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Aromatic Hydroxylation in Quinoline Alkaloids. The Biosynthesis of Skimmianine from Dictamnine, and a Convenient Synthesis of Furanoquinoline Alkaloids

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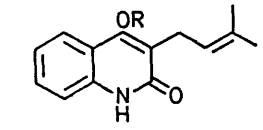
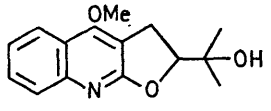
Summary The furanoquinoline alkaloid dictamnine, synthesised by a new procedure, has been shown to be a precursor of the dioxygenated alkaloid, skimmianine, in a *Skimmia* species and in *Choisya ternata*.

IN our study of the biosynthesis of quinoline alkaloids we demonstrated the specific incorporation of ^{14}C-labelled 2,4-dihydroxyquinoline and dimethylallylquinolines (1a) and (1b) into dictamnine (3a), platydesmine (2), and platydesminium metho-salt in *Skimmia japonica* Thunb.[1,2] Since platydesmine is a highly efficient precursor of dictamnine[2] the most likely biosynthetic route to the furanoquinoline alkaloids is the sequence (1b) → (2) → (3a). We noted also that feeding experiments with 2,4-dihydroxyquinoline[1] and with platydesmine[2] resulted in the isolation of radioactive skimmianine (4) (0·1 and 0·6% incorporation, respectively), suggesting that aromatic hydroxylation in this series occurs late in the biosynthetic pathway. Dictamnine frequently occurs with quinoline alkaloids containing oxygen substituents in the homocyclic ring, for example (3b), (3c), and (4), and may play a key role in hydroxylation mechanisms. We decided to test this hypothesis by feeding ^{14}C-labelled dictamnine (3a) to appropriate rutaceous plants and now report the preliminary results.

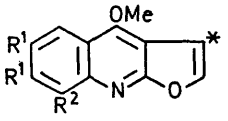
Established methods of preparing furanoquinoline alkaloids of the dictamnine type result in low yields[3] and are not suited to the synthesis of labelled alkaloids. Accordingly, we devised a new procedure for dictamnine beginning with 2,4-dimethoxyquinoline. Reaction with n-butyllithium and 1-bromo-3-methylbut-2-ene furnished the dimethylallylquinoline (5) which was converted with hydrochloric acid into the 2-quinolone (1b). The aldehyde



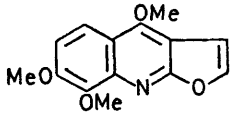
(1) a; R = H
b; R = Me



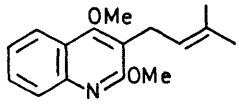
(2)



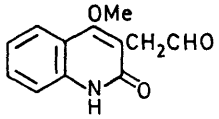
(3) a; $R^1 = R^2 = H$
b; $R^1 = H, R^2 = OMe$
c; $R^1 = OMe, R^2 = H$



(4)



(5)



(6)

(6) obtained by ozonolysis or by reaction with osmium tetroxide–periodate, was cyclised with polyphosphoric acid to dictamnine (3a) in an overall yield of 43%. Use of [1-^{14}C]-1-bromo-3-methylbut-2-ene provided dictamnine (3a) specifically labelled as indicated. Application of the

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procedure to 2,4,8-trimethoxyquinoline furnished γ-fagarine (3b) in 25% yield and skimmianine (4) was also synthesised similarly.

Biosynthetic experiments were carried out with *Choisya ternata* H.B. et K. and with a *Skimmia* variety; the latter, in contrast to *Skimmia japonica*,[4] contains skimmianine as principal alkaloid and dictamnine as a minor component. Dictamnine (3a), specifically labelled with ^{14}C was fed to shoots of the two plant species and after 3 days the alkaloids were isolated. Incorporations into skimmianine (4) were 1·7—2·1% in *Skimmia* and 1·2—3·5% in *Choisya ternata*. These results show that dictamnine is an efficient biological precursor of skimmianine. The level of incorporation is satisfactory considering that the conversion is a multi-stage process involving dihydroxylation and dimethylation, and we are now using the two plant species to investigate the sequence and mechanism of hydroxylation leading to skimmianine and to other quinoline alkaloids.

(*Received, 29th June* 1972; *Com.* 1138.)

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[3] M. F. Grundon and N. J. McCorkindale, *J. Chem. Soc.*, 1957, 2177; H. Tuppy and F. Bohm, *Monatsh.*, 1956, **87**, 735.
[4] D. R. Boyd and M. F. Grundon, *J. Chem. Soc.* (*C*), 1970, 556.

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