The Conversion of Humulene into Caryophyllene

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THE sesquiterpene hydrocarbon humulene[1] (I) reacts rapidly with *N*-bromosuccinimide in aqueous acetone to give (II) and (III), each in *ca.* 20% yield. The monobromide (II) contains five vinyl protons, two quaternary methyl groups, one methyl on a double bond, and a secondary bromine (n.m.r.). The presence of three double bonds followed from its oxidation with perbenzoic acid to a dioxide which still contained two vinyl protons (n.m.r.) and, like (II), gave formaldehyde on ozonolysis. The carbon skeleton of (II) was proved by its reduction with lithium in ammonia to a mixture of hydrocarbons containing humulene, identified as its silver nitrate adduct.[2] There are now only two possible structures for the monobromohumulene *viz*, (II) and that in which the other trisubstituted double bond has generated the allyl bromide. N.m.r. evidence favoured (II) but a definite decision could be made between them as follows. Oxidation of (II) with dimethyl sulphoxide[3] gave (IV) and (V), each isolated as the respective 2,4-dinitrophenylhydrazone; that of (IV) was identified by comparison with an authentic sample.[4] The 2,4-dinitrophenylhydrazone of (V) showed *four* protons in the aromatic region of the n.m.r. spectrum and, this, in conjuction with its ozonolysis to dimethylsuccinic, malonic, and laevulic acids,[5] establishes the structure.

The hydroxy-bromo-compound (III) contained no double bonds (n.m.r. and u.v.) but did contain four quaternary methyl groups, τ8·93—8·87 and a one proton signal at τ6·20. In addition a three-proton signal, τ9·3—9·8, suggested the presence of a trisubstituted cyclopropane ring. Compound (III) was hydrolysed [$t_{\frac{1}{2}}$ 11 min. in Me_2CO (3) : H_2O(1) at 20°] under a variety of mild conditions to the diol (VI) which had a one-proton signal at τ6·70. The diol (VI) was oxidized to a ketone (VII) ν_{max} 1690 cm.$^{-1}$ in which one of the quaternary methyls was now deshielded (τ8·56). The bromo-compound (III) was stable under the conditions where (VI) was oxidized or acetylated. On reaction with methanolic 2,4-dinitrophenylhydrazine–sulphuric acid the hydroxy-ketone (VII) gave a ring-opened derivative containing a methoxyl group (τ6·62). Further chemical evidence for the cyclopropane ring came from reaction of the hydroxy–ketone with hydrogen chloride in chloroform to give (VIII) which on further reaction with methanolic hydrogen chloride yielded the dichloro-ketone (IX) characterised as the 2,4-dinitrophenylhydrazone. Reaction of the bromo-compound (III) and the diol (VI) with hydrogen chloride in chloroform (or with thionyl chloride–pyridine) gave the bromochloride (X) and the dichloride (XI) respectively. Both could be hydrolysed to the diol (VI) under mild conditions. In all of the 8-chloro-compounds one of the quaternary methyls was strongly deshielded, the signal appearing at τ8·53.

The presence in (III) of the carbon skeleton of humulene was suggested when solvolysis of the bromo-compound (III) in aqueous acetone yielded an alcoholic fraction, oxidized with manganese dioxide to a mixture of (IV) and (V), identified as before. It was also shown that the diol (VI) could be decyclised under mildly acidic conditions, whereas (II) was stable. The evidence described leads to two possible structures for the hydroxy-bromo-compound (barring an undetected rearrangement in the cyclisation and its reversal in the decyclisation), one of these is theoretically unattractive involving initial bromination at the disubstituted double bond, whereas (III) is mechanistically justifiable.

To convert (III) into caryophyllene (XII), which occurs naturally with humulene, requires elimination of water from the 8 position and reductive rearrangement of the cyclopropyl system. The first was readily achieved using phosphorus oxychloride–pyridine, (III) giving (XIII) which was characterised by hydrolysis to the alcohol (XIV). Both compounds gave formaldehyde on ozonolysis and had appropriate n.m.r. spectra. The reductive rearrangement appeared possible since the ready hydroloysis of (III) suggested the intermediacy of a bicyclobutonium ion,[6] hydride

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[1] See M. D. Sutherland and O. J. Waters, *Austral. J. Chem.*, 1961, **14**, 596 and references there cited.

[2] R. P. Hildebrand and M. D. Sutherland, *Austral. J. Chem.*, 1961, **14**, 272.

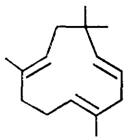
[3] N. Kornblum, J. W. Powers, G. J. Anderson, W. J. Jones, H. O. Larson, O. Levand, and W. M. Weaver, *J. Amer. Chem. Soc.*, 1957, **79**, 6562.

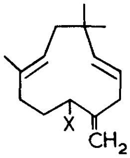
[4] N. P. Damodaran and S. Dev, *Tetrahedron Letters*, 1963, 1941.

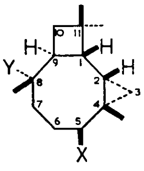
[5] The acids were identified by t.l.c. and by g.l.c. of their methyl esters.

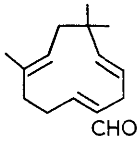
[6] S. Winstein and R. Adams, *J. Amer. Chem. Soc.*, 1948, **70**, 838; J. D. Roberts and R. H. Mazur, *J. Amer. Chem. Soc.*, 1951, **73**, 2509.

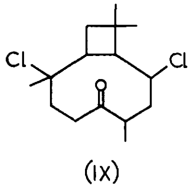
reduction of which would give an olefin as one of the products.[7] Evidence for the S_N1 reaction came from $\frac{-d\,[(\text{III})]}{dt}$ being independent of pH and the conversion of (III) into (XV) on standing in acetonitrile.[8] The approximate relative rates of solvolysis:—(III) > (X) > (XIII), showed the 8-hydroxyl had some effect on ionization at 5. In the event reduction of (XIII) with lithium aluminium hydride in tetrahydrofuran gave a hydrocarbon mixture (77%) from which, by preparative gas chromatography,[9] the tricyclic compound (XVI) (50%), caryophyllene (XII) (30%), and humulene (I) (10%) [probably containing some (XVII)] were isolated. Compound (XVI) had three quaternary methyl groups, τ9·02—8·88, two vinyl protons, τ5·31, and three cyclopropane protons, τ9·2—10·15. In principle the bicyclobutonium ion from (XIII) can be in equilibrum with others[10] which can reasonably lead to two other cyclopropanoid hydrocarbons; one of these is excluded by the n.m.r. spectrum while the stereospecific conversion of (XVI) into humulene (I) by passage over Grade I "Woelm" silica gel renders the other unlikely. The formation of caryophyllene is stereospecific; no evidence for the formation of *cis*-caryophyllene could be found. The caryophyllene was identified by i.r., g.l.c., t.l.c., and mass-spectrometric comparison with an authentic sample. Its structure was confirmed by conversion to the crystalline monoxide.[11] The humulene, like that obtained from the tricycle, was identified by its characteristic n.m.r. spectrum and as its silver nitrate adduct.

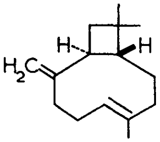

(I)

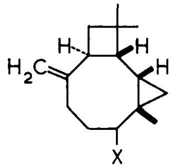

(II) (X=Br)
(IV) (X=O)
(XVII) (X=H)


(III) (X=Br, Y=OH)
(VI) (X=Y=OH)
(VII) (X=O, Y=OH)
(VIII) (X=O, Y=Cl)
(X) (X=Br, Y=Cl)
(XI) (X=Y=Cl)
(XV) [X=N=C(Br)Me
Y=OH]


(V)


(IX)


(XII)


(XIII) (X=Br)
(XIV) (X=OH)
(XVI) (X=H)

The stereochemistry indicated is that expected from 5,4-*trans*-4,2-*syn*-2,1-*trans*-9,1-*anti*-9,8-*trans*-cyclisation. 4,2-*anti*-stereochemistry is also possible but would result in a highly strained structure. Only the stereochemistry at 9,1 has been conclusively proved. The complete stereochemistry is being determined by Professor D. Rogers using *X*-ray crystallography.

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[7] P. R. Story, *J. Amer. Chem. Soc.*, 1961, **83**, 3347.

[8] It appears highly improbable in this Ritter reaction that the nitrile can carry out an S_N2.

[9] We thank Professor W. B. Whalley for kindly lending us his Reoplex 400 column.

[10] J. D. Roberts and R. H. Mazur, *J. Amer. Chem. Soc.*, 1951, **73**, 3542.

[11] W. Treibs, *Chem. Ber.*, 1947, **80**, 56.

[12] A control experiment showed that this was not an artifact arising from the tricycle during reduction or work-up.