A Possible Intermediate in Sesquiterpene Biosynthesis

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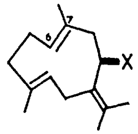
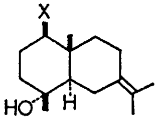
IT was originally suggested by Barton and de Mayo[1] that ten-membered-ring compounds may be intermediates in the biosynthesis of some sesquiterpenes and Hendrickson[2] expanded these views in a scheme using derivatives of the triene (I). This triene can be regarded formally as a cyclisation product of farnesol and could be a key intermediate in the biosynthesis of cyclodecane, selinane, and other sesquiterpenes.

The triene (I) has been prepared from the naturally occurring ketone germacrone[3] (II) by reduction to the alcohol (III), conversion into the acetate (IV), followed by reduction with lithium in ammonia. The n.m.r. spectrum of the triene showed four methyl groups on double bonds (two each at τ 8·52 and 8·31), a ten-proton absorption from τ 8·17 to 7·15, and a broad two vinyl proton absorption centred at τ 4·38. The spectrum also established that $<5\%$ of the isomer with the endocyclic double bond was present. A crystalline complex, $C_{15}H_{24},AgNO_3$, was prepared from (I) and its structure is being determined by *X*-ray crystallography by Prof. D. Rogers and Mr. F. H. Allen of this Department.

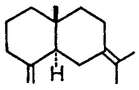
N-Bromsuccinimide in aqueous acetone has been used previously[4,5] to induce cyclisation reactions and in this case, with one mole, the bromohydrin (V) (31%) was obtained from the triene (I). The n.m.r. spectrum established the presence of two quaternary methyls (τ 8·90 and 8·81) and two methyls on double bonds (τ 8·33) and a deshielded axial proton at τ 6·13 (pair of doublets, $J = 9·5$ and 7 c./sec.).* Peracid oxidation of (V) gave a monooxide with four quaternary methyls (n.m.r.). That the τ 6·13 proton in (V) was geminal to the bromine followed from lithium-in-ammonia reduction of (V) to (VI) with the disappearance of this signal. Dehydration of (VI) with phosphorus oxychloride in pyridine gave a mixture containing the diene (VII) and $< 20\%$ of the isomer (X) proving the hydroxyl group equatorial.[7] The carbon skeleton and the ring-junction stereochemistry were proved by hydroxylation of (VI) with osmium tetroxide to a triol which on periodate oxidation gave the hydroxy-ketone (VIII). Dehydration ($POCl_3$–pyridine) of (VIII) gave the ketone (IX) identical to an authentic specimen[8] kindly supplied by Professor J. A. Marshall. Accepting that in the cyclisation of (I) to (V) *trans*-addition to the double bonds occurs, it follows from the stereochemistry established for (V) that the trisubstituted double bonds of (I) and (II) are *trans*.



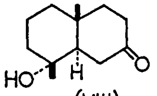
(I) X=H
(II) X=O
(III) X=OH
(IV) X=OAc



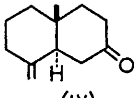
(V) X=Br
(VI) X=H



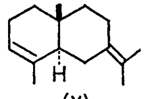
(VII)



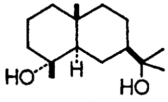
(VIII)



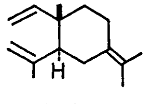
(IX)



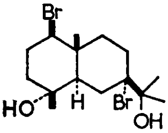
(X)



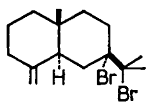
(XI)



(XII)



(XIII)



(XIV)

The reaction of (I) with a number of other electrophilic reagents has been investigated. Bromine in carbon tetrachloride gave the dibromide (XIV) (20%). Its structure was established by zinc reduction to the diene (VII) from which it can be re-formed under the reaction conditions. Evidently some of the diene (VII) is

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* The *J*-values indicate distortion of the ring from the classical cyclohexane geometry and, indeed, are consistant with a twist form (ref. 6). However, the dehydration of (V) and (VI) to give predominantly exocyclic methylene compounds suggests they have similar conformations and there is no reason to expect (VI) to have other than a chair conformation. If this argument is invalid and (V) does have a twist conformation it would not affect the relative configurations of (V) since this conformational change is understandable only if the bromine is equatorial.

formed from (I) under the bromination conditions. A similar cyclisation of (I) to (VII) (40%) and (X) (40%) is observed on percolation through Grade I alumina and again the selinane skeleton is generated by reaction of (I) with aqueous mercuric acetate. Reduction of the adduct with sodium borohydride[9] gave (VI) (24%), the diol (XI) (10%), and mixed selinadienes (VII) and (X) (3%). Like germacrone,[3] the triene (I) readily undergoes a Cope rearrangement on heating to give the hitherto unknown γ-elemene (XII), the n.m.r. spectrum of which shows a quaternary methyl at τ 8·96, three methyls on double bonds at τ 8·37, four vinyl protons at τ 5·34—4·96, and a single proton at τ 4·25 (pair of doublets J = 17 and 10 c./sec.). The stereochemistry of (XII) was established by its reaction with hypobromous acid to give (XIII) (5%), reduced with zinc to (V).

In summary, it appears that the triene (I), like other related compounds,[1,3,10] can be converted readily into selinane derivatives probably due to the 6,7-double bond being the most reactive to electrophilic reagents. So far we have been unable to obtain evidence for any other type of cyclisation.

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