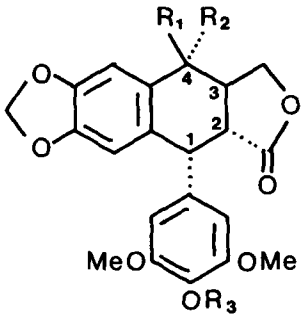
# CYTOTOXIC LIGNANS AND THEIR BIOSYNTHESIS IN PODOPHYLLUM HEXANDRUM

D.E. Jackson and P.M. Dewick, Department of Pharmacy, University of Nottingham, Nottingham, NG7 2RD, U.K.

A wide range of aryltetralin lignans and glycosides having cytotoxic and/or anti-tumour activity has been isolated from Indian Podophyllum (Podophyllum hexandrum, syn emodi), American Podophyllum (P. peltatum) and other species (Hartwell and Schrecker 1958; Cole and Wiedkopf 1978). Further examination of the non-glycosidic fraction of P. hexandrum root extract has resulted in the isolation of the cytotoxic lignans desoxypodophyllotoxin (1) and podophyllotoxone (2) as well as the previously reported podophyllotoxin (3) and 4'-demethylpodophyllotoxin (4). Podophyllotoxone has been known synthetically for several years, but has not previously been reported as a natural product. Traces of the less cytotoxic C-3 epimer of (2) (isopicropodophyllone) were also isolated, but this compound may be an artefact since (2) rapidly isomerizes on heating. Podophyllotoxone and isopicropodophyllone are also present in P. peltatum root.




(1) $R_1$=$R_2$=H, $R_3$=Me
(2) $R_1R_2$=O, $R_3$ = Me
(3) $R_1$=H, $R_2$=OH, $R_3$=Me
(4) $R_1$=$R_3$=H, $R_2$=OH

Although phenylalanine and p-hydroxycinnamic acid have been shown to be precursors of podophyllotoxin (Ayres 1969, 1978), the biosynthetic origin of the Podophyllum lignans is unknown. Feeding experiments with P. hexandrum have demonstrated the incorporation of radioactivity from phenylalanine -[U-$^{14}$C], cinnamic acid -[3-$^{14}$C] and ferulic acid -[2-$^{14}$C] into (3) (0.25%, 0.17% and 0.05% respectively) and into (4) (0.05%, 0.04% and 0.05 % resp.), supporting a mechanism involving oxidative coupling of two phenylpropane precursors. Desoxypodophyllotoxin -[4'-methyl-$^{3}$H] and podophyllotoxone-[4'-methyl-$^{3}$H] were also excellent precursors of podophyllotoxin (incorporations 0.81% and 2.2% respectively). The sequence of reactions leading to (1), (2) and (3) is under further investigation.

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Cole, J.R. and Wiedhopf, R.M. (1978) In Chemistry of Lignans (Rao, C.B.S., ed.) Andhra Univ. Press, Visakhapatnam, India, p. 39.
Hartwell, J.L. and Schrecker, A.W. (1958) Fortschr. Chem. Org. Naturstoffe. 15, 83.

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