The Acid-catalysed Cyclisation of 1,2-Humulene Epoxide, a Possible Intermediate in the Biosynthesis of Caryophyllene

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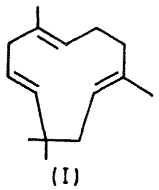
Summary Tricyclohumuladiol is formed in the acid-catalysed cyclisation of 1,2-humulene epoxide.

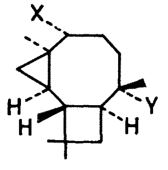
IT has been shown by Sutherland *et al.*[1] that treatment of humulene (I) with *N*-bromosuccinimide in aqueous acetone gives the tricyclic bromohydrin (II) in 20% yield. They also demonstrated that (II) can be converted stereospecifically, in two steps, into caryophyllene (III) or back into humulene, and that hydrolysis of (II) gives the diol (IV) m.p. 205—206°, with retention of configuration. In view of the co-occurrence of caryophyllene with humulene in Nature, this chemical synthesis raises the question as to whether humulene is a biosynthetic precursor of caryophyllene and whether, in particular, the tricyclic bromohydrin (II), or some closely related analogue, is of any significance in the biosynthesis. Of considerable relevance, therefore, is the recent finding by Naya and Kotake[2] that the diol (IV), for which the name tricyclohumuladiol is suggested, is a constituent of hop oil.

In view of the importance of epoxide cyclisation reactions in the bio-organic chemistry and biosynthesis of terpenes and sterols,[3] and following the discovery by Damodaran and Dev[4] that the essential oil from the rhizomes of *Zingiber zerumbet* Smith contains, in addition to humulene and caryophyllene, 1,2-humulene epoxide (V), we studied the acid-catalysed cyclisation of this epoxide to see if it would result in the formation of tricyclic products related to (IV). Treatment of (V) at room temperature with 20% sulphuric acid in acetone gave a complex mixture of at least six products from which a crystalline saturated diol (28%), m.p. 201—203°, was isolated by fractional crystallisation. Initially, this diol was assigned structure (IV) on the basis of its m.p.; the n.m.r. spectrum showed a three proton signal, τ 9·9—9·3, indicative of the trisubstituted cyclopropane ring. Confirmatory evidence was obtained by converting the diol into the chloro-ketone (VI), m.p. 113—115° (lit.[1] 114—116°), and by direct comparison of its i.r. spectrum with that of an authentic sample of (IV).

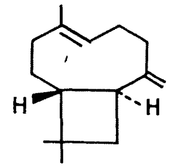
The mixture of products from (V) also contained humulenol[4] (VII) (15%) and an unsaturated diol (7%) which has been assigned structure (VIII). Humulenol, which also occurs naturally with humulene and (V), may be formed directly from the epoxide or, as has been shown by Sutherland *et al.*, [1] by acid-catalysed decyclisation of tricyclohumuladiol. These results may imply that 1,2-humulene epoxide is involved in the biosynthesis of tricyclohumuladiol and caryophyllene.



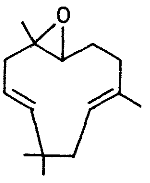
(I)



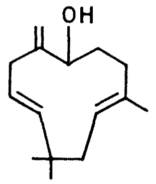
(II)(X = Br, Y = OH)
(IV)(X = Y = OH)
(VI)(X = O, Y = Cl)



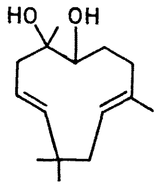
(III)



(V)



(VII)



(VIII)

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[2] Y. Naya and M. Kotake, *Bull. Chem. Soc. Japan*, 1969, **42**, 2405.
[3] For a review see E. E. van Tamelen, *Accounts Chem. Res.*, 1968, **1**, 111.
[4] N. P. Damodaran and Sukh Dev, *Tetrahedron*, 1968, **24**, 4123, 4133.