Biosynthesis of Tutin

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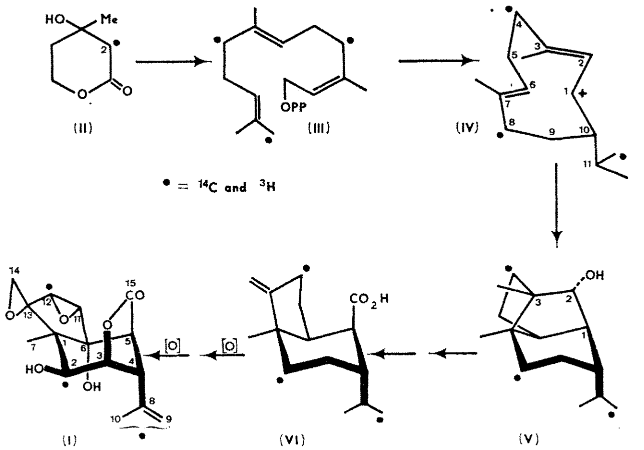
THE chemistry of tutin (I), picrotoxinin and related substances has been reviewed[1] and, more recently, the structures of other sesquiterpenes of this class have been elucidated.[2,3]



SCHEME A

Of the three hypotheses[4–6] advanced for the biogenesis of these substances, the one[6] reported in scheme A appeared the more convincing for reasons explained below. The results reported here offer valid support for such a biogenetic scheme,† thus excluding the other two hypotheses.[4,5]

Although *Coriaria japonica* biosynthesises both tutin and coriamyrtin[1] (2-deoxytutin), we have found that in the autumn this plant appears to contain tutin almost to the exclusion of coriamyrtin. A mixture of potassium (±)-[2-^{14}C]mevalonate (0·2 mc.) and potassium (±)-[2-$^{3}H_2$]-mevalonate (2 mc.) was fed in October to eight-month-old plants of *C. japonica* by the cotton-wick technique. The radioactive tutin extracted was diluted with carrier material, repeatedly chromatographed on silica gel–$AgNO_3$, and recrystallized to constant specific activity (0·03% incorp.). Oxidation[7] of the secondary hydroxy-group in (I) resulted in the loss of 24·8% of the total tritium activity. Ozonolysis (Scheme B) of 2-*O*-acetyltutin yielded radioactive formaldehyde (^{14}C 15·7%; ^{3}H 18·5% of the total) and the radioactive nor-ketone (VII) (^{14}C 83·6%; ^{3}H 83·4% of the total). The latter on treatment with potassium t-butoxide in methanol isomerized, as observed for the analogous derivative of tutin,[8] to the hydroxy-lactone (VIII) m.p.

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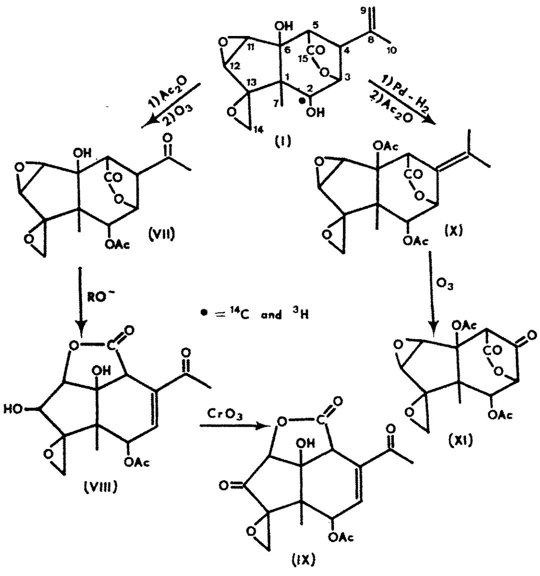
† The incorporation of labelled mevalonic acid into dendrobine has been reported (reference 6b). However, this work only demonstrated the terpenoid nature of this sesquiterpene alkaloid.

153—155°; $[\alpha]_D$ − 186° (dioxan, 1%); i.r. 1780, 1745, 1672 cm.$^{-1}$ ($CHCl_3$). Jones oxidation of the 12-hydroxy-group in (VIII) resulted in the loss of 20·6% of the total tritium (IX: m.p. 185°; $[\alpha]_D$ − 272° (dioxan 1%). Tutin (I) was isomerized with palladium black and hydrogen to neotutin[9] which on acetylation yielded the diacetate (X)[10] without change in the specific molar activity. Ozonolysis of (X) afforded the trisnor-ketone (XI) which showed losses of 36·0 and 46·0% of the total ^{14}C and ^{3}H activity, respectively.

These results indicate that labelling of the first isoprene unit is evenly distributed on C-9 and C-10 and, therefore, that the formation of $\Delta^{8(9)}$ in (I) is not stereospecific. If this is the case the ^{3}H activity at C-2, C-12, C-9, and C-10 should be respectively 27·3, 27·3, 18·1, and 27·3% of the total, while the ^{14}C activity should be 16·7% for both the C-9 and C-10, values which are in good agreement with those found.

The position of labelling in tutin strongly supports the postulated biogenesis[6c] for the bicyclic and tricyclic sesquiterpenes which are derived, presumably, from *cis*-farnesyl pyrophosphate (III) and for which few incorporation experiments have been reported. The formation of the bond between C-1 and C-6 in the intermediate (IV), or similar species, would lead to the muurolane skeleton from which copaene and copaborneol (V) can be derived biogenetically. The latter, after being postulated[6a] as a precursor of tutin, has been isolated from Swedish turpentine oil.[11] In an analogous pathway ylangene and helminthosporal can arise from an amorphene intermediate and the tricyclic sesquiterpenes longipinene, longiborneol, *etc.* from a himachalene intermediate.‡ Such a scheme explains not only the formation of the different sesquiterpenes but also their stereochemical features. With the exception of C-3, the absolute configuration of all the asymmetric centres in copaborneol (V) is the same as in tutin (I). The inversion of this centre in tutin [C-13 in (I)] can be accounted for by assuming a C-2, C-3 bond cleavage with formation of an intermediate of type (VI).

Sesquiterpenoids such as capenicine,[12] codendrine,[2] "G" substance,[3] dendrine,[13] *etc.* which contain more than 15 carbon atoms can be derived biogenetically from a tutin-like precursor if, as observed for plumieride,[14] one assumes an attack of an acetic or acetoacetic chain at C-14 of tutin (I).



SCHEME B

Analogous results for coriamyrtin from labelled mevalonic acid were obtained, independently, by D. Arigoni and his co-workers, and are reported in the previous Communication.

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‡ To our knowledge, only one example of a sesquiterpene with a stereochemistry antipodal to that of the himachalane series has been reported; this compound, culmorin, is a mould metabolite from a strain of *Fusarium culmorum* (D. H. R. Barton and N. H. Werstiuk, *J. Chem. Soc.* (*C*), 1968, 148).

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