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STUDIES IN SESQUITERPENES—XXXIX

STRUCTURE OF HUMULENOLS*†

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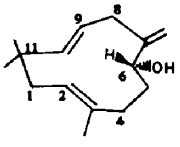
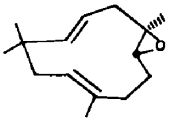
Abstract—(+)-Humulenol-II, a minor component of the volatile oil from the rhizomes of *Zingiber zerumbet*, is shown to possess the absolute stereostructure I and has been directly correlated with (—)-humulene epoxide-II. The preparation of (+)-humulenol-I is also described.

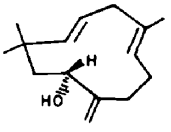
THE essential oil from the rhizomes of *Zingiber zerumbet* Smith contains, at least, four sesquiterpene alcohols as minor constituents.[1] The isolation of one of these has been described in an earlier communication[1] and we now present evidence which establishes its absolute stereostructure as I. In view of its close relationship with humulene epoxide-II (II), the alcohol has been designated humulenol-II.‡ We also describe the preparation of III (humulenol-I), possibly one of the remaining three alcohol components of the essential oil.



I



II



III

(+)-*Humulenol*-II

The alcohol analyses for $C_{15}H_{24}O$ and consumes 3 moles of perbenzoic acid (PBA). On hydrogenation in AcOH over PtO_2–catalyst it absorbed 3 moles of H_2 to give a hexahydro derivative (possibly a mixture of isomers), which shows no color with tetranitromethane. The hexahydroalcohol on Sarett oxidation[2] furnished a ketone showing $\nu^{C=O}$ 1709 cm^{-1}. Thus, humulenol-II, being $C_{15}H_{24}O$, must be a monocyclic secondary alcohol in which the alicyclic ring must be larger than 5-membered. Since humulenol-II does not show any characteristic absorption maximum above 210 mμ, the olefinic linkages are, in all probabibility§ not conjugated.

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† In part abstracted from the Ph.D Thesis (Poona University, 1965) of N. P. Damodaran.

‡ A preliminary publication appeared in *Tetrahedron Letters* 1941 (1963), wherein the name humulenol has been used; the ending II has been suffixed now to differentiate it from other isomers.

§ In certain medium-ring 1,3-dienes, the two olefinic linkages fail to achieve co-planarity and consequently do not show any UV absorption max above 210 mμ.[3]

In its IR spectrum (Fig. 1), the compound shows absorptions due to: OH 3330, 1040 cm^{-1}; $-\underset{|}{C}=CH_2$ 1800, 1648, 903 cm^{-1}; $-C=CH-$ 840 cm^{-1}; $\begin{matrix} & & H \\ & C=C & \\ H & & \end{matrix}$ 1660, 980 cm^{-1}; *gem*-dimethyl group 1360, 1380 cm^{-1}. The presence of the strong 980 cm^{-1} band (*trans*-disubstituted olefinic linkage) suggested that the new alcohol may be a humulene derivative.[1]

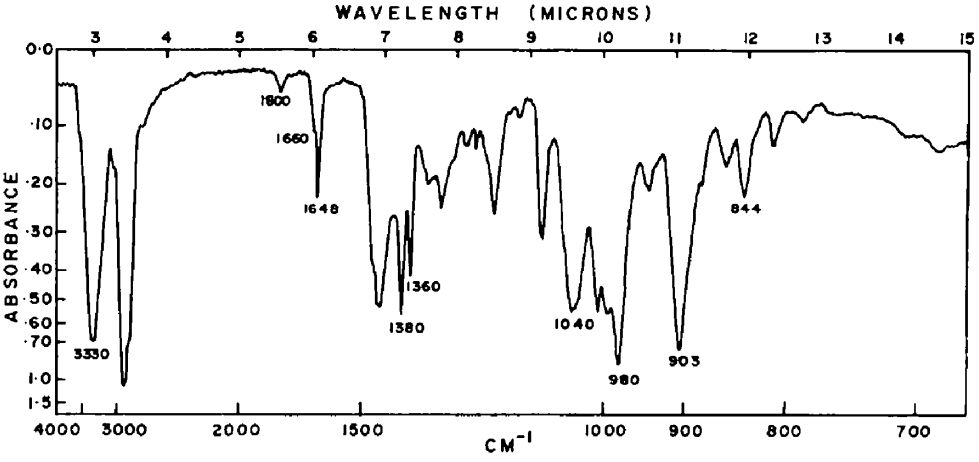


FIG. 1 IR Spectrum of humulenol-II

The above assignments are clearly supported by its PMR spectrum (Fig. 2): two quaternary Me's, 6H s at 63 c/s; one vinyl Me, 3H singlet (slightly split, $J \simeq 0{\cdot}5$ c/s) at 95 c/s; five olefinic protons, a complex multiplet between 285–308 c/s. The sec-

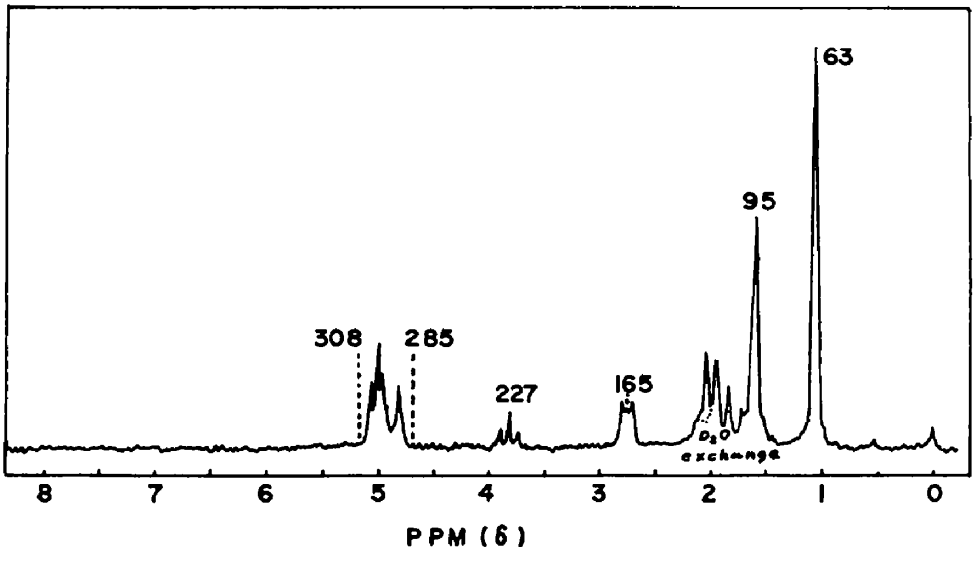
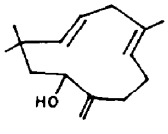


FIG. 2 PMR Spectrum of humulenol-II.

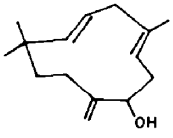
ondary nature of the alcohol, deduced earlier, is confirmed by the presence of a 1H signal (triplet, $J = 5$ c/s) at 227 c/s, which shifts to ~290 c/s (partly overlapped by vinyl proton signal) in the acetate and is assigned to the proton linked to carbon carrying OH;[4] the splitting pattern of this signal requires that —CHOH must be flanked on one side by a methylene. A 2H, m centred at 165 c/s (occurs as a 2H d centred at 167 c/s in the derived acetate) is reminiscent of the C_8-doubly allylic protons in humulene and humulene epoxide-I[5] and suggests the presence of the grouping =C—CH_2—C= in humulenol-II.

The above data are best accommodated in a humulene-based structure and formulations IV–IX come up for consideration.

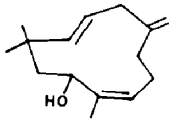
In conformity with its formulation as an allylic secondary alcohol, humulenol-II is readily oxidized to the corresponding ketone by activated MnO_2.[6] The product (m.p. 44–44·5°) as expected is optically inactive. The same ketone is obtained, in



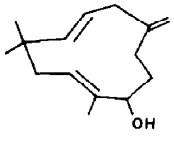
IV



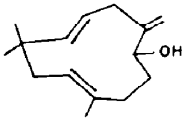
V



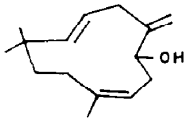
VI



VII



VIII



IX

better yield, by Sarett oxidation.[2] This ketone shows no clear K-band in the UV (in heptane solution no absorption maximum is seen between 210–270 mμ, while in ethanol solution only an inflection is discernible at 220 mμ, ε 7600; the R-band occurs at λ_{max}^{EtOH} 315 mμ, ε 40) and this must be ascribed to a significant departure from coplanarity of the concerned chromophoric components and several such instances are on record.[7–10] The semicarbazone and the 2,4-dinitrophenylhydrazone derived from the ketone show, on the other hand UV absorption in the range approaching that for these derivatives of αβ-unsaturated ketones:[11] λ_{max}^{EtOH} 256 mμ (ε 16,770) and $\lambda_{max}^{CHCl_3}$ 369 mμ (ε 17,620) respectively. The PMR spectrum (Fig. 3) of the ketone shows in its vinyl proton region signals assignable to- —C(OH)=C<u>H</u>—, 1H, triplet centred at 286 c/s, $J = 7·5$ c/s; C—C<u>H</u>=C<u>H</u>—, AB part of ABX multiplet located between 283–330 c/s; and, —C(OH)=C<u>H</u>$_2$, 2H doublet centred at 329 c/s. A comparison of these signals with those obtaining for humulenol-II (Fig. 2) clearly reveals the down-field shift of two protons, assignable to the vinylidene grouping, indicating the conjugation of this grouping with the CO function. The IR spectrum

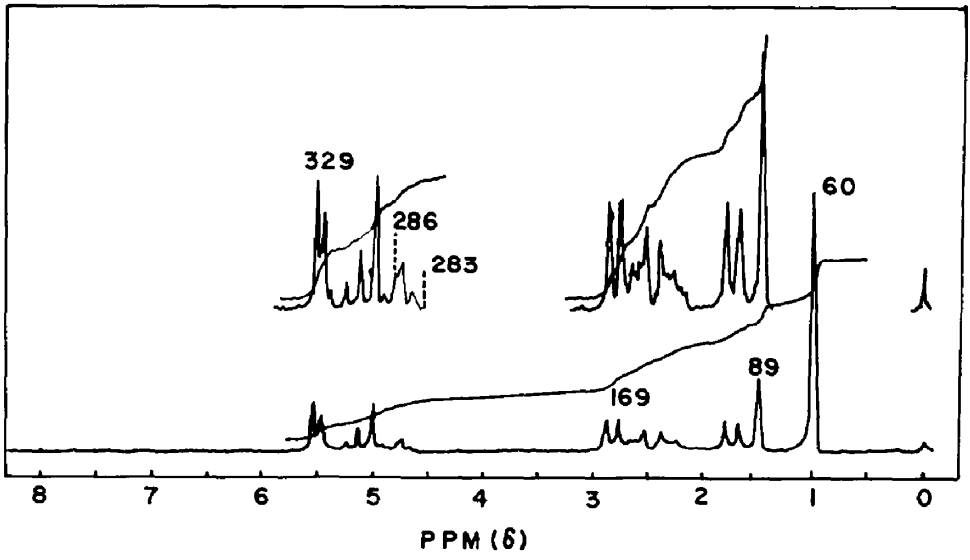


FIG. 3 PMR Spectrum of humulenone-II.

(Fig. 4)* of the ketone shows $\nu^{C=O}$ 1680 cm^{-1} and $\nu^{C=C}$ 1625 cm^{-1}; the difference between these values ($\nu^{C=O}/\nu^{C=C}$ = 55 cm^{-1}) as well as $E^{C=O}/E^{C=C}$ (3·35) strongly suggests that the vinylidene group and the CO function have essentially S-*trans* conformation, which requires the alicyclic ring to be more than 8-membered.[13] As

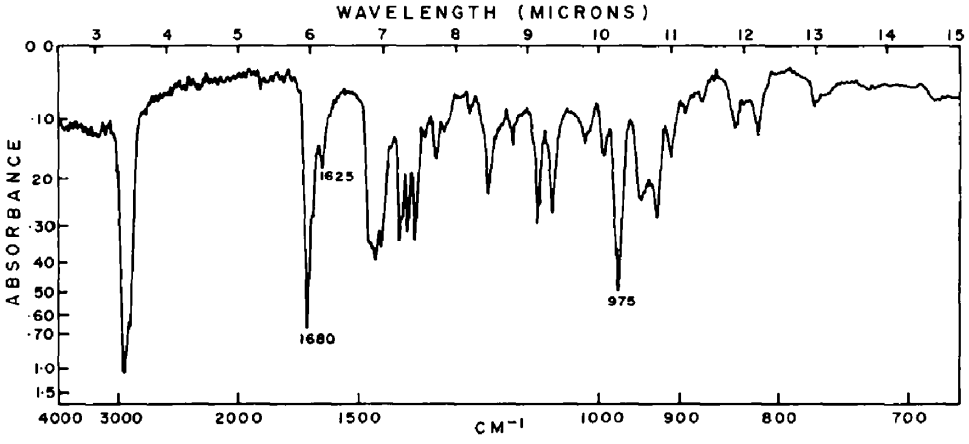
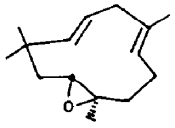


FIG. 4 IR Spectrum of humulenone-II.

* The absence of any strong absorption band around 890 cm^{-1}, region in which the out-of-plane bending frequency of a vinylidene group hydrogens normally occurs, may be noted. However, since the presence of a vinylidene group is clear from its PMR spectrum, the present case may be considered as abnormal. Substitution α to the vinylidene group has been considered[12] to severely reduce the intensity of this absorption.

expected, the ketone on hydrogenation furnished the same hexahydroketone, as was obtained earlier by the oxidation of hexahydrohumulenol.

Of the six structures listed above, the data presented so far are in accord only with IV, V, VIII and IX and of these V and IX appear less probable on biogenetic considerations. The remaining two alternatives, IV and VIII, as can be seen, are closely related to humulene epoxide-I (X)[5] and humulene epoxide-II (II)[5] respectively. A decision between these possibilities, which confirms all our previous conclusions, could be arrived at by a direct correlation of the new sesquiterpene alcohol with humulene epoxide-II (II).



X

Prelog *et al.*[14] have noted that *trans*-cyclodecene oxide on chromatography over strongly activated Al_2O_3 is transformed into an allylic alcohol. During our work[1,*] on the isolation and purification of humulene epoxides, it was noticed that unless the activity of the Al_2O_3 was carefully controlled to grade II (or weaker) considerable loss of material occurred, by conversion of the epoxides to the alcohol (IR), during contact with active Al_2O_3. In view of this it was considered worthwhile to see if humulenol-II could be correlated with either of the humulene epoxides by isomerization over Al_2O_3. As a matter of fact when (−)-humulene epoxide-II was shaken, in pet. ether solution, with Al_2O_3/I at room temp (~30°), it gave in >60% yield an alcohol, identified (TLC, GLC, IR, PMR and $[\alpha]_D$ as (+)-humulenol-II. Thus, humulenol-II must be represented by IX.

(+)-*Humulenol*-I

In extension of the above work, (−)-humulene epoxide-I (X) in pet. ether was isomerized with Al_2O_3 to give an alcohol having spectral characteristics in complete accord with the structure IV: IR spectrum (Fig. 5): OH 3300, 1030 cm^{-1}; $-\underset{|}{C}=CH_2$ 3020, 1800, 1640, 903 cm^{-1}; $\underset{H}{\overset{H}{>}}C=C<$ 1650, 980 cm^{-1}; $-C=CH-$ 1660, 835 cm^{-1}. PMR spectrum (Fig. 6): two quaternary Me, 3H singlet at 61 and 63 c/s; one vinyl methyl, 3H doublet centred at 98·5 c/s, J = 1·5 c/s; $=C-C\underline{H}_2-C=$, two 1H singlets at 148 and 154 c/s; $-CH_2C\underline{H}OH$, 1H triplet, centred at 229 c/s, J = 5 c/s; $=C\underline{H}_2$, two 1H singlets at 292 and 302 c/s; $-C=C\underline{H}-$, 1H multiplet centred at 305 c/s; $-\underline{H}C=C\underline{H}-$, AB part of an ABX multiplet located between 310–350 c/s.

Although the occurrence of the above allylic alcohol in the essential oil of *Zingiber zerumbet* has not been established by its actual isolation, its presence in the oil is clearly indicated by GLC,[1] and the alcohol has been designated humulenol-I.

* See footnote ‡ on page 4133.

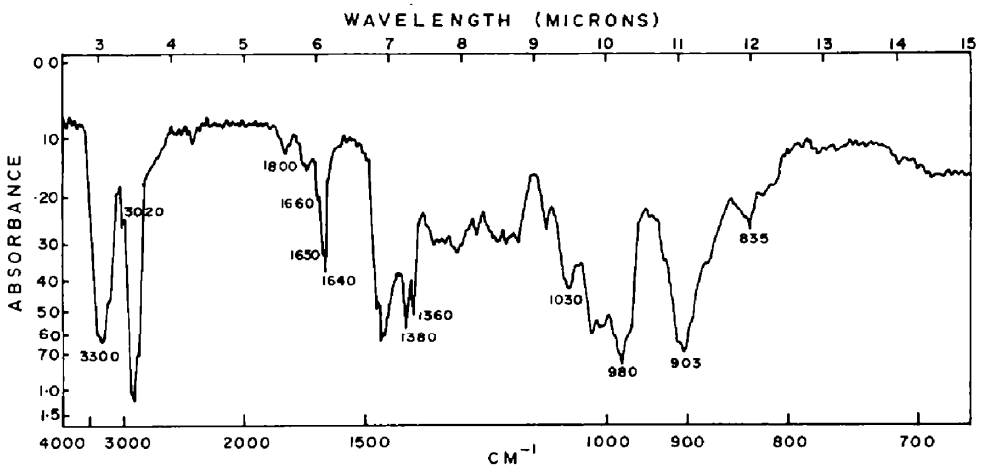


FIG. 5 IR Spectrum of humulenol-I.

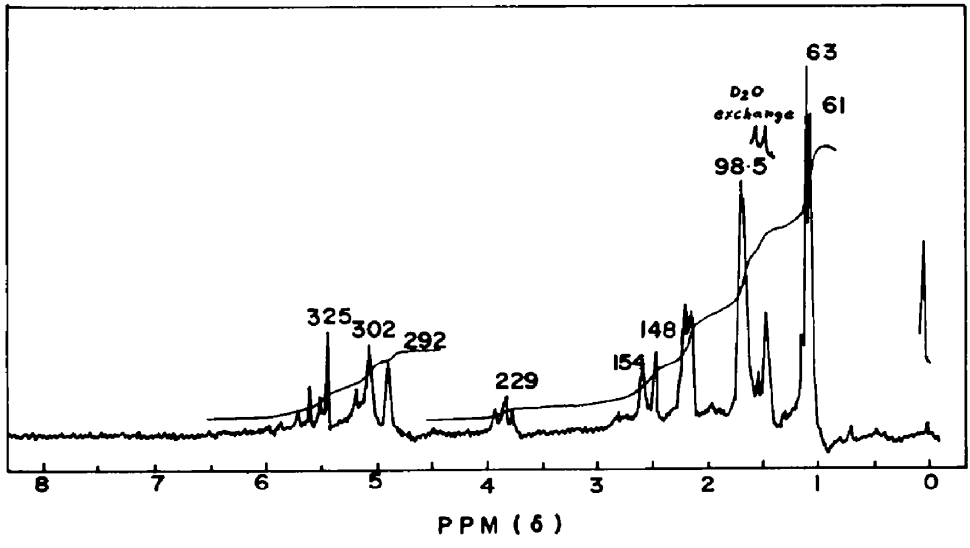
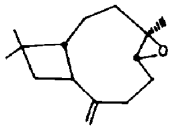


FIG. 6 PMR Spectrum of humulenol-I.

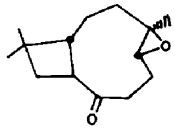
Stereochemistry

In view of the smooth conversion of humulene epoxide-I and humulene epoxide-II, on Al_2O_3, into the corresponding humulenols, the geometry of the olefinic linkages in the two (+)-humulenols must be the same as in the respective oxides viz. *trans*. Thus, the only remaining information to be gained about the structures of these alcohols is their absolute configurations.

In an investigation to be reported subsequently,[15] it has been demonstrated that the ring-cleavage of 1,2-epoxides on Al_2O_3 to allylic alcohols proceeds with retention of configuration of the C—O bond. This finding has been exploited to derive the absolute configuration of the humulene epoxides and the humulenols. Table 1 gives the molecular rotation (M_D) differences: ΔM_D (alc. − oxide). Since the absolute stereochemistry of (−)-caryophyllene oxide and Treibs epoxy ketone are well-established[16] as XI and XII respectively and since the sign and order of magnitude of the M_D are the same in the humulene and the caryophyllene series, it is reasonable to con-



XI



XII

clude that the absolute configuration of the asymmetric centre in humulenols (and consequently in humulene epoxides) must be that obtaining at C_6 in XI or XII, i.e. *R*-configuration.

The above conclusions are further corroborated by the results of the application of Horeau's method[18] of partial asymmetric esterification, to the two humulenols. In both cases the recovered α-phenylbutyric acid was dextro-rotatory (optical yield ~8%) in accord with the R chirality[19] of C_2 in (+)-humulenol-I and of C_6 in (+)-humulenol-II, as depicted in their absolute stereostructures III and I respectively.

TABLE 1. MOLECULAR ROTATION DIFFERENCES

	M_D		ΔM_D(alc. − oxide)
	Oxide	allylic alcohol	
A. Humulene series			
i. (−)-Humulene epoxide-I	−50·2	+57·1	+107
ii. (−)-Humulene epoxide-II	−68·6	+93·7	+162
B. Carophyllene series			
i. (−)-Caryophyllene oxide (XI)	−173·8	+46·2*	+220
ii. Treibs oxido ketone (XII)	−304·9	−100·9[17]	+204

* Rearrangement of (−)-caryophyllene oxide over Al_2O_3 to the corresponding secondary allylic alcohol has been studied by Dr. A. S. Gupta of this Laboratory. This work will be reported later.

EXPERIMENTAL

For general remarks see Part XXXVII of this series.[1] The PMR spectra were taken in CCl_4, unless stated to the contrary, on a Varian A-60 spectrometer; the data are reported in c/s from TMS as zero.

(+)-Humulenol-II

Its isolation from the essential oil of *Zingiber zerumbet* has been described earlier.[1] Perbenzoic acid (0·252N) titration was carried out in $CHCl_3$ soln at 0° in the usual manner; after 48 hr per-acid uptake was 2·8 mole equiv.

Acetate. Humulenol (110 mg) in dry pyridine (2 ml) was chilled to $-10°$ and mixed with Ac_2O (0·5 ml) precooled to $-10°$. The mixture was slowly allowed to attain room temp ($\sim 25°$), when it was left aside for 60 hr and then worked up in the usual manner to give the acetate (110 mg): b.p. 130–135° (bath)/1·5 mm, n_D^{31} 1·4922, $[\alpha]_D$ +42·5°. IR spectrum: OAc 1735, 1240 cm^{-1}. PMR spectrum: quaternary Me's 63, 65·5 c/s; vinylic Me 96 c/s; $C\underline{H}_3COO$ 117 c/s; —$C\underline{H}$OAc ~290 c/s; olefinic protons, complex multiplet located between 288 and 310 c/s. (Found: C, 78·40; H, 9·90. $C_{17}H_{26}O_2$ requires: C, 77·82; H, 9·99%).

3,5-*Dinitrobenzoate.* This was prepared from humulenol (175 mg) exactly as above, except that 3,5-dinitrobenzoyl chloride (370 mg) was used in place of Ac_2O. The crude product (pale yellow gum, 370 mg) obtained after usual work-up was recrystallized from pet. ether to give colorless prisms (145 mg), m.p. 116–117°, $[\alpha]_D$ +5·7° (*c*, 2·4%). (Found: C, 63·80; H, 5·95. $C_{22}H_{26}O_6N_2$ requires: C, 63·75; H, 6·32%).

Hexahydrohumulenol-II

Humulenol (415·5 mg) in gl. AcOH (4 ml) was stirred with H_2, in the presence of prereduced PtO_2 (43 mg) suspended in the same solvent (5 ml). The H_2 uptake (149 ml at 24·5° and 716 mm press; 2·95 mole equiv) ceased in about 5 hr, when the reaction mixture was filtered into water (100 ml) and worked up by extraction (pet. ether). The crude product (431 mg) was chromatographed over Al_2O_3/II (1·1 cm × 19·5 cm):

Fraction 1	pet. ether	7 × 75 ml	—
Fraction 2	pet. ether–25% C_6H_6	9 × 75 ml	210 mg of hexahydrohumulenol $[\alpha]_D$ −2·45°
Fraction 3	pet. ether–50% C_6H_6	5 × 75 ml	143 mg of hexahydrohumulenol $[\alpha]_D$ −1·34 (*c*, 3·7%).
	C_6H_6	2 × 50 ml	

Fraction 3, a colorless viscous liquid, had b.p. 105–106°/0·8 mm, n_D^{30} 1·4831. (Found: C, 79·58; H, 13·27. $C_{15}H_{30}O$ requires: C, 79·57; H, 13·36%).

Humulenone

(i) *By CrO_3-pyridine oxidation.* Humulenol-II (1·212 g) in dry pyridine (5 × 3 ml) was added with stirring to CrO_3–pyridine complex[2] (CrO_3 1·58 g, dry pyridine 20 ml) and the mixture stirred at room temp ($\sim 30°$) for 6 hr. The dark reaction mixture was poured into ice-cold 1N H_2SO_4 (50 ml) and worked up by extraction with pet. ether–ether (2:1, 40 ml × 5) in the usual manner, to give a product (1·13 g) which was distilled: 101–102°/0·8 mm, n_D^{30} 1·5076, yield 981 mg. The product slowly crystallized and was recrystallized from aqueous EtOH (with chilling) to give colorless prisms m.p. 44–44·5°. (Found: C, 82·08; H, 10·02. $C_{15}H_{22}O$ requires: C, 82·51; H, 10·16%).

The *semicarbazone* (pyridine method) was obtained as colorless needles, m.p. 202–203°, from aqueous EtOH. (Found: C, 69·80; H, 8·75. $C_{16}H_{25}ON_3$ requires: C, 69·78; H, 9·15%).

The 2,4-*dinitrophenylhydrazone* (HCl method) was crystallized from C_6H_6–pet. ether to give orange yellow leaflets, m.p. 190–191°. (Found: N, 14·40. $C_{21}H_{26}O_4N_4$ requires: N, 14·06%).

(ii) *By MnO_2 oxidation.* Humulenol-II (230 mg) in pet. ether (50 ml) was shaken with active MnO_2[20] (3 g), under N_2, for 4 hr at 25°. The reaction mixture was worked up in the usual manner to furnish a product (170 mg), which was directly converted into its semicarbazone (pyridine method) m.p. 199–200·5°, mixed m.p. with the above preparation was 201–203°. The IR spectra of the two preparations were superimposable.

Hexahydrohumulenone

(i) *By oxidation of hexahydrohumulenol.* Hexahydrohumulenol-II (163 mg) in dry pyridine (2 ml) was oxidized with CrO_3 (200 mg) in pyridine (2 ml) at room temp (25–30°) for 20 hr, as above. The usual work up gave a liquid (163 mg) which was distilled: b.p. 97–100°/1·5 mm, n_D^{30} 1·4672. This was directly converted into its *semicarbazone* (pyridine method), which was recrystallized from EtOH, colorless needles, m.p. 184–185° (dec). (Found: C, 68·32; H, 11·09. $C_{16}H_{31}ON_3$ requires: C, 68·28; H, 11·10%).

The above semicarbazone (253 mg) was ground with oxalic acid (500 mg), mixed with water (5 ml) and heptane (10 ml) and refluxed for 6 hr. The product was worked up to give pure hexahydroketone (140 mg), b.p. 97–98°/0·75 mm, n_D^{30} 1·4725. (Found: C, 80·98; H, 12·91. $C_{15}H_{28}O$ requires: C, 80·29; H, 12·58%).

The 2,4-*dinitrophenylhydrazone* (HCl method) was obtained as yellow needles from aqueous EtOH, m.p. 116–117°. (Found: C, 62·48; H, 7·68. $C_{21}H_{32}O_4N_4$ requires: C, 62·35; H, 7·97%).

(ii) *By hydrogenation of humulenone.* Humulenone (151 mg) in gl. AcOH (5 ml) was hydrogenated in the presence of prereduced PtO_2 (24 mg) in gl. AcOH (5 ml) at 30° and 711 mm press till 3 mole equiv had been consumed (~4 hr) and further absorption became very sluggish. The reaction mixture was worked up, as described earlier, to give a product which was identified (IR) as the ketone obtained under (i), and was directly converted into its *semicarbazone*, m.p. 182–184°, mixed m.p. with the above sample was undepressed.

Isomerizations over Al_2O_3

(i) *Humulene epoxide-II to humulenol-II.* (−)-Humulene epoxide-II (1·45 g, $[\alpha]_D^{30}$ −25°) was added to a slurry of basic alumina/I (70 g; −100, +250 mesh) in dry pet. ether (80 ml) and the mixture shaken (N_2) for 6 hr at room temp (~30°). The Al_2O_3 was filtered, and washed thoroughly with pet. ether–5% EtOH (50 ml × 15). All filtrates were combined and freed of solvent to give a colorless viscous liquid (1·4 g), which was shown by TLC [5% $AgNO_3$–SiO_2 gel. Solvent system: pet. ether–$CHCl_3$–EtOAc (4:2:1)] to consist of one major component, which was separated by inverted dry column chromatography (IDCC):[21] 5% $AgNO_3$–SiO_2 gel/III (150 g, 3·3 cm × 21 cms); same TLC solvent; material chromatographed, 1·0 g. TLC pure material (240 mg) had the following characteristics: b.p. 150–160° (bath)/1·5 mm, n_D^{30} 1·5143, $[\alpha]_D^{30}$ +42·6 (*c*, 3·4%).

Humulene epoxide-I to humulenol-I. (−)-Humulene epoxide-I (500 mg), $[\alpha]_D^{30}$ −16·4°) in pet. ether (5 ml) was shaken with basic Al_2O_3/I (35 g) in pet. ether (25 ml) for 4 hr at room temp (30°) and then left aside as such overnight. The reaction mixture was worked up as above to give the crude alcohol (450 mg), which was distilled: b.p. 118–119°/1·75 mm. This was purified by IDCC: SiO_2 gel/IIIA (80 g; 2·4 cm × 22 cm); solvent: pet. ether–$CHCl_3$–EtOAc (10:3:2); amount chromatographed, 350 mg. The TLC pure material (60 mg) had the following characteristics: b.p. 128–130°/3·5 mm, n_D^{30} 1·5126, $[\alpha]_D^{30}$ +25·9 (*c*, 1·8%). (Found: C, 82·30; H, 11·04. $C_{15}H_{24}O$ requires: C, 81·76; H, 10·98%).

Kinetic esterification with (±)-α-phenylbutyric anhydride

(±)-α-Phenylbutyric anhydride* was purified[18d] by refluxing with twice its weight of Ac_2O (6 hr), removing the excess Ac_2O *in vacuo* and distilling the residue:† b.p. 180–185° (bath)/1 mm, n_D^{30} 1·5219.

To a soln of the alcohol (~0·4 mmole) in dry pyridine (0·2 ml) was added the above anhydride (~1 mmole) and the reaction mixture set aside at room temp (28–32°) for 24 hr. The experiments were run in duplicate. The reaction mixture was heated (30 min) on steam-bath with one drop of water and transferred quantitatively with C_6H_6 (20 ml × 5) for titration against 0·05N. NaOH (phenolphthalein). The aqueous layer was separated, washed with benzene (15 ml × 3) and acidified with 4N H_2SO_4. This was saturated with $(NH_4)_2SO_4$ and extracted with C_6H_6 (20 ml × 4) to collect the liberated acid. The C_6H_6 extract was washed

TABLE 2. RESULTS OF ESTERIFICATION OF HUMULENOLS WITH (±)-α-PHENYLBUTYRIC ANHYDRIDE

	(+)-Humulenol-II*		(+)-Humulenol-I*	
	Expt. 1	Expt. 2	Expt. 1	Expt. 2
Alcohol (mg)	81·7	72·2	20·1	22·6
Pyridine (ml)	0·25	0·15	0·3	0·3
Anhydride (mg)	316·5	337·9	113·9	107·4
% Esterification	90·2	90·8	100	95·2
Yield of acid (mg)	295·9	305·8	96·6	90·6
$[\alpha]_D^{30}$†	+0·22	+0·20	+0·05	+0·06
Optical yield (%)	8·3	8·7	6·7	8·2

* Alcohols used were obtained by isomerization of the epoxides over Al_2O_3

† Observed rotation in 0·5 dm tube, after dissolving the total recovered acid in 1 ml C_6H_6.

* The authors are indebted to Prof. A. Horeau for a liberal supply of the anhydride.

† The thermochromism, reported earlier,[22] was noted during the distillation of the anhydride.

with satd $(NH_4)_2SO_4$ aq (10 ml × 2), dried and stripped of solvent. The optical rotation of this recovered α-phenylbutyric acid, dissolved in a known vol. of C_6H_6 was determined (Table 2).

In the case of humulenol-II, the derived ester (390 mg; neutral part extracted with C_6H_6) was hydrolysed and the acid, thus obtained (109 mg), examined for its optical activity (1 ml C_6H_6; 0·5 dm tube): $[\alpha]_D^{30}$ −0·09.

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