The Biosynthesis of Isoprenoid Quinoline Alkaloids

By J. F. COLLINS and M. F. GRUNDON*

(*The New University of Ulster, Coleraine, Northern Ireland*)

Summary 2,4-Dihydroxyquinoline and its 3-dimethylallyl derivative have been shown to be efficient precursors of a furanoquinoline alkaloid and an isopropyldihydrofuranoquinoline alkaloid.

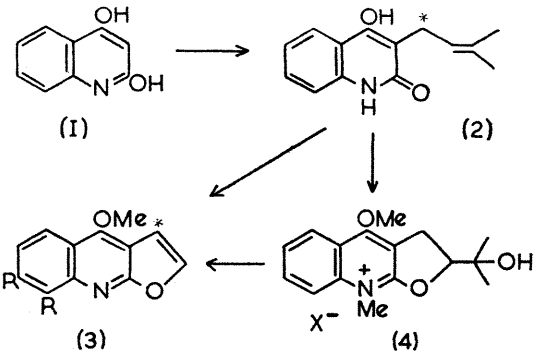
THE biosynthetic pathway to isopropyldihydrofuranoquinoline alkaloids and furanoquinoline alkaloids, which are often components of the same plant, has been the subject of considerable speculation.[1] A possible route involves the introduction of an isoprene group into a 2,4-dihydroxyquinoline, *cf.* (1), followed by oxidative cyclisation to an isopropylfuranoquinoline of type (4). Furanoquinolines *cf.* (3), may arise by loss of the isopropyl group from a dimethylallylquinoline (2) or from alkaloids (4). It was also suggested that aryl dimethylallyl derivatives related to compound (2) are key intermediates in the biosynthesis of natural isoprenoid chromenes, chromans, coumarins, benzofurans,[1] and chromones.[2] Synthetic experiments demonstrate the feasibility of these schemes,[3] but *in vivo* evidence is lacking.

We have now tested these hypotheses by means of ^{14}C feeding experiments with *Skimmia japonica* Thunb., which was shown previously[4] to contain dictamnine (3; R = H) skimmianine (3; R = OMe) and platydesminium salt (4). When [3-^{14}C]-2,4-dihydroxyquinoline[5] was fed to growing green shoots of *S. japonica*, incorporation into dictamnine

(3; R = H) and platydesminium salt (4) occurred to the extent of 1·3 and 2·0%, respectively; the corresponding figures for the dimethylallylquinoline (2) (specifically labelled as indicated by the asterisk in the formula) were 3·8 and 4·7%. Thus the precursors, especially the dimethylallyl derivative, serve as efficient precursors of alkaloids (3; R = H) and (4) in accord with the biosynthetic scheme suggested above. Incorporation of 2,4-dihydroxy quinoline into skimmianine (3; R = OMe) (0·6%) was lower than into dictamnine (3; R = H) but was still substantial, indicating that hydroxylation of the 7- and 8-positions of the quinoline nucleus probably occurs at a later stage in the biosynthetic route.

When the labelled compound (2) was used, degradation of dictamnine essentially by the method of Monković *et al.*[6] gave inactive 2,4-dihydroxyquinoline and carbon dioxide (counted as barium carbonate) containing >95% of the radioactivity present in the alkaloid; this indicates that, as expected, dictamnine was specifically labelled on the carbon atom marked with an asterisk in formula (3).

Previous biosynthetic studies showed that the quinoline nucleus of dictamnine is derived from anthranilic acid and acetate,[6] and recently 2,4-dihydroxyquinoline was shown to be a precursor of the furanoquinoline, kokusaginine.[7] Labelled mevalonic acid was incorporated into the furan ring of the coumarin pimpinellin.[8] Monkovic, Spenser, and Plunkett,[6] working with *Dictamnus albus*, were unable to demonstrate conclusively that the furan ring of dictamnine was derived from mevalonic acid, and our experience with *S. japonica* has been similar.[9] The present work provides the first clear evidence that in the biosynthesis of furano- and isopropyldihydrofurano-quinoline alkaloids the isoprene unit is incorporated into the intact quinoline nucleus; it also supports the suggestions discussed earlier concerning the biosynthesis of other isoprenoid aryl derivatives.



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