Molecular Crowding and Remote Substituent Effects in 1-Aryltetrahydronaphthalene Derivatives

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Summary Further substitution (X) in the pendant ring of lignans of the 1-aryltetrahydronaphthalene type [*e.g.* (**1**)] leads to increased strain in ring B and in the lactone function, as a result of which solvolysis reactions at C(4) are accelerated and the base-catalysed epimerisation at C(2), which occurs readily in the natural precursors, is not observed.

THE first evidence[1] of extreme crowding in molecules of the podophyllotoxin class came from ^{1}H n.m.r. spectroscopy which revealed strong shielding of the residual proton in ring C, following restricted rotation on 2′-halogenation. Related changes in the CO stretching frequencies of the 2′-halogenopodophyllotoxones[2] (**1**; C=O replaces CHY) typify increased strain in the system, since both ketone and lactone frequencies are displaced by up to 20 cm^{-1}. Similar changes have been reported[3] for the lactone frequency (1785 cm^{-1}) in podophyllotoxin (**1**; Y=OH, X=H) when it relaxes through base-catalysed epimerisation to picropodophyllin [α-H at C(2); lactone at 1770 cm^{-1}]. Increased strain due to sp^2 hybridisation in α-apopicropodophyllin (**2**) is also shown by a shift in the lactone absorption to 1790 cm^{-1}.

Chemical evidence of strain in ring B was obtained from a study of the reactions of 4-chloro-4-deoxypodophyllotoxins (**1**; α or β). The initial rates of solvolysis of a pair of epimers (X = H) were comparable, showing that the stereochemistry at C(4) is not a determining factor and this is consistent with a unimolecular mechanism. Under the same conditions the 2′-chloro-4β-isomer reacted at too great a rate for convenient measurement; a comparison

TABLE

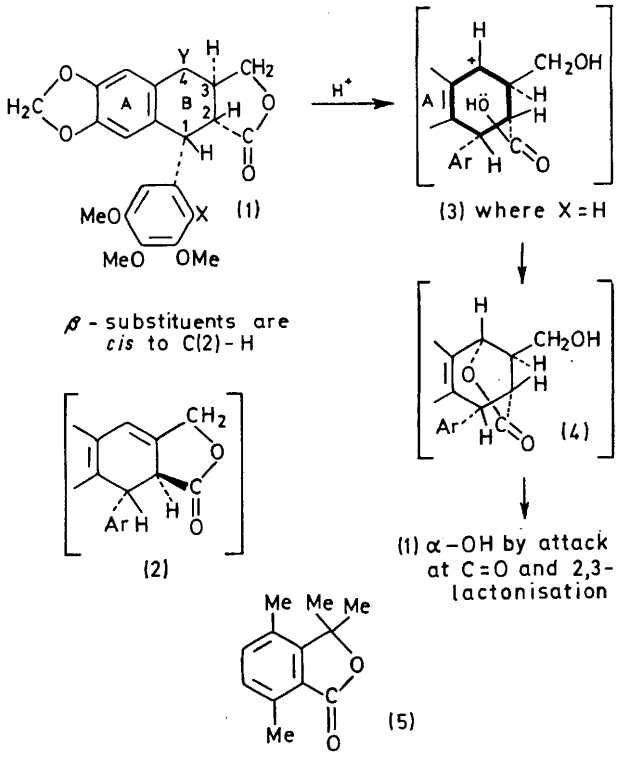
Initial rates of solvolysis of 4-halogenodeoxypodophyllotoxins (DPT)

	Conditions	k/(s^{-1} × 10^5)	$t_{\frac{1}{2}}$/min
4α-Chloro-DPT	12% H_2O in dioxan; 40°	5·36	215
4β-Chloro-DPT	12% H_2O in dioxan; 40°	4·21	274
2′,4β-Dichloro-DPT	3% H_2O in dioxan; 30°[a]	2·41	478

[a] Under these conditions there was negligible hydrolysis of the epimeric monochloro-compounds after 16 h.

(Table) was only possible by following this solvolysis at a lower temperature in a medium containing one-third the quantity of water. Evidently the strain resulting from the insertion of the remote chloro-substituent on ring C accelerates the rate-determining fission of the C(4)–Cl bond. The isolation under these conditions and in other instances[1,4] of only the 4β-oxy-compounds is characteristic of a unimolecular reaction of this kind. At higher temperatures in a strongly acidic solution the 4β-isomer with the natural substitution pattern (**1**, X = H, Y = OH) is epimerised[5] to the 4α-compound; this probably follows trapping of a revealed carboxy-group by a carbonium ion (**3**) to afford (**4**). An interaction of this type has been reported[6] and a close analogy exists in the formation[7] of the 2,4-

bridged lactone neopodophyllotoxin under acid conditions. Solvolysis of (**4**) by attack on the carbonyl group and relactonisation by 2,3-bridging accounts for the earlier observation.[5] In contrast the 2′-halogenated 4β-alcohols were not epimerised under similar conditions; this is consistent with steric hindrance by the halogen atom to formation of a bridged-lactone (**4**).



2′-Bromopodophyllotoxin[8] (**1**; X = Br, Y = α-OH) was the subject of a recent *X*-ray study[9] which corrected earlier work and finally established the absolute configuration of this class of lignans. In our earlier paper[1] we drew attention to variations in the physical constants of this compound as prepared by Kofod and Jorgensen.[8] Although it is feasible on chemical grounds that these variations arose from the formation of a mixture of C(4) epimers, this explanation is now unlikely in view of the configurational stability reported here for 2′-halogeno-compounds.

2′-Halogeno-substituents exert another stabilising effect in that the base-catalysed epimerisation at C(2) of the more strained podophyllotoxin group is no longer possible, even in the presence of bases as strong as alkoxide. There is potential value in this observation because the cancer-inhibitory action[10] of these compounds is lost when epimerisation occurs to form the 'picro'-derivative [**1**; X = H, Y = OH, α-H at C(2)]; hence if one possible catabolic path is blocked in this way the effective concentration at an infected site may rise. Steric factors are also believed to be critical here because the conditions used[1] for 2′-chlorination of podophyllotoxin are ineffective if they are applied *after* its base-catalysed epimerisation to picropodophyllin. We believe that the stability in alkali may result from a rapid re-lactonisation of a carboxylate anion which has limited freedom of movement after a halogen has been introduced. Comparable behaviour has been reported[11] for the highly hindered lactone (**5**).

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