Biosynthesis of Coriamyrtin and Tutin

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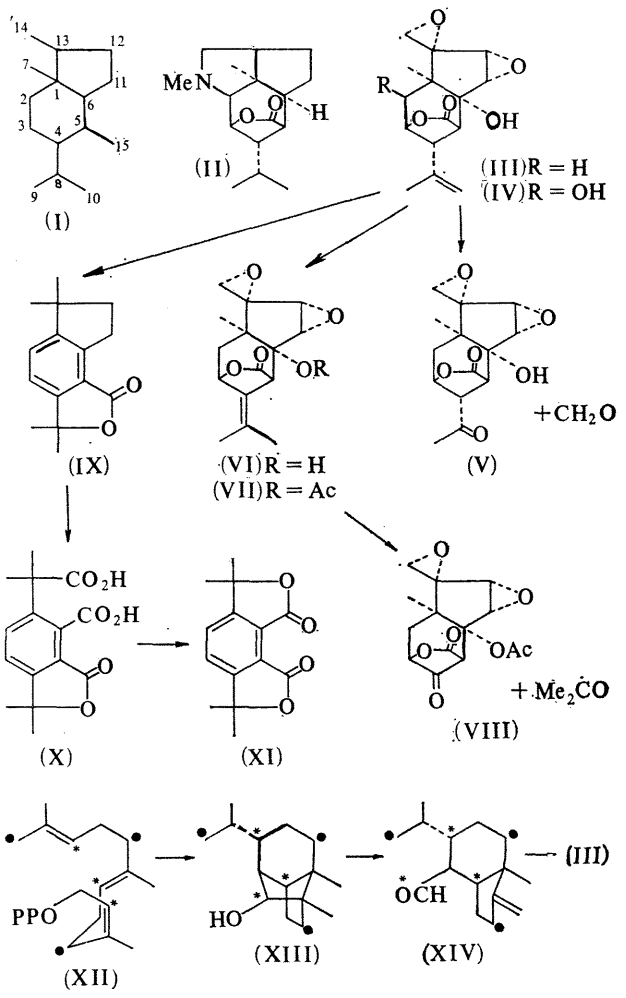
SESQUITERPENES of the picrotoxane group[1] are characterized by an unusual carbon skeleton (I), biogenetic derivation of which from a precursor of the farnesol type is not immediately apparent. Various schemes[2,3] have been put forward to account for the formation of these compounds; so far experimental support has been limited to the demonstration of a mevalonoid origin for the alkaloid dendrobine (II).[3] We now provide detailed evidence for the biosynthesis of two further representatives of this group.

Following administration of sodium (±)-[2-^{14}C]mevalonate to cut twigs of *Coriaria japonica*, radioactive samples of coriamyrtin (III)[1] and tutin (IV)[1] could be isolated, albeit with low incorporation yields (4×10^{-3}% and 10^{-4}%, respectively). The labelled coriamyrtin was subjected to the following degradations. Ozonolysis of (III) gave formaldehyde (2,4-dinitrophenylhydrazone, 9·4% of total activity) and the nor-ketone (V)[4] (89% activity). Kuhn–Roth oxidation of (V) afforded acetic acid, shown by further degradation to be labelled exclusively in the methyl group (10·7%). Neocoriamyrtin (VI), available from (III) through palladium-catalysed isomerization of the double bond,[5] was ozonized as the acetate (VII) to give acetone (2,4-dinitrophenylhydrazone, 17% activity) and the trisnoracetate (VIII) (80·4% activity). The acetic acid from the Kuhn–Roth oxidation of (VIII) was found to be inactive. Next, coriamyrtin (III) was transformed *via* the monolactone (IX) to the diacid (X) according to known procedures.[6] Treatment of (X) in acidic solution with potassium permanganate gave the dilactone (XI),[6] which retained only 40% of the activity of its precursors. Pyrolysis of (XI) in the presence of copper chromite produced CO_2 with only negligible activity (< 3%). Thus, the following labelling pattern is established: C-12 60%; C-9 and C-10 *ca.* 10% each, no activity at positions 1, 5, 7, 8, and 11. Working along similar lines with the tutin (IV) from the same feeding experiment an essentially identical pattern was observed for the distribution of label at C-9 and C-10. In addition, coriamyrtin (III) biosynthesized in the same



plant from sodium (±)-[4-^{14}C]mevalonate, yielded upon heating with copper chromite CO_2 corresponding to C-15 and carrying 27% of the original activity.

From a qualitative point of view these results are consistent with the operation of the appended biosynthetic scheme [*cf.* (XII) → → (III), and * denote atoms from C-2 and C-4 of mevalonate, respectively]; one of the postulated intermediates, the tricyclic alcohol (XIII), has been detected as a component of the oleoresin from *Pinus silvestris*.[7]

Loss of biosynthetic identity for the C-9 and C-10 in (III) and (IV), though reminiscent of a similar process in the biosynthesis of indole alkaloids[8] and some iridoids,[9] could not have been predicted by current biogenetic theories. The observed equilibration is not a direct consequence of the presence of an isopropyl chain in the postulated intermediates (XIII) and (XIV), since the two methyl groups in this chain are diastereotopic and therefore, at least in principle, distinguishable.

The preferential labelling detected for one of the participating C_5-units in the first feeding experiment is also rather unexpected. However, precedents for such behaviour are available in the monoterpene field,[10] and it may be significant that in all cases where anomalies of this type have been detected the higher degree of label is always associated with the unit added last in the formation of the aliphatic precursor.

Analogous results on the biosynthesis of tutin have been obtained by Dr. Jommi and his associates and are reported in the following communication.

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