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STUDIES IN SESQUITERPENES—XVIII*

THE PROTON MAGNETIC RESONANCE SPECTRA OF SOME SESQUITERPENES AND THE STRUCTURE OF HUMULENE

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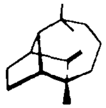
Abstract—The nuclear magnetic resonance spectra of longifolene, zerumbone, humulene, and their hydroderivatives have been studied in order to gauge the potentialities of this new tool in the field of sesquiterpenes. On the basis of present study, it has been possible to unequivocally fix the positions of the ethylene linkages in humulene and thus provide a straightforward solution of this hitherto unsolved problem.

IN recent years high-resolution nuclear magnetic resonance (NMR) spectroscopy has been applied with singular success in solving certain structural problems in organic chemistry.[1] In the present communication the results of the application of NMR to certain sesquiterpenes are discussed. In the first instance spectra of longifolene and zerumbone were studied in order to seek correlations with the known structures of these substances, and later on the method was extended to finally settle the structure of humulene.

Longifolene

The total structure I of longifolene is based essentially on the elegant X-ray crystallographic study of longibornyl chloride by Moffett and Rogers,[2] although excellent chemical evidence has been provided for certain important structural features by Naffa and Ourisson.[3–5] The proton NMR spectrum of longifolene is in complete accord with the structure I. The spectrum, with the peak assignments, is shown in Fig. 1. The integerated areas under the various peaks are



I

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* Part XVII: *Tetrahedron* **8**, 42 (1960).

[1] *a* W. G. Dauben and P. D. Hance, *J. Amer. Chem. Soc.* 77, 2451 (1955); *b* E. J. Corey, H. J. Burke and W. A. Remers, *Ibid.* 77, 4941 (1955); *c* A. T. Bottini and J. D. Roberts, *J. Org. Chem.* **21**, 1169 (1956); *d* N. L. Allinger, *Ibid.* **21**, 1180 (1956); *e* M. G. Ettlinger and F. Kennedy, *Chem. & Ind.* 166 (1956); *f* J. Gripenberg, *Acta Chem. Scand.* **10**, 487 (1956); *g* E. F. Silversmith and J. D. Roberts, *J. Amer. Chem. Soc.* **78**, 4023 (1956); *h* E. E. van Tamelen, S. H. Levin, G. Brenner, J. Wolinsky and P. Aldrich, *Ibid.* **80**, 501 (1958); *i* K. L. Rinehart, W. A. Nilsson and H. A. Whaley, *Ibid.* **80**, 503 (1958).

[2] R. H. Moffett and D. Rogers, *Chem. & Ind.* 916 (1953).

[3] P. Naffa and G. Ourisson, *Bull. Soc. Chim. Fr.* 1115, 1410 (1954).

[4] P. Ourisson and G. Ourisson, *Bull. Soc. Chem. Fr.* 1415 (1954).

[5] G. Ourisson, *Bull. Soc. Chim. Fr.* 895 (1955).

approximately[*] in accord with the populations of the various types of hydrogens in I. A point of special interest is that, as expected,[6] the allylic tertiary hydrogen (84·2 cps) is well-separated from the remaining two tertiary protons (102·6 cps) of longifolene. That these assignments are correct is borne out by the NMR spectrum of longifolane (Fig. 2), wherein the '84·2 cps band' has disappeared. There is no spin-spin splitting for the methyl hydrogens, and this is as it should be, since the methyl groups are attached to carbon atoms carrying no protons. It may be noted that, as expected, such a splitting appears in the case of longifolane (the doublet at 151·7 and 144·3 cps, the 144·3 cps peak would also contain the other nine methyl protons). Another important structural feature of I is also clearly reflected in the NMR spectrum; in longifolene, out of the two, otherwise chemically equivalent, olefin protons, one is diamagnetically more shielded due to the occurrence of a fused 7-membered ring in its immediate neighbourhood ('field effect' due to steric interactions[7]), and this should explain the presence of two olefin proton peaks at 1·9 and 11 cps.[†] That these bands represent a true chemical shift was proved by the field-dependence of the shift; when the spectrum was determined at 16 mc rf., the olefin protons appeared at

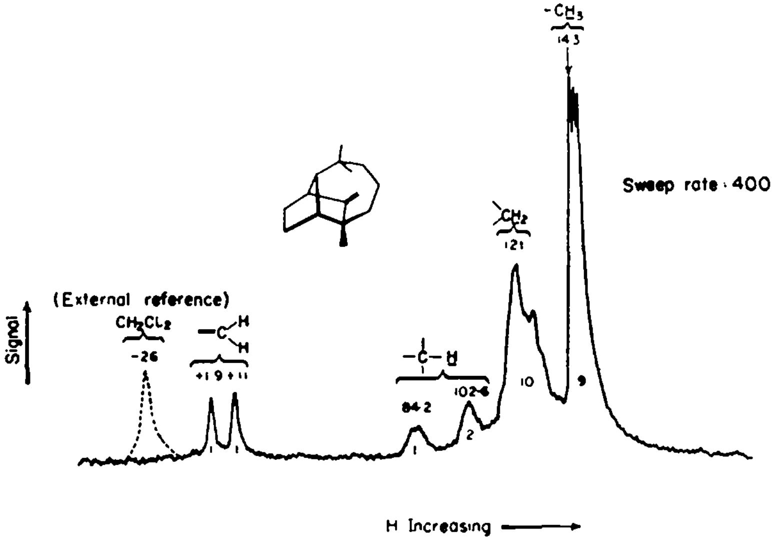

FIG. 1.

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[*] The numbers shown under the various peaks in Fig. 1, represent the number of protons, on the basis of structure I, to be associated with each peak. The actual values were as follows: The ratio of saturated to olefinic protons was calculated from the spectra taken at different sweep rates, and with the sample not spinning (this gave smooth curves with finer resolution missing, but the olefinic and saturated protons were well-separated; area measurement on such curves was easier); the observed ratio varied from 12·5 to 10·8 (calc. 11). From the high resolution curve (Fig. 1), the number of methyl hydrogens was found to be 9·5 (calc. 9). The areas were determined by the weighing method.

[†] The protons of an asymmetric disubstituted ethylenic linkage, by virtue of electron release by the alkyl groups, would be more shielded as compared to a symmetrically disubstituted (or more highly substituted) olefinic linkage and, hence, resonance will occur at higher field strength, as in the case of longifolene. This is borne out by the data available in *A catalogue of the nuclear magnetic resonance spectra of hydrogen in hydrocarbons and their derivatives.* Humble Oil and Refining Co., Texas (1959).

[6] E.g. cf. the spectrum of methyl linolenate [*Tech. Information Bulletin from the Laboratories of the Instrument Div., Varian Associates* **2**, No. 3, 10 (1959)]; N. F. Chamberlain, *Analyt. Chem.* **31**, 56 (1959).

[7] W. D. Kumler, J. N. Shoolery and F. V. Brutcher, *J. Amer. Chem. Soc.* **80**, 2533 (1958).

—15·4 and —11·2 cps, and thus, the peak separation dropped from 9·1 cps to 4·2 cps, which is in good accord with the calculated value of 3·6 cps.

Zerumbone

On the basis of chemical evidence, zerumbone has recently been shown[8] to be II. A study of its NMR spectrum appeared to be of special interest, because of the possibility of gaining some information from such a study about the precise location of the ethylenic linkages in the closely related hydrocarbon, humulene (*vide infra*). The NMR spectrum of zerumbone (Fig. 3) shows an excellent resolution into different types of protons and the different peaks would appear to correspond to the number of protons indicated under each band.* Clearly, the 147·7 cps resonance peak at the highest field strength is to be ascribed to the *gem*-dimethyl groups,[9] while the bands at 132·7 and 124·8 cps are each assignable separately to the methyl groups on the ethylenic linkages.[1d,9] This chemical shift (7·9 cps) between these two methyl groups probably arises due to some *trans*-annular shielding of one of the methyl groups; the carbonyl

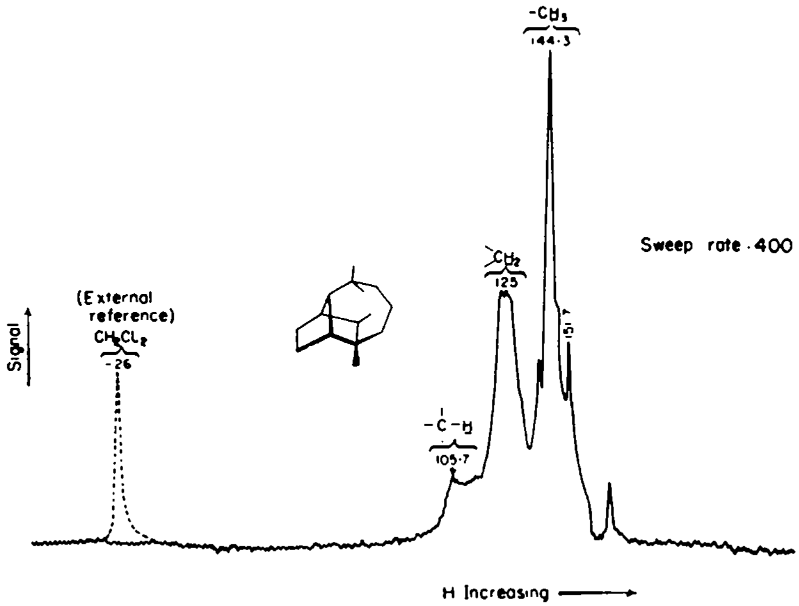
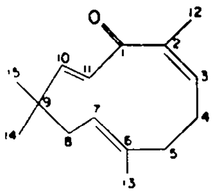
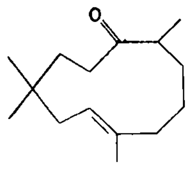


FIG. 2.



II



III

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* The values in parentheses show the relative areas from actual area measurements from the spectrum, whereas the other numbers represent the number of protons expected to occur under a given peak, according to the structure of the compound under discussion. These remarks also apply to Figs. 4–6.

[8] Sukh Dev, *Chem. & Ind.* 1051 (1956); *Tetrahedron* 8, 171 (1960).

[9] L. H. Meyer, A. Saika and H. S. Gutowsky, *J. Amer. Chem. Soc.* 75, 4567 (1953).

group is hardly expected to affect the C_{12} methyl by an inductive mechanism. The next set of peaks (104·3 and 112·2 cps) is readily assignable to the six methylene protons, which are not overlapping the C_{12} and C_{13} protons, by virtue of their being entirely situated on allylic positions.[6] The last group of resonance peaks (−37·9, −23·7, −14·2 and −6·3 cps) represents the remaining four olefinic protons. From the area measurements, it would appear that the −37·9 cps peak contains three protons, which would be the hydrogens on the 3, 10, and 11 positions, the remaining ethylenic proton, which is not subject to the diamagnetic unshielding by the carbonyl, occurs as expected, at a higher field strength. It is rather surprising that no chemical shift between the α-H (at C_{11}), and the β-protons (at C_3 and C_{10}) which are subject to a greater unshielding by the carbonyl by a congugative electron displacement, is observed.*

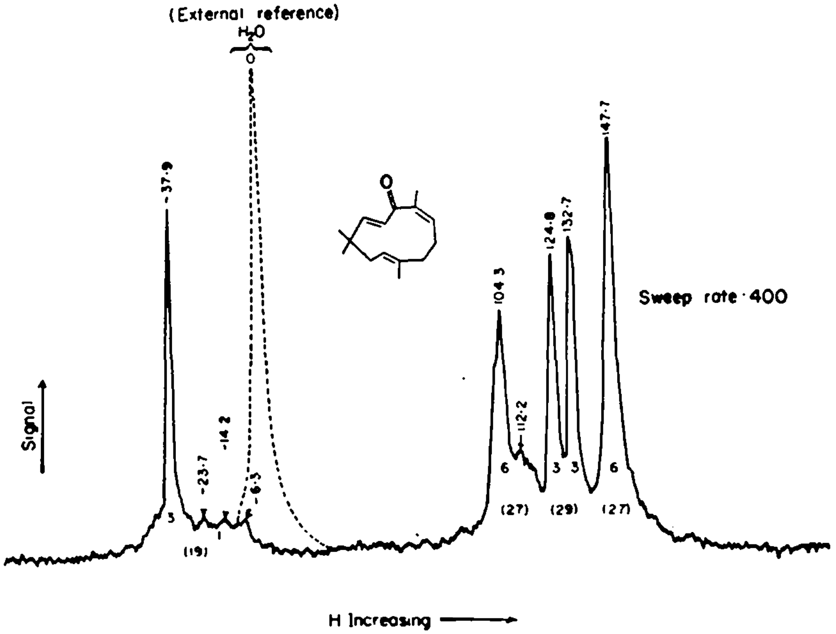

FIG. 3.

These assignments for zerumbone, which are self-consistent, are amply confirmed by the NMR spectra of tetrahydrozerumbone III (Fig. 4), hexahydrozerumbone and deoxyhexahydrozerumbone (humulane, Fig. 6). From the area measurements on Fig. 4, it is clear that the C_{13} methyl-protons occur at 127 cps; it is to be noted that this band is now being overlapped by the absorption due to some methylene protons which are no longer allylic. Tetrahydrozerumbone has only one olefinic proton, which has shown up clearly as a triplet (spin-spin splitting due to C_8-methylene hydrogens) with the centre at −15·3 cps. This confirms the ethylene proton assignments in zerumbone. The peaks at 116·3 and 107 cps would represent the methylene groups at C_5, C_8 and C_{11}, whereas the 99·5 cps band would appear to be a triplet (due to the tertiary proton at C_2) superimposed on the rising absorption of the

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* E.g. the α-olefinic proton in methyl crotonate shows up at −34 cps, while the β-hydrogen appears at −89 cps.

methylene protons. This appears to be confirmed by the NMR spectrum of hexahydrozerumbone, which has peaks, besides those due to methyl and methylene hydrogens (at 156·1, 146·9 and 137·7 cps), at 123·9 (a septet) and 99·5 cps (a triplet), and which from peak inspection would correspond to two and one protons respectively, and thus would be assignable to the C_{11}-methylene protons and the tertiary hydrogen at C_2 respectively. Finally, the NMR spectrum of humulane clearly shows the two

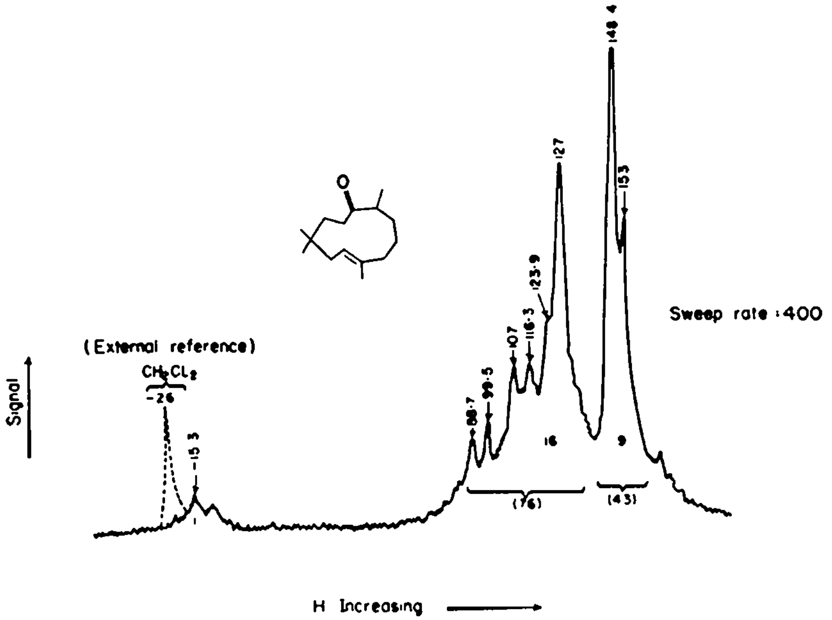

FIG. 4.

types of protons with the expected populations. As a part of special interest, it may be noted in the present series, that as the π-electron centres are removed from the molecule the methyl hydrogens get more and more shielded (147·7 → 156 cps), this possibly has its origin in the expected progressive crowding in the ring.

*Humulene**

Various structures (IV[10], V[11], VI[12], VII[13]) have been proposed for humulene. While the nature of the carbon-skeleton is well-established,[14] the position of the olefinic linkages is not known with any certainty. Humulene is known to yield *as*-dimethylsuccinic acid on oxidation with chromic acid[15] or ozone,[16,17] and formaldehyde[16,17] and laevulinic aldehyde[17,18] have also been isolated after ozonolysis. These

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* A preliminary note appeared in *Tetrahedron Letters* No. 7, 12 (1959).

[10] F. Sorm, M. Streibl, J. Pliva and V. Herout, *Coll. Czech. Chem. Comm.* **16**, 639 (1951).

[11] G. R. Clemo and J. O. Harris, *Chem. & Ind.* 799 (1951); R. W. Fawcett and J. O. Harris, *Ibid.* 18 (1953); *J. Chem. Soc.* 2673 (1954).

[12] Sukh Dev, *Curr. Sci.* **20**, 296 (1951).

[13] P. Clarke and G. R. Ramage, *J. Chem. Soc.* 4354 (1954).

[14] F. Sorm, M. Streibl, V. Jarolim, L. Novotny, L. Dolejs and V. Herout, *Coll. Czech. Chem. Comm.* **19**, 570 (1954).

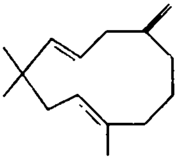
[15] A. C. Chapman, *J. Chem. Soc.* **83**, 505 (1903).

[16] F. Sorm, J. Mleziva, Z. Arnold and J. Pliva, *Coll. Czech. Chem. Comm.* **14**, 699 (1949).

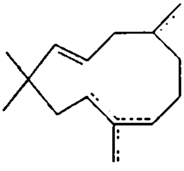
[17] G. R. Clemo and J. O. Harris, *J. Chem. Soc.* 22 (1951).

[18] E. R. Klein and N. F. Lahey, *Chem. & Ind.* 760 (1951).

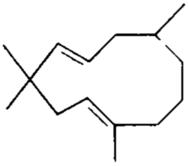
data are readily understandable, if humulene is considered to be IV or VII, with the provision that bond-mobility (as in VI) is involved in some of its oxidative degradations. Such a behaviour has previous precedent.[19] The presence of a semi-cyclic methylene group in purified humulene has been claimed[16] on the basis of quantitative ozonolysis and infra-red spectral measurements. On the other hand, Clarke and Ramage[13] favour the structure VII* on the basis of oxidative degradation of some crystalline humulene derivatives.



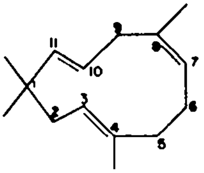
IV



V



VI



VII

Ozonolysis of certain compounds lacking in an asymmetric disubstituted ethylenic linkage, has been known to yield formaldehyde or formic acid.[20] On the other hand some compounds containing such a linkage have failed to give more than a trace of these products after ozonolysis.[1c,3,21] Similarly, at least some compounds without RR'C=CH$_2$ linkage have been shown[22] to absorb, often strongly, around 890 cm^{-1} in the infra-red. In view of these, it seemed desirable to re-examine the whole problem by a method which could offer an unequivocal answer. In this connexion, the NMR spectrum of humulene has been studied, especially because in the NMR spectrum of zerumbone, the closely related sesquiterpene ketone, the various methyl and methylene protons were so nicely resolved.

The NMR spectrum of humulene, with the proton populations of the various peaks, is shown in Fig. 5. It is at once apparent from this spectrum, that the methyl and methylene proton region of the NMR curve of humulene is *almost identical* with that of the corresponding region in the zerumbone spectrum (cf. Fig. 3), both as regards the relative disposition of the peaks as well as the area under each peak

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* Very recently [R. P. Hildebrand, M. D. Sutherland and O. J. Waters, *Chem. & Ind.* 489 (1959)] fresh chemical evidence, based on LiAlH$_4$ reductive cleavage of the humulene ozonide, in favour of structure VII has been published.

[19] R. Kuhn and H. Roth, *Ber. Dtsch. Chem. Ges.* 65, 1285 (1932); A. E. Bradfield, A. R. Penfold and J. L Simonsen, *J. Chem. Soc.* 309 (1935); G. R. Ramage, R. Whitehead and B. Wilson, *Ibid.* 4341 (1954).

[20] J. Knights and E. S. Waight, *J. Chem. Soc.* 2830 (1955).

[21] J. T. Gragson, K. W. Greenlee, J. M. Derfer and C. E. Boord, *J. Amer. Chem. Soc.* 75, 3344 (1953).

[22] For example, n-octane, 3-ethylhexane, 3 methyl-3-ethylpentane, geranylamine hydrochloride [D. Barnard, L. Bateman, A. J. Harding, H. P. Koch, N. Sheppard and G. B. B. M. Sutherland, *J. Chem. Soc.* 915 (1950)], Δ^{8}-*p*-menthene [R. L. Frank and R. E. Berry, *J. Amer. Chem. Soc.* 72, 2985 (1950)], and α-pinene [J. Pliva and V. Herout, *Coll. Czech. Chem. Comm.* 15, 160 (1950)] absorb strongly near 890 cm^{-1}, although the grouping RR'C=CH$_2$ is certainly absent.

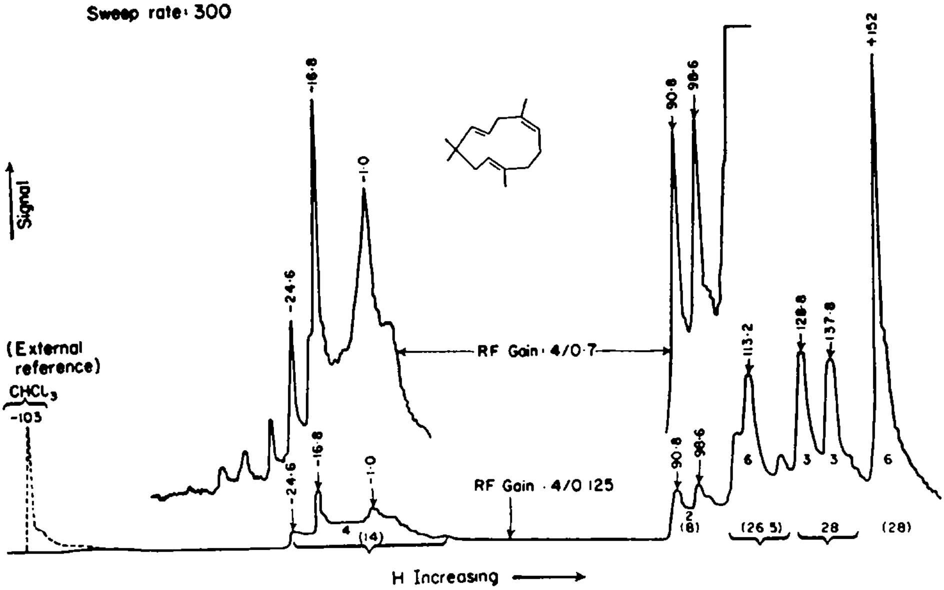

FIG. 5.

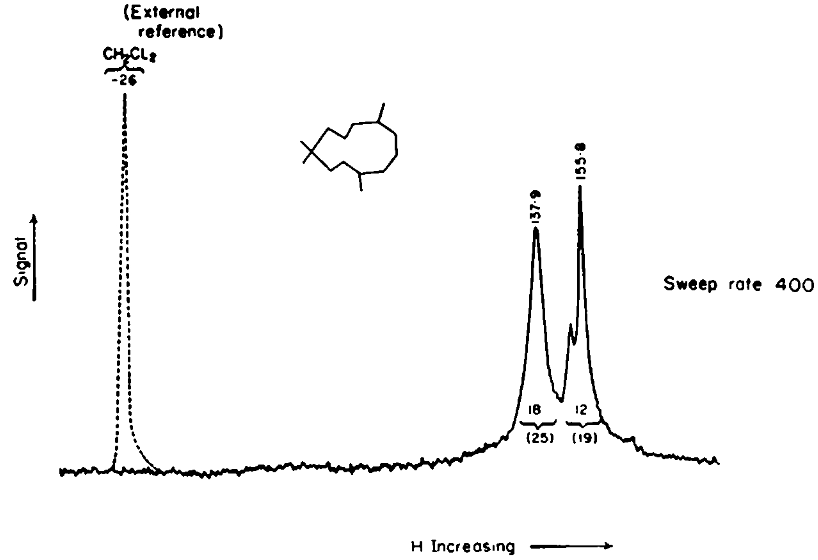

FIG. 6.

(average shift of these bands relative to those of zerumbone is ∼6 cps). This forces us to the only conclusion that humulene, like zerumbone, has *four methyl groups* and all of its methylene groups are located at allylic positions. This is in accord with structure VII only. The 'new' methylene group at position 9 in humulene, as expected,[6] showed up at a still lower field strength (peaks at 90·8 and 98·6 cps with the areas approximately in the ratio 1 : 1), and the olefinic protons formed a complex multiplet in the expected region. As a point of further evidence in favour of structure VII, it may be noted that from the relative areas of the olefinic and 'saturated' protons, the number of ethylenic hydrogen atoms in humulene works out to be 3·3, a figure which is closer to that required for VII as compared to that required for IV.

As discussed earlier, the presence of a band around 890 cm^{-1} in the infra-red spectrum of humulene does not constitute a strong argument for the presence of $RR'C{=}CH_2$ group. We have re-examined quantitatively the infra-red absorption of humulene (Fig. 7), especially because from the published spectra[16] of humulene and caryophyllene (in which the presence of the grouping $RR'C{=}CH_2$ is based on sound chemical evidence), the absorption of humulene around 890 cm^{-1} appeared to be much smaller as compared to that of caryophyllene in the same region. As would be clear from an examination of the results (Table 1), the intensity of the 890 cm^{-1}

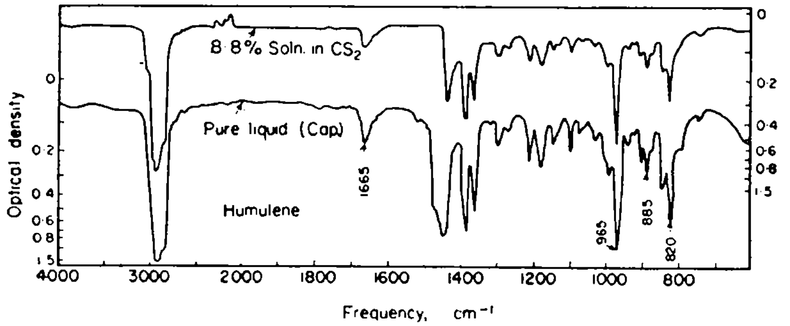

FIG. 7.

TABLE 1. APPARENT MOLECULAR EXTINCTION CO-EFFICIENTS OF SOME RELEVANT BANDS IN THE INFRA-RED ABSORPTION OF HUMULENE

Peak (cm^{-1})	Assignment	No. of groups	$\varepsilon^{(a)}$	
			Found	Average val. from lit.[23]
1665	$RR'C{=}CHR''$ $RHC{=}CHR'$ (*trans*-)	2 1	20·8	$RR'C{=}CHR''$? $RHC{=}CHR'$ ~2 $RR'C{=}CH_2$ 30–45
965	$RHC{=}CHR'$	1	125	100–110
820	$RR'C{=}CHR''$	2	64	33–50
885*	—	—	32	$RR'C{=}CH_2$ 120–160

* Many *trans*-olefins absorb in this region.[23c]

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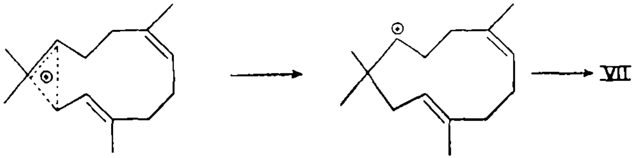
[23] *a* R. N. Jones and C. Sandorfy in A. Weissberger's, *Technique of Organic Chemistry* Vol. IX, pp. 367–384. Interscience, New York (1956); *b* D. Barnard, L. Bateman, A. J. Harding, H. P. Koch, N. Sheppard and G. B. B. M. Sutherland, *J. Chem. Soc.* 915 (1950); *c* H. L. McMurry and V. Thornton, *Analyt. Chem.* **24**, 318 (1952).

peak is not consistent* with the presence of $RR'C{=}CH_2$ system in humulene. Thus the evidence presented in this paper allows the unequivocal formulation of humulene as VII. Like zerumbone, the Δ^{10}-ethylenic bond in humulene has a *trans*-configuration, and the precise steric arrangement of the other two olefinic linkages remains as yet uncertain. This structure of humulene is directly related to that of zerumbone by an oxidation–reduction system, and we are currently trying to effect such interconversions.

Theoretically, humulene now becomes biogenetically related[24] to farnesol by a simple path involving no rearrangement of the ethylenic linkages.



Farnesyl cation

EXPERIMENTAL

Materials. Longifolene, zerumbone and their derivatives employed for the determination of their NMR spectra were all purified samples and their preparation has been described previously (Parts XVI and XVII of this series).

Humulene was isolated from the essential oil of *Zingiber zerumbet*[12] and after precise fractionation had: b.p. 114–115°/5 mm, n_D^{25} 1·5015, $[\alpha]_D^{25}$ − 0·31, *nitrosochloride*[25] m.p. 175–176°, *trioxide*[16] m.p. 122°.

Proton magnetic resonance spectra. All proton magnetic resonance spectra were determined at 40 mc rf., except when stated to the contrary, with a Varian Model V-4300B high-resolution spectrometer fitted with a field-sensing stabilizer. Chemical shifts were measured by superimposing an audiofrequency, and using the side bands which develop, to determine the chemical shifts between two signals in cycles per second.[26] The compounds were measured as 25 per cent solutions in carbon tetrachloride. An external reference was employed using a concentric-tube cell;[27] the reference used in each case has been indicated on the NMR curve, the solid line represents the signal without the reference compound, while the broken line shows how the signal was modified, when the reference compound was also introduced in the magnetic field. All chemical shifts described herein have been expressed relative to water (zero standard), though for most of the measurements the actual external reference used was other than water; in such cases the shifts in cps relative to water were figured out by subtracting from the observed shifts (relative to the actual standard) the chemical shift in cps between water and the actual reference compound (for CH_2Cl_2 26 cps and for $CHCl_3$ 103 cps; these values were obtained from actual runs). All spectra were taken at 25°.

Infra-red spectra. These were determined with a Perkin–Elmer double-beam instrument, both on the pure liquid and on its 8·8 per cent solution in CS_2. Sodium chloride optics were employed.

Acknowledgements—This work was carried out at the Noyes Chemical Laboratory, University of Illinois, Urbana, and the author wishes to place on record his sincere gratitude to Prof. E. J. Corey for these facilities. The NMR spectra were kindly obtained by Mr B. A. Shoulders.

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* The intensity of the 890 cm^{-1} band is known to be considerably reduced in certain compounds containing $RR'C{=}CH_2$ grouping [D. H. R. Barton, P. de Mayo and M. Shafiq, *J. Chem. Soc.* 3314 (1958); L. Dolejs, M. Soucek, M. Horak, V. Herout and F. Sorm, *Coll. Czech. Chem. Comm.* **23**, 2195 (1958); cf. W. H. T. Davison and G. R. Bates, *J. Chem. Soc.* 2607 (1953)]. However all such compounds are substituted in the α-position by an oxygen function.

[24] L. Ruzicka, *Experientia* **9**, 357 (1953).

[25] G. S. Krishna Rao, Sukh Dev and P. C. Guha, *J. Ind. Chem. Soc.* **29**, 589 (1952).

[26] J. T. Arnold and M. E. Packard, *J. Chem. Phys.* **19**, 1608 (1951).

[27] J. R. Zimmerman and M. R. Foster, *J. Phys. Chem.* **61**, 282 (1957).