BIOSYNTHESIS OF TUMOUR-INHIBITORY LIGNANS OF INDIAN PODOPHYLLUM (PODOPHYLLUM HEXANDRUM)

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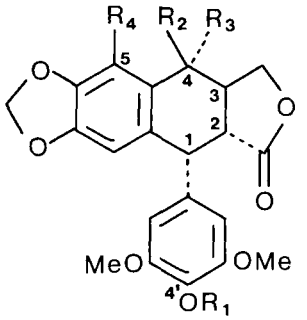
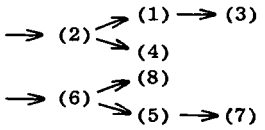
The tumour-inhibitory properties of Indian Podophyllum (Podophyllum hexandrum, syn emodi) result from a range of aryltetralin lignans and their glycosides present in the root (Jardine 1980). In addition to the major lignans podophyllotoxin (1) and 4'-demethylpodophyllotoxin (5) we recently reported the presence of desoxypodophyllotoxin (2), podophyllotoxone (3) and isopicropodophyllone (Dewick & Jackson 1981). Further examination of the non-glycosidic fraction of P. hexandrum root has resulted in the isolation of 4'-demethyldesoxypodophyllotoxin (6), 4'-demethylpodophyllotoxone (7), 4'-demethylisopicropodophyllone, α-peltatin (8) and β-peltatin (4). α- and β-Peltatins are the major lignans in American Podophyllum (P.peltatum), but have not been reported in P. hexandrum. 4'-Demethyldesoxypodophyllotoxin has previously been isolated as its glucoside from both P.hexandrum and P. peltatum (Wartburg et al 1964). 4'-Demethylpodophyllotoxone is a new natural product. The isopicro derivatives are C-3 epimers of (3) and (7), but may be obtained by heating the ketones (3) and (7), and could therefore be artefacts.



(1) R_1=Me, R_2=R_4=H, R_3=OH
(2) R_1=Me, R_2=R_3=R_4=H
(3) R_1=Me, R_2R_3=O, R_4=H
(4) R_1=Me, R_2=R_3=H, R_4=OH
(5) R_1=R_2=R_4=H, R_3=OH
(6) R_1=R_2=R_3=R_4=H
(7) R_1=R_4=H, R_2R_3=O
(8) R_1=R_2=R_3=H, R_4=OH

The range of lignans in P. hexandrum and P. peltatum are thus now demonstrated to be very similar, though the relative proportions differ markedly. Structural analysis indicates two main groups, those with 3', 4', 5'-trimethoxy substitution in the pendent ring, and the corresponding 4'-demethyl series. Each can give rise to two sub-groups by further oxygenation at either C-4 or C-5 (Scheme).



Scheme. Probable biosynthetic relationships amongst Podophyllum lignans

This scheme is borne out by biosynthetic experiments with isotopically labelled lignans. Thus, 4'-demethyldesoxypodophyllotoxin (6) is incorporated into 4'-demethylpodophyllotoxin (5), but not into podophyllotoxin (1); desoxypodophyllotoxin (2), but not 4'- demethylpodophyllotoxin (5) is a precursor of podophyllotoxin. The branch-point to (2) and (6), and thus the two major groups, is being investigated further.

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Jardine, I. (1980) 'Anticancer Agents Based on Natural Product Models' Cassady, J.M., Douros, J.D. eds Academic Press, New York, p.319
Wartburg, A.von, Kuhn, M., Lichti, H. (1964) Helv. Chim. Acta. 47 : 1203

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