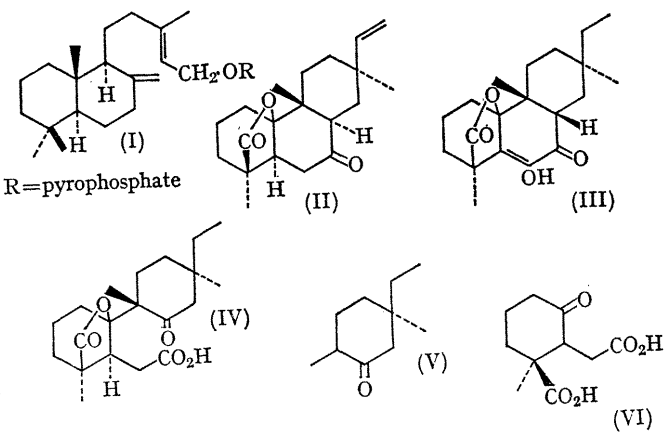
The Rearrangement During Rosenonolactone Biosynthesis

By B. ACHILLADELIS and J. R. HANSON*
(*School of Molecular Sciences, University of Sussex, Brighton*, BN1 9QJ)

Summary The incorporation of mevalonoid hydrogen at C-1, C-5, and C-6 in rosenonolactone excludes unsaturated intermediates involving these centres during the biosynthesis of the rosane skeleton.

WE have shown[1] that labda-8,13-dien-15-ol pyrophosphate (I) acts as a precursor of rosenonolactone (II) and that the cyclization is accompanied by a rearrangement in which the C-9 hydrogen migrates to C-8 when the C-10 methyl migrates to C-9. This poses the question of the fate of the C-10 carbonium ion. Our studies with 4(*R*)-[4-^{3}H]mevalonic acid also showed that the C-5 hydrogen was mevalonoid in origin. This we have confirmed.

Rosenonolactone (^{3}H : ^{14}C, 16·1 : 1) biosynthesized from 4(*R*)-[4-^{3}H,2-^{14}C]mevalonate, was converted to dihydroisorosenonolactone (^{3}H : ^{14}C, 11·8 : 1), with loss of label from C-8. This ketone was oxidized[2] with selenium dioxide to the diosphenol (III) (^{3}H : ^{14}C 8·4 : 1) showing a stepwise drop from four to two tritium atoms. Thus a mevalonoid hydrogen was located at C-5. In order to exclude a more deep-seated process such as the migration of the C-5 hydrogen to C-10 with the formation of a C-5–C-6 double



bond (*cf.* rimuene) and then the reversal of this with lactone formation, the incorporation of [5-$^3H_2$,2-^{14}C]mevalonate was studied. Doubly-labelled [5-$^3H_2$,2-^{14}C]mevalonic acid (^3H : ^{14}C 11·5 : 1) was fed to *Tricothecium roseum*. Rosenonolactone showed a ^3H : ^{14}C ratio of 11·2 : 1 corresponding to the incorporation of eight tritium atoms. Treatment with base gave isorosenonolactone (^3H : ^{14}C 8·1 : 1) which had thus lost two tritium atoms from C-6.

An alternative reaction of the C-10 carbonium ion is loss of proton from C-1. This corresponds to a C-2 mevalonoid hydrogen. Doubly-labelled [2-$^3H_2$,2-^{14}C]mevalonic acid (^3H : ^{14}C 7·34 : 1) was fed to *Tricothecium roseum*. Rosenonolactone showed a ^3H : ^{14}C ratio of 5·24 : 1 corresponding to the retention of six tritium atoms whilst desoxyrosenonolactone showed a ^3H : ^{14}C ratio of 7·16 : 1 corresponding to the retention of eight atoms. The rosenonolactone was converted to dihydroisorosenonolactone and the latter oxidized to rosoic acid (IV). This was subjected to a base-catalysed retro-aldol cleavage.[3] The ketonic fragment (V) isolated as its semicarbazone, showed a ^3H : ^{14}C ratio of 6·44 : 1 corresponding to the presence of two tritium atoms and one carbon-14. The acidic fragment (VI) however showed a ^3H : ^{14}C ratio of only 2·39 : 1 corresponding to the presence of two tritium atams to three carbon-14. During this degradation a new enolizable position is generated at C-1 which thus carries two mevalonoid hydrogens excluding a C-1–C-10 unsaturated intermediate from the biosynthesis.

Since the migrating methyl group is *cis* to the lactone ring, a concerted lactonization is unlikely and hence it would seem likely on the basis of these results that an α-oriented C-10–enzyme or C-10–hydroxyl bond is formed which is displaced with inversion when the lactone ring is formed.

(*Received, March 17th,* 1969; *Com.* 373.)

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