In vitro and *In vivo* Rearrangement of Eudesmanes to Eremophilanes. Substantiation of Robinson's Hypothesis

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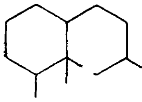
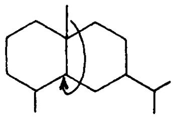
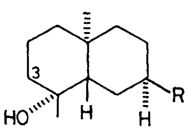
Summary Two further examples of the acid-catalysed rearrangement of eudesmanes to eremophilanes *in vitro* are revealed; Robinson's suggestion that eremophilanes arise *in vivo* from eudesmanes *via* a 1,2 methyl shift has been vindicated by tracer studies with grapefruit.

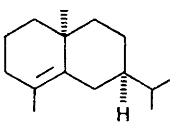
THE sesquiterpenes of the eremophilane family, now a large subgroup, are unusual in that their carbon skeleton (I) does not conform to the well known isoprene rule.[1] Nearly forty years ago, soon after the first members of the family had been found in nature,[2] Robinson proposed that these sesquiterpenes are biosynthesised *via* eudesmane (isoprenoid) precursors (II) which undergo a 1,2-methyl migration from one angular position to the other.[3]


(I)

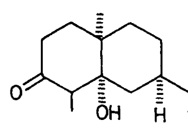

(II)



(III) R = Me_2CH
(IV) R = $MeC{=}CH_2$

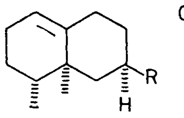


(V)

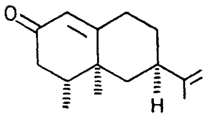


(VI)

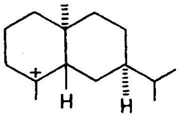
Hitherto this proposal has not been substantiated *in vivo*, but two examples of the methyl migration *in vitro* have been documented.[4,5] Here we describe two additional cases. The alcohol (III) (dihydroparadisiol) was obtained by the catalytic hydrogenation of paradisiol (IV) ($4\alpha H$,-5β,10α-eudesm-11-en-4-ol).[6] Paradisiol may, based on g.l.c. analysis, be present in grapefruit oil.† On refluxing with formic acid or with hydrogen bromide–acetic acid both (V), prepared from (VI),[7] and (III) give the same mixture of products, one of which was identified as dihydrovalencene (VII). Compound (VII), synthesised in four steps from nootkatone (VIII), with the same acid treatment, gave a mixture, the composition of which was identical with that obtained from (III) and (V). Evidently three rapidly equilibrating carbonium ions, (IX), (X), and (XI) must be involved.



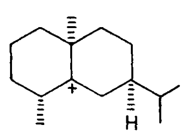
(VII) R = Me_2CH
(XII) R = $MeC{=}CH_2$



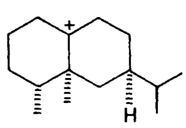
(VIII)



(IX)



(X)



(XI)

Attention was next directed towards substantiation of Robinson's postulate. Paradisiol (IV) appeared an attractive possible precursor with a stereochemistry favourable for rearrangement to valencene (XII), a known constituent of grapefruit. A suspension of [3-^{14}C]-paradisiol[6,8] (1·0 g, activity 6×10^5 d.p.m. mmol^{-1}) in phosphate buffer (pH 7) and Triton X-100 was injected in aliquot portions into 20 unripe grapefruit and exposed to sunlight for 8 days at ambient temperature. Steam distillation of the homogenised pulp followed by ether extraction gave an oil (1·3 g),

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from which radioactive valencene (XII) (7·6 mg, activity 570 d.p.m.) was isolated, representing an incorporation of 0·02%.

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