Claisen Rearrangements in the Biosynthesis of 1,1- and 1,2-Dimethylallyl Derivatives. The Biosynthesis of the Quinoline Alkaloid, Ravenoline

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Summary The origin of 1,1- and 1,2-dimethylallyl residues in aryl and heterocyclic compounds is discussed, and the biosynthesis of the 1,2-dimethylallyl derivative, ravenoline, is shown to occur by rearrangement of a 3,3-dimethylallyl ether.

NATURAL compounds containing aryl or heterocyclic rings substituted by 1,1-dimethylallyl groups are usually considered to arise by reaction with 3,3-dimethylallyl pyrophosphate at its tertiary centre,[1] but an alternative biosynthetic route involving a Claisen rearrangement has

been suggested.[2] We consider that the following chemotaxonomic evidence supports the latter possibility:

(a) Murray and his collaborators[3] showed that pyrolysis of the 3,3-dimethylallyl ether of 7-hydroxy-6-methoxycoumarin resulted in migration of the allyl group to the coumarin ring to yield the 1,1-dimethylallyl derivative (**1**; R^1 = OMe, R^2 = H). Subsequently, a group of 7-oxygenated coumarins substituted at position 3 by a 1,1-dimethylallyl group, for example, 3,-(1,1-dimethylallyl)-herniarin (**1**; R^1 = H, R^2 = Me), were isolated;[4] direct allylation of the coumarin ring is unfavourable, and in these cases a more likely biosynthetic route involves Claisen rearrangement as shown to occur *in vitro*.[3]

(b) In addition to the 1,1-dimethylallyl derivative, ifflaiamine (**6**),[5] we find that *Flindersia ifflaiana* F. Meull.† contains the isomer (**5**), which can be regarded as a derivative of a (1,2-dimethylallyl)quinoline. Paul and Bose[6] established recently the structures of the alkaloids of *Ravenia spectabilis* Engl.† and showed that ravenine is the 3,3-dimethylallyl ether (**2**) and ravenoline the 1,2-dimethylallyl derivative (**3**). An attractive hypothesis for the biosynthesis of the alkaloids of the two rutaceous plants involves 'normal' and 'abnormal' Claisen rearrangement of ravenine. During our synthesis of ifflaiamine,[7] we showed that these reactions occurred readily *in vitro*. The two 1,2-dimethylallyl alkaloids (**3**) and (**5**) are optically active and therefore are not artifacts arising by rearrangements of the ether (**2**) during isolation.

Barton and his co-workers[8] showed that anisoxide (**7**) was a 1,2-dimethylallyl derivative and it may also arise by 'abnormal' Claisen rearrangement of an appropriate 3,3-dimethylallyl ether; the biosynthetic sequence is less clear in this case since anisoxide, although containing an asymmetric centre, is optically inactive.

The co-occurrence of 1,2-dimethylallyl derivatives (which are unlikely to arise by direct substitution) and the more usual isoprenyl compounds certainly favours biosynthetic routes involving Claisen rearrangements. However, the alternative pathway involving formation of 1,1-dimethylallyl compounds by substitution, followed in some cases by rearrangement to 1,2-dimethylallyl derivatives must also be considered. We decided to test these theories by ^{14}C-feeding experiments and now report preliminary results with *Ravenia spectabilis*.

The 3,3-dimethylallyl ether (**2**), specifically labelled with ^{14}C as indicated by an asterisk in the formula, was fed to incised shoots of *Ravenia spectabilis*. The radioactivity of the isolated ravenoline (**3**) indicated that the precursor had been incorporated to the extent of 0·75%. Labelled ether (**2**) was added to inactive ravenoline, and the total sample was submitted to the isolation and separation procedure; inactive ravenoline was recovered, thus establishing that the radioactive product obtained from biosynthetic experiments was not formed by rearrangement of the ether (**2**) during isolation. The result shows that the 3,3-dimethylallyl ether is a precursor of ravenoline (**3**) and indicates that, in accord with the accepted mechanism of the 'abnormal' Claisen rearrangement,[9] the biosynthesis of the alkaloid proceeds by Claisen reaction (**2**) → (**4**) and subsequent rearrangement of the 'normal' Claisen product. A similar pathway, is likely to apply to the 1,2-dimethylallyl derivative (**5**) and ifflaiamine is probably formed by cyclisation of the initial Claisen product (**4**).

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