate of rate enhancement in the 2′-chloro-derivative can be made by using the extensive compilation [3] of solvolysis rates for benzyl and diphenylmethyl chlorides in mixtures of water and dioxan. This indicates an increase of over 30 in the 12% water mixture with a further increment of about 2.5 due to the temperature coefficient.[4] The steric acceleration observed is therefore *ca.* 50—100 fold and is attributed to strain relief in forming the carbocation during an S_N1 reaction; evidence in support of such a mechanism has been quoted.[2] It is further supported by the observed sensitivity to small amounts of a polar solvent and by the participation of electron-donating ring-A substituents.[4]

Steric acceleration has been observed in the solvolysis of 2,4,6-tri-t-butylbenzyl chloride [5] and of 8-substituted 1-chloromethylnaphthalenes.[6] The interpretation is complicated in the former by congestion at the reaction site and in the latter there is some direct electronic interaction of the *peri*-substituent: 8-CH_3 effects a rate increase of 21 relative to 8-H. In our model the remote triggering group cannot interact electronically or spatially with the reaction site and the similar rates found for the epimeric pair (I; X = H) show that steric factors are unimportant here. The products of reaction have been characterised and there is no evidence of a rearrangement reaction which could have led to rate enhancement.



U.v. absorption (solutions in methanol) of (a) 2′-chloro-α-apopodophyllotoxin (II) and (b)—(d) dehydroanhydropicropodophyllins [(6) (III; X = H), (c) (III; X = Cl); (d) (III; X = Br)]

Although the unknown α-apopodophyllotoxin (II; X = Br or Cl) derivative is the expected first product of 4-OH elimination it could not be purified for full characterisation owing to the ease of the subsequent dehydrogenation step which rapidly affords the arylnaphthalene

† The β-face is taken as that bearing the C-2 proton, as this is the reference point for determining absolute configuration.

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[2] D. C. Ayres and C. K. Lim, *J.C.S. Chem. Comm.*, 1973, 487.

[3] H. Böhme and W. Schürhoff, *Chem. Ber.*, 1951, **84**, 28.

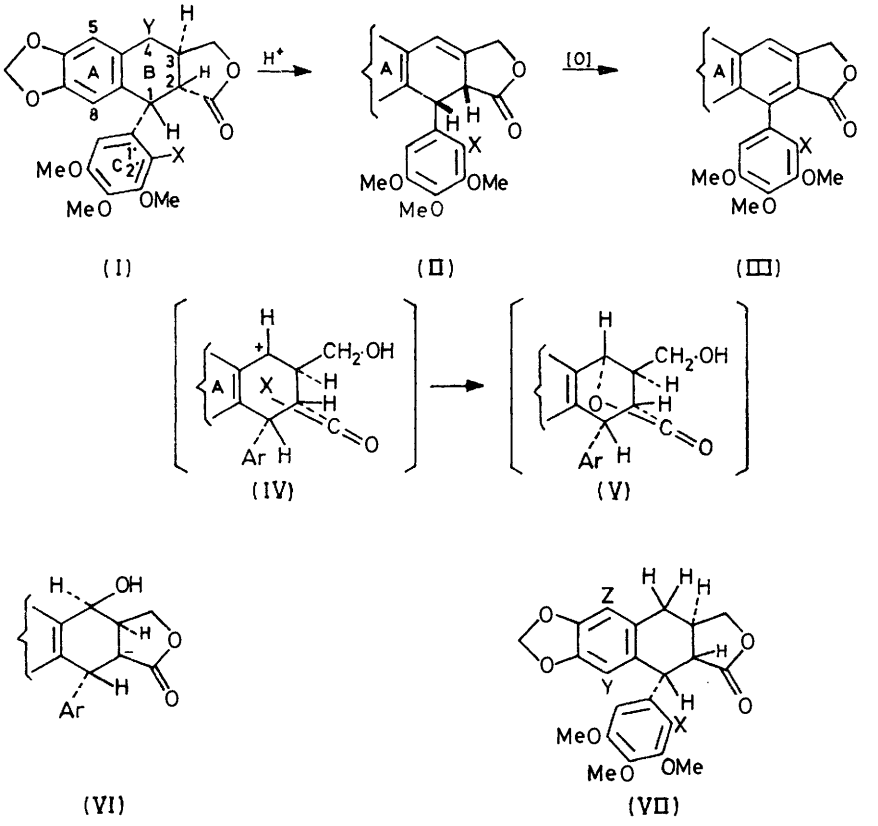
[4] E. L. Kulin and K. T. Leffek, *Canad. J. Chem.*, 1973, **51**, 687.

[5] L. R. C. Barclay, H. R. Sonawane, and J. C. Hudson, *Canad. J. Chem.*, 1972, **50**, 2318.

[6] D. C. Kleinfelter and P. H. Chen, *J. Org. Chem.*, 1969, **34**, 1741.

(III; X = Br or Cl). Crude material obtained under mild conditions had an i.r. spectrum typical of a strained α-apo-compound [2] and its n.m.r. spectrum included a peak at δ 6.56 broadened by coupling to the lactone methylene protons which is similar to the vinylic proton signal in apo-compounds.[7] Spontaneously or when recrystallisation was attempted, the n.m.r. spectrum simplified to that of an arylnaphthalene;[8] a similar progressive replacement of the peak in the u.v. spectrum (Figure) at 311 nm characteristic of an α-apo-compound by absorption typical [9] of the highly fluorescent arylnaphthalene was also observed.

An unusual property of these aromatised products (III) is the ease with which the 2'-halogeno-substituent is extruded; the bromo- and chloro-compounds remelted at a common temperature of 270°, the m.p. of the dehydroanhydropicropodophyllin (III; X = H). Stored samples were examined comparatively by t.l.c. and by n.m.r. and were found to have been dehalogenated to a degree dependent upon their age: the three non-equivalent methoxy-signals (δ 3.84, 4.03, and 4.06) were gradually replaced by the two signals [δ 3.85 (6 H) and 3.98 (3 H)] typical of dehydroanhydropicropodophyllin. This change probably proceeds *via* a free-radical mechanism since it could only be prevented during recrystallisation from acetone or chloroform if the heating period in daylight was restricted to a few minutes. Loss of the 2'-halogeno-substituent is another indication of the high degree of compression in these molecules and is comparable to the reductive dechlorination of 2,2',4,4',5,5'-hexachlorobiphenyl [10] in methanol where the more hindered chlorine atoms are the first to be extruded.



As podophyllotoxin (I; X = H, Y = α-OH) does not undergo the acid-catalysed elimination of the α-OH group, apo-compounds are normally obtained from the epimeric picropodophyllins (I; X = H; 1,2-*trans*), where the epimerisation at C-2 relieves strain in the lactone function and takes place so readily that artefacts have been formed on brief contact with weak bases.[11] The failure of the elimination in podophyllotoxins has been attributed [12] to excessive strain in the model with *cis*-related C-3 and C-4 substituents which inhibits either the formation of the carbocation or the final insertion of the double bond. However, a model of α-apopodophyllotoxin may readily be constructed and our demonstration of accelerated carbocation formation in halogeno-analogues, where levels of hindrance are higher than in the parent substance, shows that another explanation is needed. There is substantial evidence [2] that the

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[8] (*a*) R. S. Burden, L. Crombie, and D. A. Whiting, *J. Chem. Soc.* (*C*), 1969, 693; (*b*) Z. I. Horii, K. Ohkawa, S.-W. Kim, and T. Momose, *Chem. and Pharm. Bull*, (*Japan*), 1971, **19**, 535.
[9] J. L. Hartwell and A. W. Schrecker, 'Progress in the Chemistry of Organic Natural Products,' Springer, Vienna, 1958, vol. 15, pp. 140—141.
[10] L. O. Ruzo and M. J. Zabik, *Bull. Environ. Contamination Toxicol.*, 1975, **13**, 181.
[11] J. L. Hartwell and A. W. Schrecker, *J. Amer. Chem. Soc.*, 1959, **72**, 3320.
[12] A. W. Schrecker and J. L. Hartwell, *J. Amer. Chem. Soc.*, 1954, **76**, 752.

initial change leads predominantly to the 4β-isomer, irrespective of whether this occurs by halogen displacement or by acid-catalysed epimerisation of an alcohol; indeed no 4α-isomer can be detected by chromatography when solvation of the carbocation occurs. It follows that the α-face offers much more hindrance than the β-face and that a mechanism other than direct approach to the carbocation controls 4α-substitution. In acidified ethanol the carbonyl group of the primary lactone will be revealed and the podophyllotoxin configuration is favourable for an α-interaction with the carbocation (IV; X = OH); this can lead to the isolation of the bridged lactone neopodophyllotoxin (V) [13] and inhibits the elimination of the C-3 proton. This feature also accounts for variations in the type of reaction between these lignan alcohols and acetic anhydride. Thus in the absence of a catalyst acetates are formed with retention, but in the presence of acid picropodophyllin undergoes elimination whereas podophyllotoxin and its C-4 β-epimer both afford the 4α-acetate of podophyllotoxin; these last results [12] are also consistent with capture of the acetoxy-group following a bridged α-interaction of a mixed acetic anhydride revealed as above [*cf.* (IV; X = AcO)]. The contrast between the retention of the C-4 substituent in podophyllotoxins and its elimination in the 2′-halogeno-derivatives is also explicable, since in the latter the effective stabilisation by bridging will be subject to considerable steric hindrance; this is clear from a comparative study of models of 2′-chloroneopodophyllotoxin (V; Ar bears 2′-Cl) and 2′-chloroepipodophyllotoxin (I; X = Cl, Y = β-OH). The resistance of the latter to base-catalysed isomerisation provides chemical evidence of extreme crowding, for the insertion of the halogen prevents epimerisation at C-2 even on prolonged contact with alkoxide ion. The control must arise from the greater bulk and restricted rotation [14] of the pendant ring which directs reprotonation of the conjugate base (VI) to the β-face. The pendant ring resists chlorination if this is attempted with phosphorus pentahalides *after* epimerisation to picropodophyllin. This feature supports the argument for steric control but has also prevented a synthesis of halogenopicropodophyllins, since this direct approach afforded the α-apo-compound (II; 1,2-*trans*). The last observation shows that the podophyllotoxin configuration is not lost during halogenation, and retention of this geometry in the products follows from (*a*) earlier n.m.r. evidence [14] of ring B coupling constants, (*b*) that now presented of increased strain in the system, and (*c*) the *X*-ray study [15] of 2′-bromopodophyllotoxin.

The effect of remote substituents in controlling reaction types and increasing rates is of interest chemotherapeutically. Amongst the podophyllotoxin group a high proportion of compounds are active against experimental tumours [16] but applications in chemotherapy have been restricted by their toxicity. It is logical to explore the use of analogues with additional substituents because the demonstrated effects on reaction rates and product type are expected to change the balance of *in vivo* reactions and hence the therapeutic index. The index may of course be determined by the properties of metabolites of the test substance and increased toxicity can result. As the base-catalysed change produces picropodophyllins which are physiologically inactive, podophyllotoxins stable to bases were attractive as test substances. 2′-Chloroepipodophyllotoxin was tested initially, as epipodophyllotoxin itself had recently been found [17] to have potential as an antimitotic agent; however there was no increase in the survival time of animals infected with the TLX/5 lymphoma at a dose level of 150 mg kg^{-1}. The elimination of the 4-OH group in this compound and the aromatisation of ring B would lead to loss of activity [16] and formation of a toxic [18] arylnaphthalene.

We have subsequently synthesised, but have not yet tested, a derivative which is susceptible to neither epimerisation by base nor acid-catalysed elimination. Here the starting material was β-peltatin,[19] an antimitotic 4-deoxy-lactone (VII; X = Y = H, Z = OH) which on treatment with phosphorus pentabromide in benzene afforded a phenolic product with an i.r. spectrum typical of additional substitution in the pendant ring in which the aromatic peak (1 590 cm^{-1}) of the precursor was replaced by three typical minor peaks. The presence of a strained lactone group which absorbed at 1 785 cm^{-1} was noted, together with another strong carbonyl peak at 1 700 cm^{-1}; the n.m.r. spectrum established that the latter arose from acetone of crystallisation which was retained in an equimolar ratio after an extended period of drying under vacuum. The presence of a 2′-substituent was confirmed by three non-equivalent methoxy-signals in the n.m.r. spectrum; variations in the solvent were made to obviate screening of aromatic signals,[14] but only one aromatic proton was detected. The signal for this fell at δ 6.35 in trifluoroacetic acid but in the spectrum of the more soluble acetate in deuteriochloroform the resonance was shifted to δ 5.98, characteristic of the strongly shielded 6-position. Despite the opposing steric factors, substitution at the 8-position is implicit in the n.m.r. evidence, and this was confirmed by the mass spectrum which had the peak distribution and fragmentation pattern of a dibrominated compound and characterised the product as 2′,8-dibromo-β-peltatin (VII; X = Y = Br, Z = OH). This orientation is substantiated on chemical grounds, for dihalogenation of ring C in comparable models [14] is not possible under the same conditions, whilst the prior replacement of the 4-OMe group by halogen prevents further substitution altogether. Apart

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[15] T. J. Petcher, H. P. Weber, M. Kuhn, and A. von Wartburg, *J.C.S. Perkin II*, 1973, 288.
[16] E. Shreier, Symposium on Tumour Inhibitors from Plant Sources, 152nd meeting of the American Chemical Society, September 1966.
[17] A. R. Broc *et al.*, *Brit. Med. J.*, 1972 (2), 744.
[18] K. Munakata, S. Marumo, and K. Ohta, *Tetrahedron Letters*, 1965, 4167.
[19] Ref. 9, p. 126.

from steric hindrance the insertion of bromine *para* to the phenolic OH group is to be expected and it is possible that the initially formed aryl phosphorodibromidite (VII; X = H or Br, Y = H, Z = O–PBr_2) assists substitution by co-ordination with a molecule of bromine. The participation of this group in a dealkylation reaction under conditions similar to our own was described recently.[20]

In order to account for the effect of solvation on our first analytical results we examined the *O*-acetyl derivative (VII; X = Y = Br, Z = AcO), which retains solvents less tenaciously than the phenol, permitting a satisfactory analysis of acetone-free material. Clathrate inclusion of solvents by aryltetrahydronaphthalenes is to be expected in view of their close structural affinity with Dianin's compound [21] and its thio-analogue.[22] The interstitial inclusion of ethyl acetate by 2'-bromopodophyllotoxin was established by the *X*-ray study [15] and the large n.m.r. shifts observed for these lignans in benzene solution, relative to those in chloroform, are evidence of the magnetic effect of guest molecules. The 2',8-dibromoacetate (VII) is the most hindered derivative we have examined and in chloroform ghost peaks of similar intensity appeared close to the main ether and acetate n.m.r. signals; these disappeared when the solvent was changed to benzene. Further investigation of this behaviour is needed but it may arise from the restriction of guest chloroform molecules to two different average orientations with respect to the host.

EXPERIMENTAL

M.p.s were taken on a hot-stage apparatus. I.r. spectra (KBr discs) were recorded with an Infracord 237 spectrometer and u.v. spectra for solutions in chloroform with a Unicam SP 800 instrument. N.m.r. spectra were obtained with a Varian HA100 spectrometer and the mass spectra were taken by the Physico-chemical Measurements Unit, Harwell, and by the U.L.I.R.S. at the London School of Pharmacy; the microanalyses were also carried out in the latter Department. Kieselgel G was used for t.l.c., with benzene–ethyl acetate as eluant.

Determination of the Rate Constants for Solvolysis of 4-Chloro-4-deoxypodophyllotoxins.—Owing to the sensitivity of the reaction rate to the polarity of the water–dioxan medium, the solvent mixtures were made up accurately by weighing distilled water and dioxan (dried by distillation from lithium aluminium hydride).

The rates of solvolysis of analytically pure samples of 4α- and 4β-chloro-4-deoxypodophyllotoxins were similar in 12% water–dioxan at 40 °C and comparable (Table 1) with that of the more reactive 2',4β-dichloro-4-deoxypodophyllotoxin in 3% water–dioxan at 30 °C. The chloro-compounds (concn. 24—32 mmol l^{-1}) were dissolved in the mixed, solvent (10 ml) at zero time and samples were withdrawn at intervals up to *ca.* 90 min. The reaction was stopped by pipetting into chloroform (5 ml) and water (10 ml); after rejection of the major part of the organic layer, washings were added and the combined aqueous layer was re-extracted with chloroform (5 ml) before titration of liberated acid with sodium hydroxide solution (0.8850 g l^{-1}).

The rate constants (k_1) were obtained from the first-order relation: $k_1t = 2.303 \log [a/(a - x)]$, where $(a - x)$ is the concentration of reactant after time t, by determining the slope of the initial straight-line plot of $\log [a/(a - x)]$ against t. The half-life is given by the expression $t_{\frac{1}{2}} = 2.303 \log (2/k_1)$.

TABLE 1

Initial rates of solvolysis of 4-chloro-4-deoxypodophyllotoxins (DPT)

	Limit of observations	$10^{-5}k_1$ s^{-1}	$t_{\frac{1}{2}}$/min
4α-Cl-DPT } (40 °C, 12% H_2O)	30% reaction	5.36	215
4β-Cl-DPT }		4.21	274
2',4β-Cl_2-DPT (30 °C, 3% H_2O)	15% reaction	3.4	340

2'-*Halogenopodophyllotoxones.*— 2'-Bromoepipodophyllotoxin [14] (84 mg) dissolved in chloroform (15 ml) was stirred under reflux for 5 h with active manganese dioxide (1 g; Merck). Evaporation of the dried ($MgSO_4$) filtrate afforded a pale yellow solid (25 mg, 30%), m.p. 200—202° (from water–methanol), identical (i.r. and u.v. spectra) with the 2'-bromopodophyllotoxone prepared [14] by oxidation with bromate.

2'-*Chloropodophyllotoxone* was obtained in a similar way, m.p. 190—191°, in 32% yield (this is not optimal and should be improved on scaling up when losses by adsorption on the catalyst should be relatively smaller); $\lambda_{max.}$ ($CHCl_3$) 321 and 285 nm, $\nu_{max.}$ 1 785 (lactone C=O) and 1 685 cm^{-1} (ketone C=O) (Found: C, 58.9; H, 4.3%; M^+, 466. $C_{22}H_{19}{}^{35}ClO_8$ requires C, 59.2; H, 4.3%; *M*, 466).

Products from the Acid-induced Reactions of 2'-Halogenoepipodophyllotoxins.—A solution of 2'-chloroepipodophyllotoxin (105 mg, 0.23 mmol) in methanol (6 ml) containing 2N-hydrochloric acid (0.5 ml) was warmed on a water-bath for 5 min; crude 2'-chloro-α-apopodophyllotoxin was obtained by dilution with ice–water and dried *in vacuo*. There was no evidence of OH absorption in the i.r. spectrum and the lactone C=O peak had shifted from 1 780 in the precursor to 1 790 cm^{-1} in the product; the u.v. spectrum showed $\lambda_{max.}$ 311 nm (Figure). Attempts to purify the α-apo-compound by recrystallisation were frustrated by contamination with the dehydro-compound (III; X = Cl), which was best prepared by boiling a solution of the alcohol (230 mg, 0.51 mmol) in acetone (5 ml) containing 2N-hydrochloric acid (2 drops) for 2 h in the dark. Addition of a little more water gave a hot saturated solution which deposited crystals (80 mg, 35%) of *2'-chlorodehydroanhydropicropodophyllin*, m.p. 257°; the 2'-bromo-analogue (m.p. 262°) was prepared in the same way and the characteristics of these products are compared with those of dehydroanhydropicropodophyllin (DHAPP) [23] in the Figure and Table 2.

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[22] D. D. MacNicol, A. D. U. Hardy, and J. J. McKendrick, *J.C.S. Chem. Comm.*, 1975, 343.

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Extrusion of Halogeno-substituents.—2′-Chloro-DHAPP (75 mg, 0.18 mmol) was suspended in refluxing acetone (5 ml) in daylight for 30 min; needles of dehydroanhydropicropodophyllin (50 mg, 72%) slowly crystallised from the clear solution obtained. The same product (*cf.* Table 2) was obtained in 64% yield on heating 2′-bromo-DHAPP in chloroform (5 ml) for 30 min followed by precipitation with light petroleum (b.p. 40—60°) and crystallisation from acetone.

Treatment of 2′-Halogenoepipodophyllotoxins with Bases.—The bromo- and chloro-compounds (*ca.* 150 mg) were treated for 30 min under reflux (*a*) in methanol (5 ml)–piperidine (2 drops); (*b*) in acetone (8 ml)–sodium acetate (0.2 g); (*c*) in ethanol (5 ml)–sodium ethoxide (*ca.* 0.1 g). Evidence from m.p., mixed m.p., and i.r. and n.m.r. spectra showed that starting material could be recovered in 85—95% yield.

trum of a solution in trifluoroacetic acid [δ 2.38 (6 H, s, Me_2CO), 3.73 (3 H, s, OMe), 4.04 (3 H, s, OMe), 4.08 (3 H, s, OMe), 6.04 (2 H, d, O·CH_2·O), and 6.36 (1 H, s, 6′-H). The product was characterised as 2′,8-dibromo-β-peltatin by its mass spectrum [*m/e* 570 (M^+), 491 (M^+ — Br), and 411 (M^+ — 2Br)] and by analysis (Found: C, 47.3; H, 4.3; Br, 25.2. $C_{22}H_{20}{}^{79}Br_2O_8$,$Me_2CO$ requires C, 47.8; H, 4.1; Br, 25.2%).

O-*Acetyl-2′,8-dibromo-β-peltatin A.*—The dibromo-phenol (500 mg, 0.88 mmol) was heated in refluxing acetic anhydride (8 ml) for 1 h and the cool solution was stirred into ice–water (30 ml). The white solid precipitated after refrigeration overnight had m.p. 243—245° (from water–methanol), (459 mg, 90%), $\nu_{max.}$ 1 785br cm^{-1} (lactone and acetate C=O) and no OH absorption. An unsolvated sample of the *acetate* was obtained by vacuum drying (Found: C, 47.2;

TABLE 2

Physical constants of aromatised ligands

				100 MHz; $CDCl_3$				
	$\nu_{C=O}/cm^{-1}$	M^+	M required	4-H	5-H	8-H	Ring c H	Lactone
DHAPP	1 770			7.70	7.20	7.13	6.56(2 H)	5.40
2′-Cl-DHAPP	1 760, 1 715s	428.0661	428.0663 ($C_{22}H_{17}{}^{35}ClO_7$)	7.79	7.29	6.88	6.64(1 H)	5.43
2′-Br-DHAPP	1 765, 1 720s	472	472 ($C_{22}H_{17}{}^{79}BrO_7$)	7.79	7.29	6.88	6.66(1 H)	5.44

Action of Phosphorus Pentahalides on Picropodophyllin.—Picropodophyllin (1.0 g) was heated under reflux in benzene (10 ml) with either the pentabromide or the pentachloride (*ca.* 0.5 g) for 1 h. Evaporation, washing (H_2O–EtOH), and recrystallisation from ethyl methyl ketone gave a 67% yield of α-apopicropodophyllin in each experiment; the products had m.p. and mixed m.p. 243°.

2′,8-*Dibromo-β-peltatin A.*—β-Peltatin A was isolated from *Podophyllum peltatum* resin as described by Hartwell and Detty,[24] and a sample (1.5 g, 0.28 mmol) was heated with phosphorus pentabromide (*ca.* 1.5 g) by suspension in refluxing benzene (20 ml; sodium-dried) for 1 h. The residue was filtered off, washed with hot benzene (2 × 10 ml), and recrystallised from acetone. After drying *in vacuo* (at *ca.* 10^{-4} mmHg) the m.p. was unchanged (274—275°) and solvation of the *crystals* was confirmed by the n.m.r. spec-

H, 3.5; Br, 25.9. $C_{24}H_{22}Br_2O_9$ requires C, 47.1; H, 3.6; Br, 25.8%). N.m.r. assignments for C_6D_6 solution were made by comparison with earlier results [25] and are given with δ values for $CDCl_3$ in parentheses: 1-H, 5.45 (5.38); 2-H, *ca.* 2.7 (*ca.* 3.0); 3-H, 2.50 (2.80); 6′-H, 6.18 (6.05); O·CH_2·O, 5.05, non-equiv. (6.10); OAc, 1.86 (2.42 with 'ghost' at 2.36). In C_6D_6 three non-equivalent MeO signals appeared at δ 3.24, 3.62, and 3.78 but in the $CDCl_3$ spectrum two of these peaks had 'ghosts' and five peaks of similar intensity appeared at δ 3.62, 3.67, 3.86, 3.89, and 3.94.

We acknowledge the collaboration of Dr. T. A. Connors who did the toxicological testing at the Chester Beatty Institute.

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