Biological Conversion of Copaborneol into Tutin

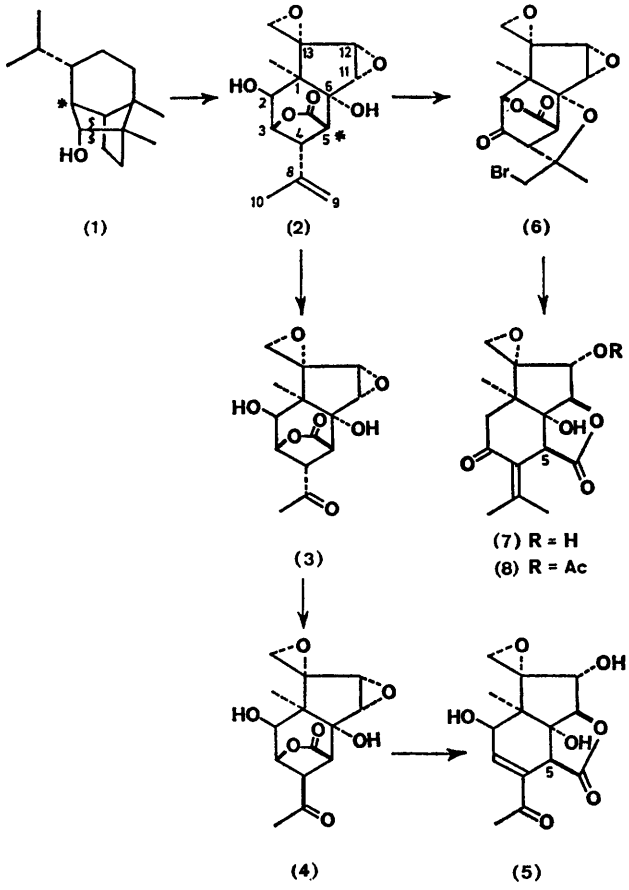
By K. W. TURNBULL, W. ACKLIN, and D. ARIGONI*
(*Organisch-chemisches Laboratorium, Eidgenössische Technische Hochschule, Zürich, Switzerland*)
and A. CORBELLA, P. GARIBOLDI, and G. JOMMI
(*Istituto di Chimica Organica dell'Università di Milano, Via Saldini* 50, 20133 *Milano, Italy*)

Summary A specifically tritiated specimen of copaborneol (**1**) is transformed by *Coriaria japonica* into tutin (**2**) without randomization of the label.

AVAILABLE data on the incorporation of labelled mevalonic acids into representatives of the picrotoxane group of sesquiterpenoids (*e.g.* coriamyrtin,[1] tutin,[1-3] and dendrobine[4]) are consistent with the operation of a biosynthetic scheme[1,2] involving ring cleavage of the tricyclic intermediate copaborneol (**1**)[5] as illustrated. We have now checked the precursor role of (**1**) in the formation of tutin (**2**) in *Coriaria japonica*.

A sample of copaborneol specifically labelled with tritium at the starred position [*cf.* (**1**), spec. act. $1{\cdot}33 \times 10^{11}$ d.p.m./

mM] was obtained by reduction (Na–EtOH of the corresponding ketone, which in turn is available by the exchange method outlined in the preceding communication.[6] The radioactive material was emulsified in water–tween 80 and fed to *C. japonica* using (*a*) cut twigs (total activity



4×10^9 d.p.m.) and (*b*) intact plants (5×10^9 d.p.m., cotton-wick method); elaboration of the plant material and rigorous purification gave radioactive tutin (**2**) with incorporation yields of 10^{-3} and 10^{-1}% respectively.

The labelled samples of tutin from experiments (*a*) and (*b*) were separately submitted to the following degradation: ozonolysis of (**2**) gave the norketone (**3**),[7] easily transformed upon chromatography on SiO_2 into the more stable C-4 epimeric compound (**4**), m.p. 260°, $[\alpha]_D^{23}$ −51° (EtOH), containing 99% of the original radioactivity. The latter upon treatment with catalytic amounts of NaOMe in MeOH was isomerized to (**5**)[7] which retained less than 5% of the original radioactivity. In a separate experiment with deuteriated solvent it was shown that under the conditions which led to its formation compound (**5**) exchanges only 50% of the protons of the MeCO group and 15% of the proton at C-2. A very rapid and complete exchange of the proton at C-5 in (**5**) is evident from the almost instantaneous disappearance of the corresponding n.m.r. signal at 4·96 p.p.m. ([$^2H_5$]pyridine solution) upon addition of a drop of D_2O. The ease of enolization towards C-5 is such that all the deuterium so introduced into the molecule is lost back to the medium during mild work-up of this solution in the presence of water. Hence it can be concluded that the bulk of the label in the radioactive tutin was specifically located at C-5.

This result was verified in a second degradation sequence in which the labelled tutin from experiment (*b*) was converted without loss of tritium into the known α-bromoisotutinone (**6**).[8] Treatment of the latter with activated zinc[9] and NH_4Cl in EtOH–H_2O solution under carefully controlled conditions led *inter alia* to the formation of (**7**),† m.p. 183—184°, $[\alpha]_D^{20}$ −232° (dioxan), (94% tritium retention); the corresponding acetate (**8**), decomp. 212°, $[\alpha]_D^{20}$ −159° (dioxan), lost 85—88% of its radioactivity within 30 min in wet pyridine at room temperature. With D_2O–[$^2H_5$]pyridine under the same conditions, a rapid and selective exchange at C-5 was shown by the disappearance of the n.m.r. singlet at 4·70 p.p.m.

The biosynthetic link established in this work indicates that the anomalous carbon skeleton of tutin (**2**), and possibly of all other members of the picrotoxane subgroup,[10] represents indeed the outcome of an extensive oxidative modification of a biogenetically normal tricyclic intermediate.

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† The arguments for this structural assignment and the nature of further products of the reaction will be detailed in a forthcoming note by A. Corbella, P. Gariboldi, and G. Jommi.

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