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THE BIOSYNTHESIS OF ROSENONOLACTONE

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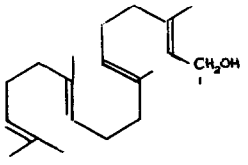
Geranylgeraniol (I), probably as its pyrophosphate, has been proposed[1] as an intermediate in the biosynthesis of the tricyclic diterpenes. Previously we have shown[2] that geranyl and farnesyl pyrophosphates are incorporated into rosenonolactone (III). We have now extended this to include the C-20 alcohol. The alcohol, prepared by standard methods from farnesyl acetone, was tritiated at C-1 by oxidation to the aldehyde and reduction with sodium borotritiide. It was solubilized in Tween 80 and fed to Tricothecium roseum. Rosenonolactone (III) showed an incorporation of 0.09%. Ozonolysis and isolation of the formaldehyde as its dimedone derivative, led to the recovery of 96% of the radioactivity from C-19.

We have demonstrated the intervention of the bicyclic alcohol (II) as its pyrophosphate, in the biosynthesis of rosenonolactone. It has been proposed[1,3] that this biosynthesis involves a 9 → 8 hydride shift and a 10 → 9 methyl migration. The 10-carbonium ion may then react in a number of ways. It may be discharged by the concerted loss of a trans 1 or 5 proton to give the corresponding rosadiene. Alternatively migration of the 5-proton produces a carbanium ion at C-5 which can lead to systems reminiscent of the erythroxydiols and of rimuene. In the case of rosenonolactone in which the lactone bridge is cis to the migrating methyl group two possibilities must be considered. Either a non-concerted discharge of the carbonium ion with direct lactone formation occurs or a rosadiene perhaps related to desoxyrosenolic acid may act as an intermediate. In this context we should note that the C-5 proton is trans to the lactone oxygenation. Recently two reports have appeared[4] of the isolation of a rosadiene (V) from the model acid-catalysed cyclization of manool, 13-epimanool and the bicyclic alcohol (II). Details of the biological process can be demonstrated through the study of the incorporation of 4R-tritiated mevalonic acid lactone.[5]

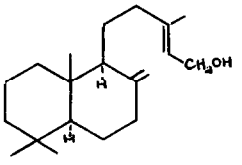
Doubly-labelled 4R-[4T : 2-^{14}C] mevalonic acid lactone [T : ^{14}C ; 13. 39 : 1] was fed to Tricothecium roseum. Rosenonolactone (III) and rosololactone (IV) were isolated. They showed a T : ^{14}C ratio of 13. 5 : 1 and 13. 1 : 1 respectively. Since rosenonolactone is known to incorporate four molecules of 2-^{14}C-mevalonate, four tritium atoms must be retained throughout the biosynthesis. Degradation[6] revealed the location of three of these. Rosenonolactone was converted to isorosenonolactone (VI) which showed a T : ^{14}C ratio of 9. 46 : 1 (i. e. loss of 1 tritium). During this process the 8-proton is exchanged and epimerized and was thus labelled. Ozonolysis of rosenonolactone and oxidation gave the 19-noracid in which the T : ^{14}C had dropped to 9. 98 : 1 thus locating the second tritium atom at C-18. Dihydro rosenonolactone (T : ^{14}C; 13. 3 : 1) was oxidized with selenium dioxide in acetic acid to the $\alpha\beta$-unsaturated ketone (VII) which showed a T : ^{14}C ratio of 7. 83 : 1 corresponding to the loss of 1. 7 tritium atoms locating a third tritium atom at C-5 whilst that at C-8 was exchanging with the solvent. To confirm the location of a tritium atom at C-5 rosenonolactone was reduced to rosenololactone (T : ^{14}C ; 13. 3 : 1) and this converted with methanolic hydrochloric acid to rosenolic acid (VIII) (T : ^{14}C; 9. 52 : 1). One tritium atom was again lost.

From these results we conclude that the postulated hydride shift occurs and that the mevalonoid proton at C-5 is retained and thus a $\Delta^{5:10}$-rosadiene is excluded from the biosynthesis of rosenonolactone.

Desoxyrosenonolactone appears to be precursor of rosenonolactone and rosololactone.[2] Doubly-labelled desoxyrosenonolactone (from 4R-4T-2-C^{14} mevalonate)(T : ^{14}C; 11. 7 : 1) was red to Tricothecium roseum. Rosenonolactone (III) and rosololactone (IV) were both isolated retaining the same T : ^{14}C ratio (12. 0 : 1 and 11. 9 : 1 respectively). The incorporation was 3. 7% and 1. 1%,[7] thus confirming our earlier deductions.



I



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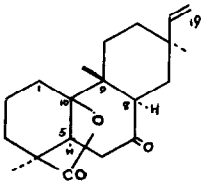

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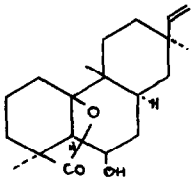

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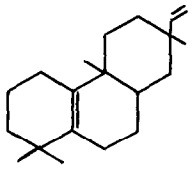

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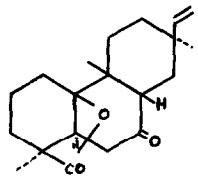

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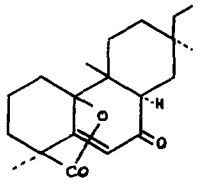
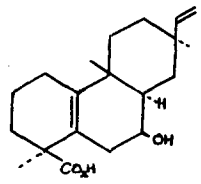


VII



VIII

References

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7 Dr. Holzapfel informs us that he has obtained similar results.