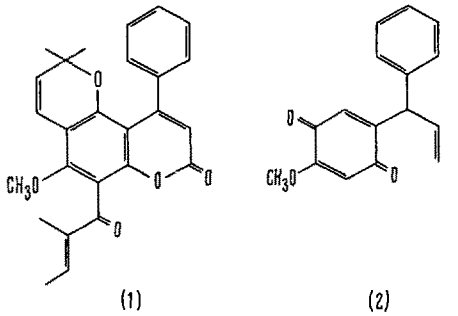
SPECIALIA

On the Biogenesis of Neoflavanoids: A New Hypothesis

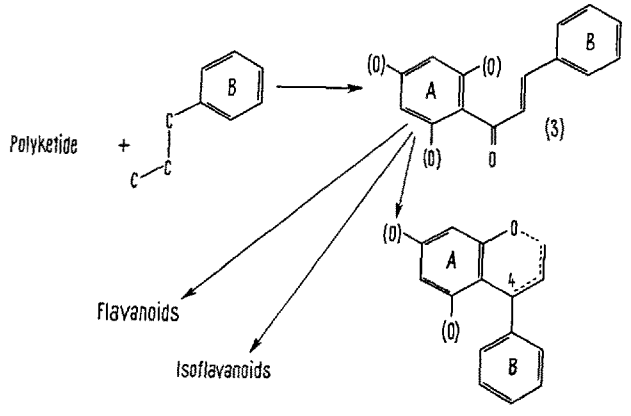
It has been suggested[1,2] that the naturally occuring 4-arylcoumarins, such as calopyllolide[3] (1) and the dalbergins[4], and the dalbergione[5] (2), may be biosynthetically related; the class-name Neoflavanoid was coined[1].



(1) (2)

In a recent communication reporting on the biosynthesis of calophyllolide, KUNESCH and POLONSKY[6] succinctly reviewed the hypotheses that have been advanced for the biogenesis of the neoflavanoids as follows:

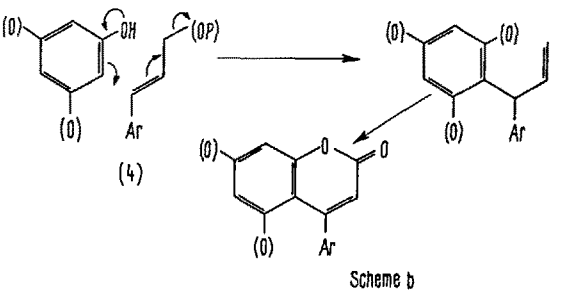
'(1) Their biosynthetic pathway might parallel the route established for the flavanoid – and isoflavanoid-type structures. Just as the formation of the isoflavanoid skeleton involves a 1, 2-aryl shift, that of the neoflavanoid skeleton might require 2 such shifts[7], (Scheme a).



Scheme a

(2) The 4-arylcoumarins might arise, as suggested by SESHADRI in 1957[8], by an alternative linking of the C_9-compound with the phenolic unit. (This is supported by laboratory analogy[9] and by the existance of 4-alkylcoumarins[10] whose formation requires a similar biosynthetic reaction involving acetate.) More recently, OLLIS and his co-workers suggested[1] that the C_9-compound involved in the formation of the neoflavanoids could be cinnamyl pyrophosphate (4), 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).

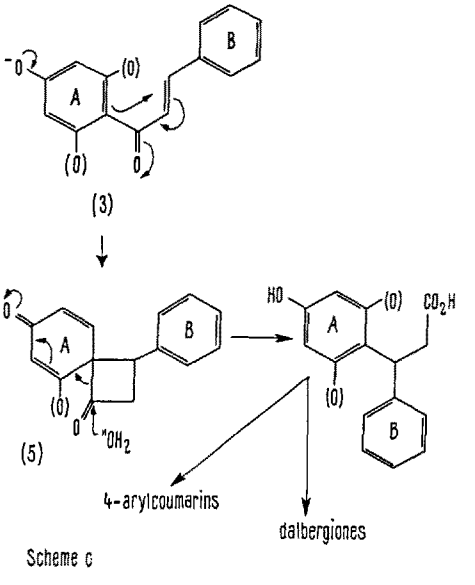
KUNESCH and POLANSKY reported[6] that (+)-[3-^{14}C] phenylalanine was incorporated into calophyllolide (1),



Scheme b

in *Calophyllum inophyllum*, and that 92% of the label was located at C-4. They conclude that this result is compatible with Scheme b, but not with Scheme a.

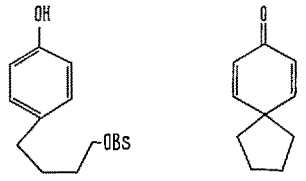
It is the purpose of this communication to point out that there is another plausible biogenetic hypothesis which has not yet been considered; the intermediate (3) in Scheme a might give rise to neoflavanoids by the process which we sketch below (Scheme c).



Scheme c

[1] W. B. EYTON, D. W. OLLIS, I. O. SUTHERLAND, O. R. GOTTLIELB, M. TAVEIRA MAGELHAES and L. M. JACKMAN, Tetrahedron *21*, 2683 (1965).
[2] H. GRISEBACH and W. D. OLLIS, Experientia *17*, 4 (1961).
[3] J. POLONSKY, C. r. hebd. Séanc. Acad. Sci., Paris *242*, 2961 (1956); Bull. Soc. Chim. biol. 1079 (1957); 929 (1958).
[4] V. K. AHLUWALIA and T. R. SESHADRI, J. chem. Soc. 970 (1957).
[5] W. D. OLLIS, Experientia *22*, 777 (1966).
[6] G. KUNESCH and J. POLONSKY, Chem. Commun. 317 (1967).
[7] T. A. GEISSMAN and E. HINREINER, Bot. Rev. *18*, 77 (1952) – H. GRISEBACH, Z. Naturf. *14b*, 802 (1959) – H. GRISEBACH and N. DOERR, Z. Naturf. *15b*, 284 (1960) – H. GRISEBACH and G. BRANDER, Z. Naturf. *16b*, 2 (1961).
[8] T. R. SESHADRI, Curr. Sci. *26*, 239 (1957); Tetrahedron *6*, 173 (1959).
[9] J. D. STEPHENS and H. STEPHENS, J. chem. Soc. 1382 (1956).
[10] G. H. STOUT and L. K. STEVENS, J. org. Chem. *29*, 3604 (1964).

We have chosen to represent the formation of the spiro intermediate (5) from (3) by way of an anionic process, an intramolecular C-arylation of the chalcone by the phenolic ring-A, an Ar_1-3 mechanism in WINSTEIN's notation[11], analogous to the formation of (7) from (6)[12]. However, Ar_1 participation may equally well occur in a radical process[11] and the intermolecular C-arylation of chalcones by phenols has been reported to occur under acid-oxidizing[13] as well as alkaline conditions[14].



(6) (7)

The net effect of Scheme c is to generate the neoflavanoid skeleton from (3) by way of a single 1,3-aryl migration of the polyketide derived ring-A, rather than by the two 1,2-aryl migrations of the shikimate-prephenate derived ring-B previously considered.

The new hypothesis requires that [3-^{14}C] phenylalanine should lead to a neoflavanoid labelled specifically at C-4. In contrast to OLLIS's hypothesis, the dalbergiones are not visualized as precursors of the 4-arylcoumarins. An attractive feature of the new hypothesis is that is preserves a close biosynthetic relationship between the neo- and other flavanoids.

Discrimination between the biogenetic routes suggested by SESHADRI, by OLLIS, and that given here will have to await the results of further experiments.

Zusammenfassung. Eine neue Hypothese für die Biogenese der Neoflavanoide wird vorgeschlagen, indem dasselbe Chalkon als Zwischenstufe wie für die Flavanoide postuliert wird. Nach dieser Hypothese sollte sich nach Verabreichung von [3-^{14}C]-Phenylalanin die Markierung an C-4 des Neoflavanoids befinden, wie es beim Calophyllolid[6] tatsächlich der Fall ist.

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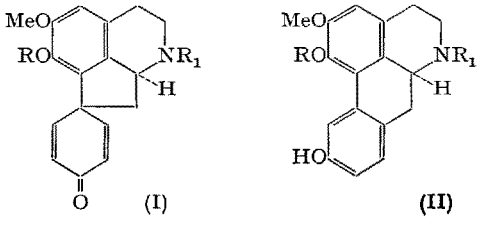
Dyson Perrins Laboratory, South Parks Road, Oxford (England), 19 June 1967.

[11] S. WINSTEIN, R. HECK, S. LAPPORTE and R. BAIRD, Experientia *12*, 139 (1956).
[12] R. BAIRD and S. WINSTEIN, J. Am. chem. Soc. *79*, 756, 4239 (1957).
[13] R. ROBINSON and J. WALKER, J. chem. Soc. 1435 (1934).
[14] R. ROBINSON and S. A. MILLER, J. chem. Soc. 1535 (1934).

Crotsparine, a New Proaporphine Alkaloid from *Croton sparsiflorus* Morong

Reinvestigation of the alkaloids of *Croton sparsiflorus* Morong (N. O. Euphorbiaceae) has resulted in the isolation of a new proaporphine base ($C_{17}H_{17}NO_3$), m.p. 193–195 °C, $(\alpha)_D$ – 30° (c, 1.22 $CHCl_3$) from extracts of the whole plant and is now designated as crotsparine. Crotsparine is different to sparsiflorine[1], an amorphous base previously isolated from the same plant but a second base m.p. 125–127 °C, $C_{19}H_{21}NO_3$ isolated with crotsparine proved to be identical with pronuciferine[2–6] (IR- and mass-spectra).



(I) (II)

Crotsparine has been assigned the structure (I, $R = R_1 = H$). It is susceptible to aerial oxidation and forms a crystalline hydrochloride m.p. 278 °C (decomp.). The presence of a secondary >NH group and a bound -OH group in the crotsparine molecule is suggested by bands at 3490 and 2896 cm^{-1} respectively in its IR-spectrum and is confirmed by the formation of a *N,O*-diacetyl derivative, m.p. 185–186 °C. The IR-spectrum of this derivative also has absorption bands at 1772, 1260 (phenolic OAc), 1642 (amide) and at 1670 cm^{-1} (dienone C=O). Further, IR-bands in the spectrum of crotsparine at 1664 and 1624 cm^{-1} in conjunction with an UV-absorption maxima at 235 nm (log ε, 3.37) are indicative of a cross-conjugated dienone system[7]. The mass-spectrum of crotsparine shows a molecular ion peak (M^+) at m/e 283 and other prominent peaks are m/e 282, 254, 211, 165, 118 and 87. The NMR-spectrum of crotsparine is in agreement with the proposed formula (I, $R = R_1 = H$). Singlets at 3.40 (1 H), at 6.21 (3 H) τ and multiplets centred around 2.9 (2 H) and 3.6 (2 H) τ are due to an aromatic proton, an OMe group and 4 olefinic protons respectively.

N-methylation of crotsparine with formic acid-formaldehyde affords *N*-methyl crotsparine (I, $R_1 = Me$, $R = H$) ($C_{18}H_{19}NO_3$), m.p. 223–225 °C, $(\alpha)_D$ – 113° (c, 1.52 $CHCl_3$). The mass spectrum of this compound shows a molecular ion peak at m/e 297 and other significant peaks at m/e 296, 268, 254, 225, 165, 115 and 97. This fragmentation pattern is the same as has been observed for glaziovine[4]. The IR-spectrum of the *N*-methyl derivative still has a band at 2860 cm^{-1} (bonded OH) but the >NH band at 3490 cm^{-1}, which is present in the spectrum of crotsparine is absent. The dienone system is unaffected during methylation as the compound shows IR-absorption at 1672 cm^{-1}, an UV-maximum at 235 nm and the loss of 28 mass units in the mass spectrum.

[1] S. K. SAHA, Sci. Cult. (India), *24*, 572 (1959).
[2] K. BERNAUER, Helv. chim. Acta *46*, 1783 (1963).
[3] K. BERNAUER, Experientia *20*, 380 (1964).
[4] B. GILBERT, M. E. A. GILBERT, M. M. DE OLIVEIRA, O. RIBEIRO, E. WENKERT, B. WICKBERG, V. HOLLSTEIN and H. RAPOPORT, J. Am. chem. Soc. *86*, 694 (1964).
[5] L. J. HAYNES, K. L. STUART, D. H. R. BARTON and G. W. KIRBY, Proc. chem. Soc. 261, 280 (1964); L. J. HAYNES and K. L. STUART, J. chem. Soc. 1784, 1789 (1963).
[6] M. P. CAVA, K. NOMURA, R. H. SCHLESSINGER and K. T. BUCK, Chemy Ind. 282 (1964).
[7] D. H. R. BARTON and A. I. SCOTT, J. chem. Soc. 1767 (1958).