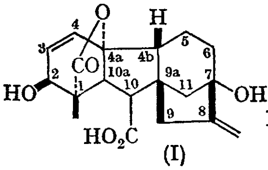
The Mevalonoid Origin of Some Hydrogen Atoms in the Tetracyclic Diterpenes

By J. R. HANSON*, MRS. ANGELA HOUGH, and A. F. WHITE
(*The Chemical Laboratory, University of Sussex, Brighton* BN1 9QJ, *Sussex*)

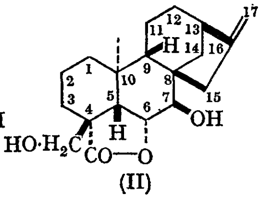
THERE are a number of stages in the biosynthesis of the tetracyclic diterpenoids that remain to be clarified. The availability[1] of 4*R*-tritiated mevalonic acid lactone enables us to define the origin of certain key hydrogen atoms. The labelling pattern of gibberellic acid (I)[2] and 7,18-dihydroxykaurenolide (II)[3] derived from [2-^{14}C]mevalonic acid lactone has already been described.

Doubly-labelled 4*R*-[4T and 2-^{14}C]mevalonic acid lactone (T:^{14}C 12:1) was fed to *Gibberella fujikuroi*. 7,18-Dihydroxykaurenolide was isolated. This showed a T:^{14}C ratio of 12·65:1. In confirmation, oxidation to the 18-nor-keto-lactone (III) altered this ratio to 12·65:0·8 (theory 12·65:0·75). The gibberellic acid, purified as its methyl ester, showed a T:^{14}C ratio of 9·75:1.

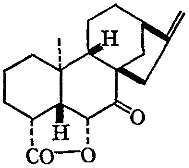
Whereas the kaurenolide retained all the tritium of the parent mevalonate, the gibberellic acid had lost one tritium atom. The [2-^{14}C]-pattern indicates that this should be from position 7 where a bridgehead hydroxyl has been inserted. Degradation of the methyl gibberellate to methyl gibberate (IV) resulted in almost complete loss of tritium. In this degradation the 10a-proton is eliminated and the 4b-proton epimerized, thus accounting for the loss of two of the tritium atoms. The last tritium label was rather more slowly lost (6% remaining after 1 hr., 4% after 3 hr. under reflux). This would be expected from the exchange of an aromatic proton, *i.e.* the third tritium atom is probably located in the expected position on ring A.



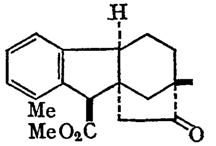
(I)



(II)



(III)



(IV)

A number of conclusions may be drawn from these results. Firstly, the C-9-hydrogen atom of the tetracyclic diterpenes remains throughout the cyclization stages including the formation of ring D and a $\Delta^{8(9)}$-pimaradiene is excluded at this stage. This point is fundamental to biogenetic arguments.[4] Secondly, during the elimination of a C-20 substituent and the formation of the lactone ring of the gibberellins a $\Delta^{4a(4b)}$ or a $\Delta^{4a(10b)}$ olefin is precluded—both the 4b and 10a-protons are *trans* to the lactone ring. Thirdly, cyclization of a geranylgeranylpyrophosphate derived from 4*R*-[4T]mevalonic acid lactone would be expected to produce an axial tritium atom at position 3 in a kauranoid precursor. Since this atom is retained in gibberellic acid, inversion must have taken place at this centre on hydroxylation. These conclusions are the subject of further confirmatory studies.

(*Received, February 26th,* 1968; *Com.* 233.)

---

[1] J. W. Cornforth, R. H. Cornforth, C. Donninger, and G. Popjak, *Proc. Roy. Soc.*, 1966, *B*, **163**, 492.
[2] A. J. Birch, R. W. Rickards, H. Smith, A. Harris, and W. B. Whalley, *Tetrahedron*, 1959, **7**, 241.
[3] B. E. Cross, R. H. B. Galt, and J. R. Hanson, *J. Chem. Soc.*, 1964, 295.
[4] E. Wenkert, *Chem. and Ind.*, 1955, 282.
[5] J. W. Cornforth, R. H. Cornforth, C. Donninger, G. Popjak, Y. Shimizu, S. Ichii, E. Forchielli, and E. Caspi, *J. Amer. Chem. Soc.*, 1965, **87**, 3224.