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SOME NEW HUMULENE-BASED SESQUITERPENOIDS

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DURING our work on zerumbone[1], it was noticed that the fraction (b.p. 91-115°/1 mm) of the essential oil from *Zingiber zerumbet*, distilling between humulene and zerumbone cuts, still exhibited strong absorption at ~ 970 cm^{-1}, which we consider as a useful pointer for humulene-based sesquiterpenoids. This material has now been thoroughly investigated and has been found to contain two ketones ($\sim 6\%$), two α-epoxides ($\sim 65\%$), a diepoxide ($\sim 4\%$) and an alcohol ($\sim 3\%$), all belonging to the humulene group; besides, (+)-*ar*-curcumene ($\sim 2\%$) and caryophyllene epoxide ($\sim 20\%$) could also be isolated. In this communication, we report on the structures of the α-epoxides and the alcohol.

In an earlier paper[2] from this Laboratory, the isolation of an humulene epoxide and humulene dioxide has been reported. Thin-layer chromatography of this 'humulene epoxide' (b.p. 108-109°/1.5 mm, n_D^{30} 1.4938, α_D^{25} -40) over

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[1] Sukh Dev, *Tetrahedron* **8**, 171 (1960).

[2] S.K.Ramaswami and S.C.Bhattacharyya, *Tetrahedron* **18**, 575 (1962).

silver nitrate-clad-silica gel[3] revealed the gross inhomogeneity of this material as it gave three spots of almost equal area and intensity. Gas-liquid chromatography (GLC) over 20% diethylene glycol polysuccinate on Chromosorb W also gave three peaks with areas in the ratio 34:35:31[4]. By a combination of fractionation, column chromatography over neutral alumina and over silica gel-silver nitrate, it has now been possible to isolate these components in a state of purity. The compound corresponding to GLC peak I had m.p. 61.5 - 62°, $[\alpha]_D$ -74.2 ($CHCl_3$; c, 4.2%) and has been identified as caryophyllene epoxide[5] by its mixed m.p. and comparison of its infrared spectrum with that of an authentic specimen. The material representing GLC peak II had b.p. 104-105°/1.5 mm, n_D^{30} 1.4935, d_4^{30} 0.9541, $[\alpha]_D^{30}$ -22.8 ($CHCl_3$; c, 3.6%) and analysed for $C_{15}H_{24}O$; this is now shown to possess structure (I) and shall be designated *humulene epoxide-I*. The third component had b.p. 105-106°/1.5 mm, n_D^{30} 1.4962, d_4^{30} 0.9477, $[\alpha]_D^{30}$ -31.2 ($CHCl_3$; c, 4.2%)

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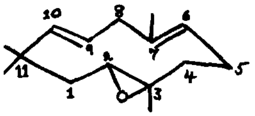
[3] A.S.Gupta and Sukh Dev, *J. Chromatog.* (1963).

[4] The peaks are numbered starting from the side of air peak. The material underwent profound decomposition on untreated celite supports but this was completely absent when, instead, Chromosorb W (Johns-Manville) was used. The authors wish to record their indebtedness to Dr.Rudloff (Saskatoon, Canada) for help in GLC.

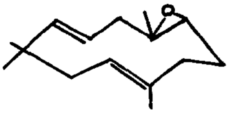
[5] W.Treibs, *Chem. Ber.* **80**, 56 (1947).

and also analysed for $C_{15}H_{24}O$ and has been shown to be (II) and hence shall be termed *humulene epoxide-II*.

The evidence leading to the establishment of structure I for humulene epoxide-I is briefly summarised. The compound



I



II

did not exhibit any hydroxyl or carbonyl absorption in the infrared, but displayed bands (1242, 887 and 792 cm^{-1}) assignable[6] to an oxirane ring; other peaks of diagnostic value were at 1360, 1380 (*gem*-dimethyl) and, 1650 and 972 cm^{-1} $(\underset{H}{>}C=C\overset{H}{<})$. Its proton magnetic resonance (PMR) spectrum[7] showed singlets at 62, 66 (quaternary methyl protons) and 72 cps (quaternary methyl on carbon attached to oxygen) each corresponding to three protons; a doublet (3H; J = 1) at 101 cps is assignable to a methyl on a trisubstituted olefinic linkage; a complex multiplet located between 300 and 357 cps accounted for three vinyl protons $(\underset{H}{>}C=C\overset{H}{<}$ and $CH_3-\underset{|}{C}=CH-)$. Catalytic hydrogenation over prereduced PtO_2

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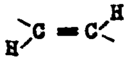
[6] W.A.Patterson, *Anal. Chem.* 26, 823 (1954); J.Bomstein, *Anal. Chem.* 30, 544 (1958).

[7] All PMR spectra were taken on ~20% solution in CCl_4 on a Varian A-60 High Resolution NMR Spectrometer, with tetramethylsilane as an internal reference. The values are reported in cycles/sec. from tetramethylsilane as zero.

in ethanol gave a dihydro compound b.p. 102-103°/1 mm, n_D^{30} 1.4870, $[\alpha]_D^{30}$-26.1 ($CHCl_3$; c, 2.1%); an examination of its infrared and PMR spectra revealed that  $\overset{}{\underset{H}{>}}C=C\overset{H}{<}$ grouping has been reduced, and $CH_3-\underset{|}{C}=CH-$ is still present. All these data can be accommodated in an humulene α-epoxide, wherein the trans-disubstituted ethylenic linkage remains intact; such a formulation was strongly suggested on biogenetic considerations. Confirmation of this was obtained by a study of its reaction with perbenzoic acid, two molar equivalents of which were consumed to give in ~ 50% yield a solid, m.p. 108-114°, $[\alpha]_D$ +1.26, $[\alpha]_{313}$ -2.34, the m.p. could not be improved by further crystallisations; this material had an infrared spectrum completely superimposable on that of humulene triepoxide (m.p. 121-22°). This leads to the formulation of the new sesquiterpenoid as either (I) or (II). A distinction between these could be made on the basis of its PMR spectrum. The compound exhibited two sharp signals (2H) at 147 and 153 cps reminiscent of the 143 and 149 cps peaks in the PMR spectrum of humulene and, assignable to the two allylic protons at C_8; these signals, as would be expected, were absent from the PMR spectrum of the dihydroepoxide. This information establishes the structure of humulene epoxide-I as (I), a conclusion, further supported by the settlement of the structure of the second epoxide, as described below.

The infrared spectrum of humulene epoxide-II was found to be identical with that of an humulene oxide of undetermined structure prepared by Šorm and coworkers[8] by the pervanadic acid oxidation of humulene. Like the synthetic material[8], the natural epoxide also yielded a crystalline dihydro derivative, m.p. 69-69.5°, $[\alpha]_D$ -0.27 (CCl_4; c, 2.5%), on catalytic hydrogenation over prereduced PtO_2 in ethanol; its infrared spectrum was identical with that of an authentic sample (m.p. 69-69.5°) prepared by the hydrogenation of Šorm *et al.*'s synthetic humulene monoxide. On treatment with perbenzoic acid, it took up two equivalents of the peracid to yield, after repeated crystallisations, a product of m.p. 121-22°, $[\alpha]_D$ +1.37 (CCl_4; c, 1.5%); its infrared spectrum was identical with that of (±)-humulene triepoxide and did not depress its m.p. (121-22°). Since the trans-disubstituted olefinic linkage is present (infrared and PMR spectra) in humulene epoxide-II and, furthermore, since structure (I) has been assigned to humulene epoxide-I, the constitution (II) follows for humulene epoxide-II. This was confirmed by a study of its oxidative ozonolysis, when *as*-dimethylsuccinic acid could be isolated in over 50% yield.

We shall, now, turn to the structure of the alcohol, which is isolable from the later portions of the fraction, of the essential oil, under consideration. By a combination of chromatography and preparative GLC, an alcohol, which we shall designate *humulenol* could be obtained in a state of

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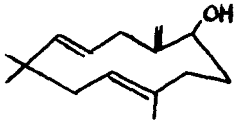
[8] F.Šorm, M.Streibl, J.Pliva, and V.Herout, *Coll. Czech. Chem. Comm.* **16**, 639 (1951).

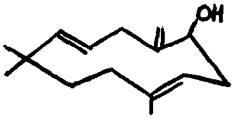
purity (GLC, thin-layer); this had b.p. 115-16°/1 mm, n_D^{30} 1.5127, $[\alpha]_D^{30}$ +30.0 ($CHCl_3$; c, 3.6%), and analysed for $C_{15}H_{24}O$. Humulenol (ν^{OH} 3330 cm^{-1}) on treatment with perbenzoic acid consumed three moles of the per acid, and on catalytic hydrogenation (Pt/AcOH) took up three moles of hydrogen to yield a saturated alcohol, $C_{15}H_{30}O$: b.p. 105-106°/0.8 mm, n_D^{30} 1.4831, $[\alpha]_D^{28}$ -2.4 ($CHCl_3$; c, 1.06%). Thus, humulenol should contain three olefinic linkages and from its molecular formula, then, its monocyclic nature follows.

The absence of any absorption peak above 200 mμ in the ultraviolet region indicated that the olefinic linkages are not conjugated. The infrared spectrum of humulenol indicated the presence of $>=CH_2$ (1648, 903, 1800 cm^{-1}), ${}_{\mathrm{H}}{>}{=}{<}^{\mathrm{H}}$ (1660, 980 cm^{-1}), ${>}{=}{<}^{\mathrm{H}}$ (840 cm^{-1}) and a *gem*-dimethyl group (1360, 1380 cm^{-1}). These assignments were confirmed by a study of its PMR spectrum: a complex multiplet between 288 and 303 cps accounted for a total of five vinyl protons; it also revealed the presence of two quaternary methyl groups (6H; 63 cps) and one methyl on a trisubstituted olefinic bond (3H; 95 cps, partly split). A clean triplet (1H) centred at 227 cps (J = 5 cps) indicated humulenol to be a secondary alcohol, the signal being due to the proton α to the hydroxyl and being split by an adjacent CH_2 group; this absorption disappeared in the PMR spectrum of the ketone (*vide infra*) derived from this. Another, significant absorption occurs as a multiplet (2H) at 162-167 cps in its PMR spectrum, indicating the presence of $=\underset{|}{C}-CH_2-\underset{|}{C}=$ in the molecule (cf. humulene, humulene epoxide-I).

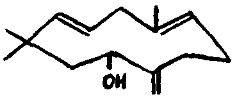
All these data can best be accommodated in an humulene-based structure and four formulae III, IV, V or VI come for consideration:



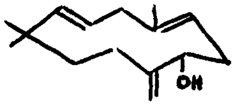
III



IV



V



VI

The formulation of humulenol as an allylic alcohol is supported by its ready oxidation to the corresponding ketone with active manganese dioxide (4 hrs at ~ 25°); the product (m.p. 44-44.5°; semicarbazone m.p. 202-203(d); 2,4-dinitrophenylhydrazone m.p. 190-191°), as expected, was optically inactive. The ketone displayed its $\nu^{C=O}$ at 1680 cm^{-1}, but surprisingly showed no K band in the ultraviolet region (in alcoholic or heptane solutions); this absence of K band must be ascribed to a significant departure from co-planarity of the concerned groups ($>=CH_2$ and $>=O$) and such cases are on record[9]; its semicarbazone, however, had λ_{max}^{EtOH} 256 mμ (ε 16,770), a value very close to that expected of a derivative from an αβ-unsaturated ketone.

Of the four possible structures noted above, III and V would be preferable on biogenetic grounds. A distinction between these possibilities and a final confirmation of the structure, however, could be made in a surprisingly simple and straightforward way. Prelog et al.[10] have noted that trans-cyclodecene epoxide on chromatography over strongly activated alumina gave an allylic alcohol. During our work on the isolation and purification of humulene epoxides, it was noticed that unless the activity of alumina is carefully controlled to grade-II (Brockmann scale) considerable loss of the material occurred. In view of this, it was thought that humulenol could possibly be correlated, this way to humulene epoxide-I or -II. As a matter of fact, when humulene epoxide-II was shaken with alumina (grade I) in an hexane solution about 60% conversion to an alcohol[11], identified as humulenol by various physical constants and infrared spectrum, took place. This would fix the structure of humulenol as (III).

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[9] E.E. van Tamelen, S.H.Levin, G.Brenner, J.Wolinsky and P.E. Aldrich, J.Amer.Chem.Soc. **81**, 1666 (1959); A. Hassner and T.C.Mead, Tetrahedron Letters **25**, 1223 (1962); J. Wolinsky and D.Chan, J.Amer.Chem. Soc. **85**, 937 (1963).

[10] V. Prelog, K.Schenker and H.H.Günthard, Helv. Chim. Acta **35**, 1598 (1952).

[11] The reaction has been found to be general and humulene epoxide-I, dihydro humulene epoxides, humulene dioxide, caryophyllene epoxide all yielded alcohols by this treatment; these will be discussed in a fuller paper.