Rearrangement of Zizaene-related Sesquiterpenes

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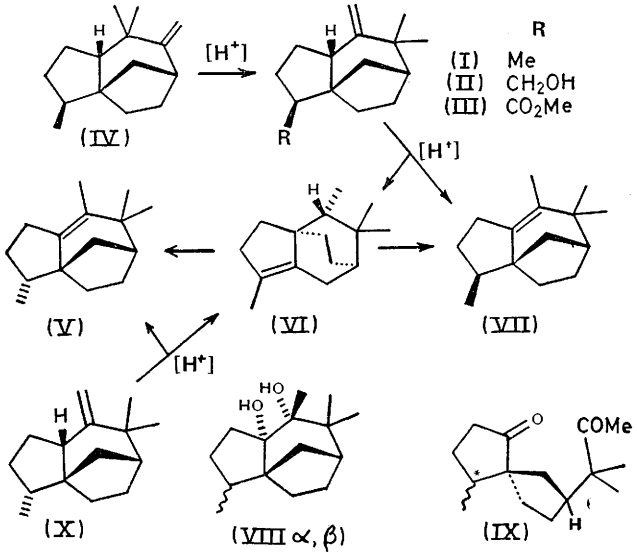
Summary When set aside in formic acid, zizaene (I) and its presumed precursor (IV), yield a mixture of olefins [(V) and (VII)], epimeric at a centre separated from the olefinic bond by a quaternary centre.

VETIVER oil has figured centrally in the study of unusual sesquiterpenes and their biogenesis.[1] Among the intriguing components of this complex oil are zizaene (I) and a number of additional compounds of the tricyclovetivane (or ziza-

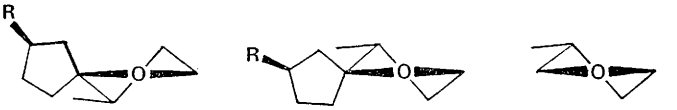
ane) skeleton. The key observation that allowed a decision between alternative biogenetic hypotheses[2,3] for this skeleton was the discovery of prezizaene (IV) among the minor constituents of the oil.[3] It was further noted that prezizaene and zizaene gave, on reaction with formic acid, the same mixture of products and the same time course for the development of each rearrangement product. We now report that this rearrangement involves a novel epimerization at a *centre remote* from the olefinic bond.

After several days in 3:1 HCO_2H–THF at ambient temperature, zizaene (I) afforded a 48:7:39 (V:VI:VII) mixture of tricyclic olefins each displaying in the n.m.r. spectrum 2 singlet Me, one vinyl Me, and a doublet Me resonance. Of the two major products, one is produced at *ca.* 10 times the rate of the other in the initial stages of the reaction. This isomer was readily isolated in a pure state, and treated with OsO_4 in pyridine. The *endo*-glycol (m.p. 146—146·7°) proved suitable for *X*-ray crystallography. Structure (VIIIβ) was arrived at by use of the weighted tangent formula and refined by full-matrix least-squares (R = 0·037).[4]



SCHEME

The spectra (n.m.r., i.r., and mass) of the major product at equilibrium were strikingly similar to those of the initial product; the only difference in the assignable signals was a 0·09 p.p.m. downfield shift of the doublet Me of the more stable isomer (V), suggesting an epimeric relationship at that centre. On this basis, structure (VI) suggests itself as the logical intermediate in the epimerization. Osmylation of the stable isomer also afforded a crystalline glycol (VIIIα), m.p. 130·8—131·9°, which displayed cell constants similar to (VIIIβ) and the same morphology. Here too the doublet Me signal was the only one showing a significant shift difference, 0·22 p.p.m. downfield for (VIIIα), in accord with expectations assuming that glycol formation had occurred *endo* to the bicyclo[3,2,1]octene ring system.†



	(IXβ)	(IXα)	(+)-3-methyl-cyclopentanone
Δε	−0·83	0·51	2·26 (299 nm)
	1·5 (196)	−2·7 (192)	−6·1 (189)

Reasoning that these differences are due to the conformational constraints imposed by the tricyclic system, we next examined the two diones [(IX), $\nu_{C=O}$ 1705 and 1735 cm^{-1}] obtained from the glycols on treatment with excess of $Pb(OAc)_4$ in pyridine. Although distinguishable by high resolution g.l.c. and minor differences in the n.m.r. resonances due to methylene groups, the epimeric diketones were virtual enantiomers from circular dichroism measurements (below). The comparison with (+)-3-methylcyclopentanone is in accord with the structure assignments for (V) and (VII), and points out the importance of ring skew in determining the opposing sign of the $n \rightarrow \pi^*$ and $n \rightarrow \sigma^*$ bands.[7]

To confirm these assignments we have prepared epizizaene (X)[8] and examined its rearrangement under similar conditions. Natural khusimol (II)[1,3] was oxidized to zizanoic acid with Jones' reagent. Esterification afforded methyl zizanoate (III), which was epimerized (to 45% of the epimer) on refluxing with 6 equiv. of NaOMe–MeOH for 70 h. The epimers were separated by preparative g.c. and each was converted into the olefin by the sequence: (i) $LiAlH_4$–Et_2O, (ii) TosCl–pyridine, (iii) $LiAlH_4$–THF. On reaction in the two-phase system, decane–HCO_2H, each isomer produced the same equilibrium distribution of products (Scheme). Each epimer afforded solely the same transient intermediate [presumably (VI)] and the isomer of retained stereochemistry initially.

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† The observation that the olefin (VII) afforded the *endo*-glycol (VIIIβ) was somewhat surprising in the light of the contrary result reported in course of the structure elucidation of zizanoic acid.[5] A related *endo* attack has now been confirmed for the epoxidation and hydroboration of isolongifolene.[6]

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