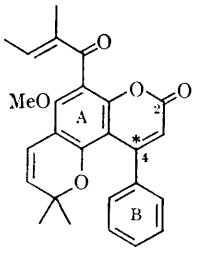
On the Biosynthesis of Neoflavanoids: Calophyllolide (4-Phenylcoumarin)

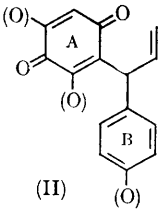
By GERHARD KUNESCH and JUDITH POLONSKY

(*Institut de Chimie des Substances Naturelles, C.N.R.S., 91-Gif-sur-Yvette, France*)

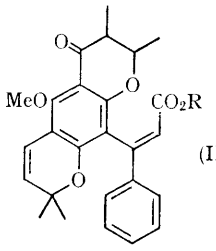
THE natural 4-phenylcoumarins whose structures were first established were calophyllolide[1] (I) and inophyllolide[1] from *Calophyllum inophyllum* (Guttiferae). During the last ten years several other members of this class of compounds have been isolated. These include the dalbergins from *Dalbergia sissoo*,[2] the 4-phenylcoumarins from *Mammea americana*[3]* and mesuol[4] from *Mesua ferrea* L.



(I)



(II)

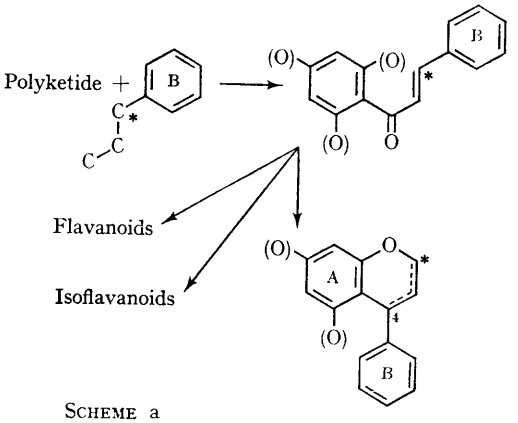


(III) a; R=H
b; R=Me

A new group of natural quinones, the dalbergiones, (type structure II) has been discovered recently.[5] Because of the possible biogenetic relationship between the dalbergiones and the 4-arylcoumarins, Ollis and his co-workers proposed to designate this class, collectively, by the name *Neoflavanoid*.[6]

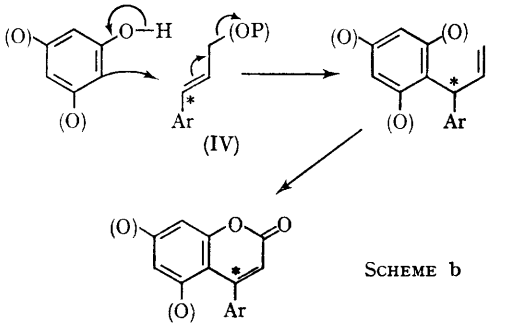
No experimental results concerning the biogenesis of these neoflavanoids have, so far, been reported. The following hypotheses for their genesis have, however, been formulated:

(i) Their biosynthetic pathway might parallel the route established for the flavanoid- and isoflavanoid-type structures. Just as the formation of the isoflavanoid skeleton involves one 1,2-aryl shift, that of the neoflavanoid skeleton might require two such shifts[7,8] (Scheme a).



SCHEME a

(ii) The 4-arylcoumarins might arise, as suggested by Seshadri in 1957,[9] by an alternative linking of the C_9-compound with the phenolic unit.† More recently, Ollis and his co-workers[5] suggested that the C_9-compound involved in the formation of the neoflavanoids could be cinnamyl pyrophosphate (IV), and that alkylation, by this derivative, of a phenolic C_6-unit (or its polyketide equivalent) could lead to the dalbergiones. The oxidation of the latter would then afford the 4-arylcoumarins (Scheme b).



SCHEME b

* Studies on several new 4-phenylcoumarins isolated from *Calophyllum tomentosum* and *C. apellatum* by C. R. Mitra *et al.* (Lucknow, India) are in progress.

† This is supported by laboratory analogy (ref. 10) and by the existence of the 4-alkylcoumarins (ref. 11) whose formation requires a similar biosynthetic reaction involving acetate.

We now report our first experiments with the seeds of *Calophyllum inophyllum* using specifically labelled phenylalanine (a demonstrated precursor of cinnamic acid[8]). The results obtained eliminate the first biogenetic suggestion and provide strong support for the second.

(±)-[3-^{14}C]Phenylalanine (0·1 mc) was administered to young shoots of *Calophyllum inophyllum*. After 8 days calophyllolide (I) was isolated and, after rigorous purification by chromatography and crystallisation, was found to be radioactive ($3{\cdot}35 \times 10^4$ d.p.m./mmoles; *ca.* 0·02% incorporation). The constancy of the radioactivity was demonstrated by hydrolysis to calophyllonic acid (IIIa) and methylation to methyl calophyllonate[1] (IIIb) ($3{\cdot}32 \times 10^4$ d.p.m./mmoles).

The radioactive calophyllolide was degraded by chromic acid oxidation to benzoic acid which, after purification by repeated sublimation, was shown to be radioactive (92% of the total activity). Schmidt reaction of the benzoic acid showed that the label was located in the carboxyl group (79·5% of the original activity in $BaCO_3$). Thus, C-4 of calophyllolide (I) carries essentially all the activity of this compound.

These results establish the specific incorporation of carbon-3 of phenylalanine which becomes the starred atom (C-4) in calophyllolide. The shikimic–prephenic pathway in the formation of the C_9-unit of the 4-phenylcoumarins is therefore indicated and the results are compatible with the second, but not the first, hypothesis.

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