Tetrahedron. Vol 24, pp. 4123 to 4132. Pergamon Press 1968. Printed in Great Britain

STUDIES IN SESQUITERPENES—XXXVIII

STRUCTURE OF HUMULENE EPOXIDE-I AND HUMULENE EPOXIDE-II*†

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(*Received in the UK* 27 *September* 1967; *accepted for publication* 14 *December* 1967)

Abstract—Evidence leading to the assignment of absolute stereostructures I and II to (−)-humulene epoxide-I and (−)-humulene epoxide-II respectively is presented. Partial synthesis of (±)-humulene epoxide-I and -II by epoxidation of humulene, adsorbed on SiO_2 gel–$AgNO_3$, with one mole of per acid is described.

In a previous paper[1] we have described, besides others, the isolation of two new sesquiterpenoids from the essential oil of *Zingiber zerumbet* Smith. We present evidence, here, to show that these compounds possess the absolute stereostructures I and II and have consequently named them humulene epoxide-I and humulene epoxide-II respectively.[2] Table 1 enumerates some of the physical constants of the two oxides.

Table 1. Some characteristics of humulene epoxides

	Humulene epoxide-I	Humulene epoxide-II
b.p./mm	104–105°/1·5	105–106°/1·5
n_D^{30}	1·4935	1·4962
d_4^{30}	0·9507	0·9477
M_D: Found	67·44	67·72
Calc.*	67·78	67·78
$[\alpha]_D$ ($CHCl_3$)	−22·8°	−31·2°
RRT†	1·12	1·29
R_{dye}‡	0·28	0·43

* Calculated using the atomic and group refractivities of Auwers and Eisenlohr.[3] The anticipated M_D depression due to the presence of a medium ring[4,5] appears to have been compensated by an exaltation due to the oxirane ring.

† Relative retention time with respect to caryophyllene oxide as 1; column, 150 cm × 5 mm packed with 20% diethyleneglycol polysuccinate on 60–80 mesh Chromosorb W; column temp. 150°; carrier gas (H_2), 30 ml/min.

‡ $R_{dye} = \dfrac{\text{Movement of substance from start in mm}}{\text{Movement of Sudan III from start in mm}}$;

silica gel–$AgNO_3$[6] (0·3 mm) layer; Solvent: 5% acetone in C_6H_6; solvent front, 12 cm; temp 28°. On this scale caryophyllene oxide has R_{dye} = 0·87.

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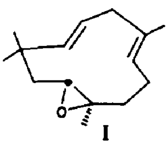
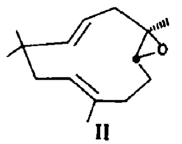
* Communication No. 1133, National Chemical Laboratory, Poona.

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



I



II

Humulene epoxide-I

Humulene epoxide-I, $C_{15}H_{24}O$, shows only end absorption in the UV (ε_{210} 3540, ε_{215} 3070, ε_{220} 2460, ε_{225} 1840) and is devoid of C=O or O—H bands in the IR (Fig. 1). Hence, the oxygen must be present as an ether linkage, in all probability as an oxirane function, as suggested by the bands at 1248, 887 and 792 cm^{-1} in the IR spectrum, assignable to a 1,2-epoxide.[7,8] Other bands of diagnostic value in the IR spectrum consist of a doublet at 1360, 1380 cm^{-1} (*gem*-dimethyl group) and the strong absorption at 971 cm^{-1}, assignable to a *trans*-disubstituted olefinic bond; the latter absorption in a sesquiterpene is considered as a pointer to a humulenoid skeleton.

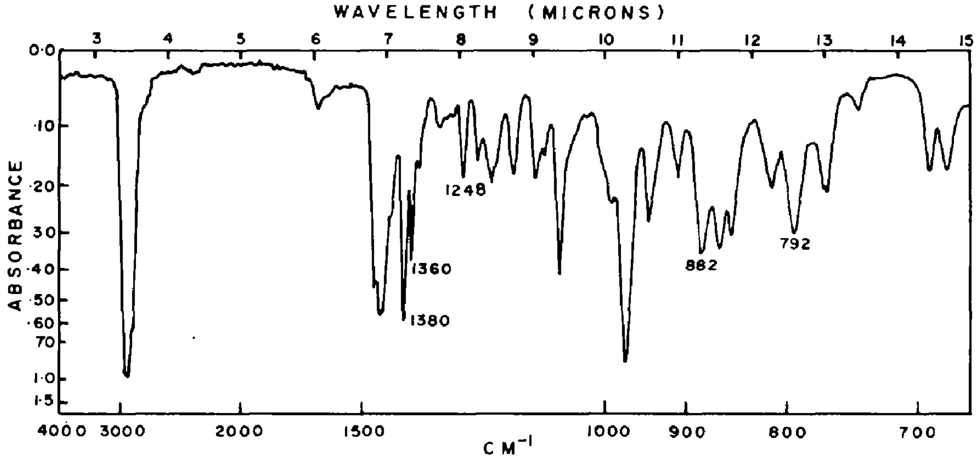


FIG. 1 IR Spectrum of humulene epoxide-I.

Its PMR spectrum (Fig. 3) shows signals assignable to: three quaternary Me's (3H sharp s's at 62, 66 and 72 c/s), one vinylic Me (3H d centred at 101 c/s, $J = 1$ c/s) and three olefinic protons (complex m between 300–357 c/s); the quaternary Me signal at 72 c/s suggests its being attached to a carbon linked to oxygen.[9]

Selective hydrogenation (Pt/EtOH, one mole equiv) of the compound affords a liquid dihydroderivative, $C_{15}H_{26}O$, having no 971 cm^{-1} absorption in the IR. Its PMR spectrum shows only one vinyl proton (1H m centred at 308 c/s) and the vinylic Me is still present (at 100 c/s, $J = 0{\cdot}5$ c/s). These results are consistent with the selective hydrogenation of the *trans*-disubstituted ethylenic linkage in the compound.

All the above data can be readily accommodated in a 1,2-epoxide derived from humulene (III);[10–12] such a formulation was also suggested on biogenetic considerations,* because of its co-occurrence with humulene. Confirmation of this conjecture

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* We emphasize the value of the working hypothesis[13] concerning the existence of pools of intermediate compounds in a living plant at a given time. We have found this concept of great utility in the structure determination and identification of terpenoids isolated from the same source.

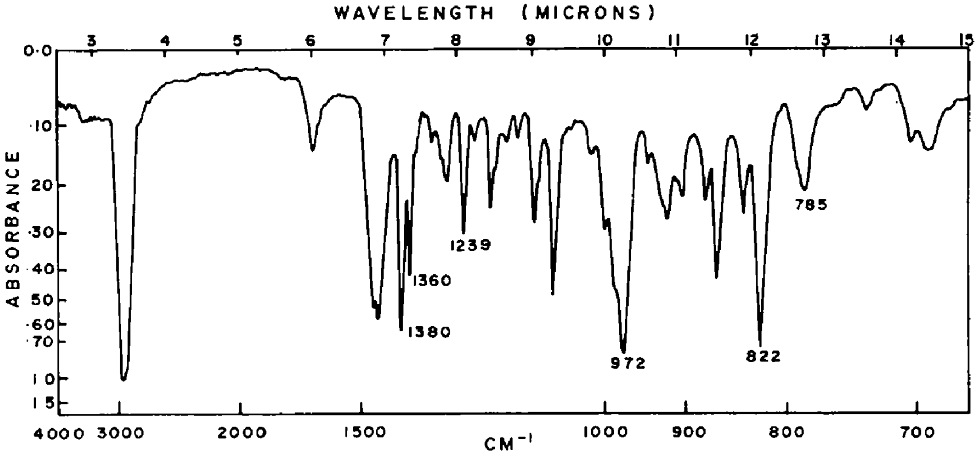

FIG. 2 IR Spectrum of humulene epoxide-II.

was obtained by a study of its further epoxidation with perbenzoic acid (PBA), two moles of which were used up per mole of the compound. The reaction afforded in ~30% yield a product m.p. 114–117°, $[\alpha]_D$ $-4{\cdot}4°$, the m.p. of which could not be raised further; mixed m.p. with an authentic sample (m.p. 121–122°) of (±)-humulene trioxide (IV)[14] was 116–118° and the IR spectra of the two preparations were indistinguishable.[*] This correlation not only fixes the carbon-skeleton of the new sesquiterpenoid but also limits its structure to I and II.

A decision in favour of I could be arrived at by a critical study of its PMR spectrum (Fig. 3). As can be seen from Fig. 3, the oxide shows two sharp signals (1H each) at

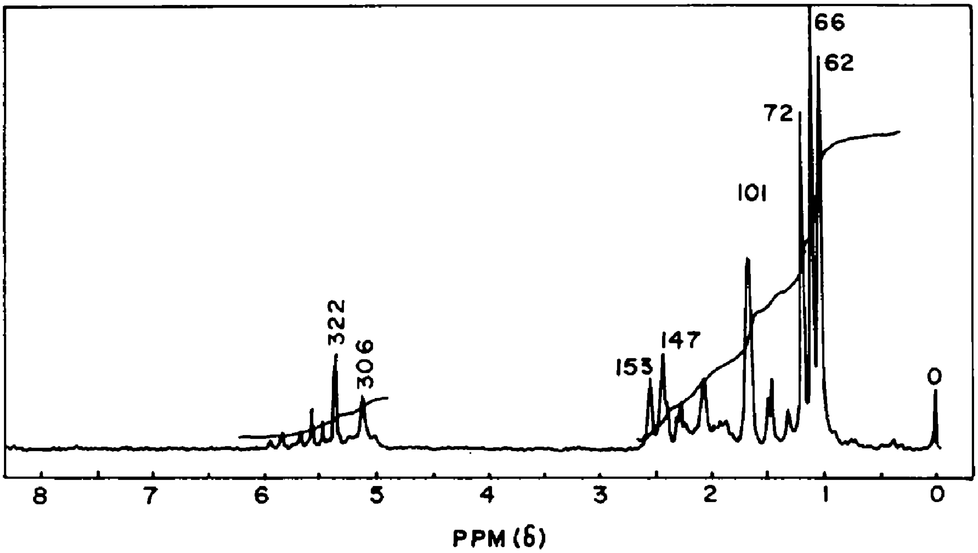

FIG. 3 PMR Spectrum of humulene epoxide-I.

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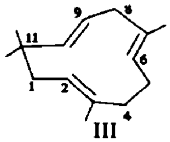
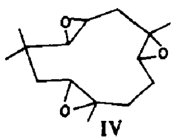
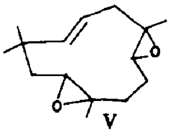
[*] Throughout this series of compounds it has been observed that the m.p. of an optically active derivative is not depressed on admixture with its racemic modification, a behaviour characteristic of racemic solid solutions.[15] Besides humulene trioxide other examples are: dihydrohumulene epoxide-II and humulene dioxide.



III



IV



V

147 and 153 c/s. These absorptions are reminiscent of the 143 and 159 c/s peaks (singlets) in the PMR spectrum of humulene[10] and are assignable to the doubly allylic methylene* at C_8, which is present only in I. In support of this assignment the PMR spectrum of the dihydroderivative described earlier, as expected, does not display these signals. The data presented above suffice to establish the gross structure of humulene epoxide-I as (I), a conclusion which is confirmed by the settlement of the alternate II for humulene epoxide-II (*vide infra*).

During the chromatographic separation of humulene epoxides, a small amount of a crystalline compound, $C_{15}H_{24}O_2$, m.p. 106–106·5°, was invariably obtained. The suspicion that this material may be an artefact, was strengthened by the observation that pure humulene-epoxide-I, after storage (air enclosed) at 5° for a few weeks always showed on TLC (SiO_2–gel–$AgNO_3$) a spot (R_{dye} = 0·47; see footnote to Table 1) corresponding to this compound and, as a matter of fact, after prolonged storage (~ a year), rechromatography of the material, furnished this crystalline compound in a 40% yield. It was soon recognized that this compound is identical (IR) with humulene diepoxide (V, m.p. 103°) described by Šorm *et al.*[17] and also isolated from the essential oil of *Zingiber zerumbet* by Ramaswamy and Bhattacharyya.[18]

Humulene epoxide-II

This compound, $C_{15}H_{24}O$, does not show any C═O or O—H absorption in the IR (Fig. 2) and consequently must be an oxide, possibly an oxirane (IR absorption bands at 1239, 822 and 785 cm^{-1}).[7,8] The presence of a strong band at 972 cm^{-1} in the IR spectrum, assignable to a *trans*-disubstituted olefinic linkage, pointed to its having originated from humulene. As a matter of fact, its IR spectrum was found to be very similar to that recorded for a preparation of humulene monoxide of undetermined structure, obtained by Šorm *et al.*[19] by the action of H_2O_2–V_2O_5 on humulene. An authentic sample of this material, prepared according to their method, was found to be identical with the natural epoxide in all respects, except the fact, that the synthetic material, as expected, was racemic.

Since in this epoxide of humulene the *trans*-Δ^9 linkage is still intact (IR evidence), and since structure I has been assigned to humulene epoxide-I, structure II follows for this oxide. This is fully corroborated by its spectral characteristics. Thus, in the UV, it does not show, as expected, any absorption maximum above 210 mμ. Its PMR spectrum (Fig. 4) shows three quaternary Me's (64, 64 and 73 c/s), one vinylic Me (3H s at 92 c/s) and three olefinic protons located as a multiplet between 281–325 c/s.

This epoxide, like humulene epoxide-I, also reacted with 2 mole equivalents of PBA to furnish a trioxide m.p. 121–122°, $[\alpha]_D$ +0·57, the IR spectrum of which was identical with that of (±)-humulene trioxide.[14] Ozonolysis of the oxide and oxidative

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* For acyclic systems $\delta \simeq 2{\cdot}9$ ppm.[16a] For cyclic systems containing a doubly allylic methylene see Refs 10 and 16*b*.

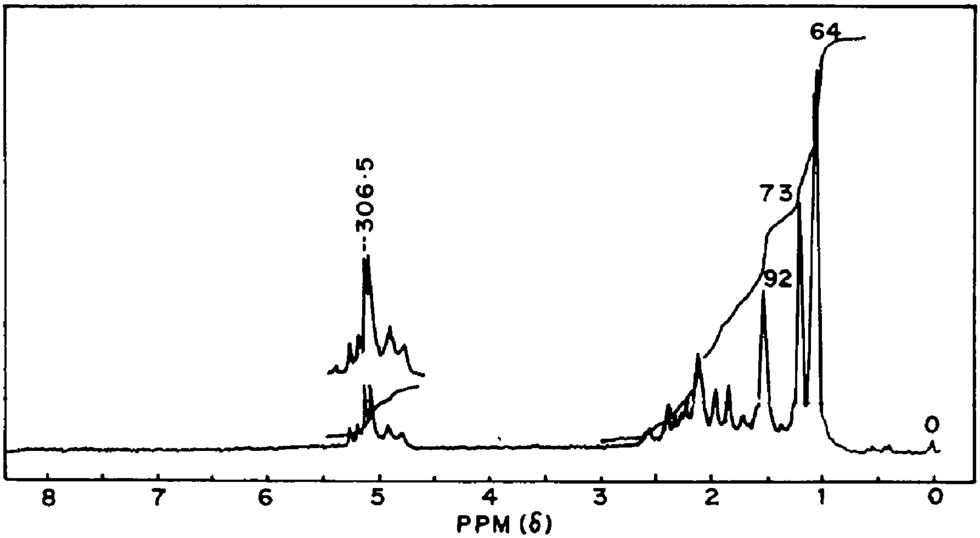

FIG. 4 PMR Spectrum of humulene epoxide-II.

work-up of the ozonide yielded *as*-dimethyl succinic acid in good yield. All these results provide clear support for the structure II for humulene epoxide-II.

Selective epoxidation of humulene

In view of the above work, it was of interest to investigate the product composition, after reacting humulene with one mole equivalent of a per acid. Three sets of reaction conditions were intially employed: (i) pervanadic acid (H_2O_2–V_2O_5)[20] in acetone solution at 0–10°; (ii) PBA in benzene–pet. ether solution at 0° and, (iii) PBA in $CHCl_3$ solution at 0°. Humulene epoxide-II was the major product under all the conditions, except for the formation of traces of humulene epoxide-I under (ii) and (iii) and traces of the diepoxide (V) with (i). The results are in accord with the high reactivity[21] of Δ^6-linkage of humulene.

Since it is established[12] that in the crystalline humulene–$AgNO_3$ adduct, the Δ^6- and Δ^9-double bonds are π-complexed with Ag^+,* it was thought whether this situation could be exploited, at least to some extent, in the preferential epoxidation of Δ^2-linkage of humulene with the electrophilic PBA.† In actual practice, the slow addition of 1 mole equiv of PBA (in benzene–pet. ether; 0°) to a stirred, chilled suspension of humulene–$AgNO_3$–SiO_2 gel in pet. ether, gave a product consisting (GLC) of humulene epoxide-I (I), humulene epoxide-II (II), humulene epoxide-III‡

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* Earlier we had examined the IR spectrum of the humulene–$AgNO_3$ adduct (Nujol mull) in which the 965 cm^{-1} band (*trans*-disubstituted olefinic bond, Δ^9-linkage in humulene) can no longer be seen, indicating that this linkage is involved in complexing with Ag^+.

† In order to ensure sufficient dispersion of the adduct, the adduct was prepared *in situ* by the adsorption of humulene on $AgNO_3$–SiO_2 gel. It was also realized that once the Δ^2-,Δ^6-linkage of humulene had reacted, the resulting humulene monoepoxide being much less complexing[1] with Ag^+, may be released to the reaction medium to react further with PBA to give the dioxide, etc.

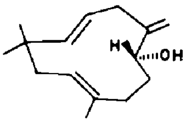
‡ This is 9,10-epoxyhumulene, recently isolated in this Laboratory from the essential oil of *Dipterocarpus pilosus*: A. S. Gupta, Ph.D. Thesis, p. 100, Panjab University (1965).

and humulene diepoxide (V), besides unchanged humulene (III) and some hydroxylic material, not investigated further. The various products were next actually isolated and identified by the usual methods. Thus, the idea of preferential reactivity in humulene–$AgNO_3$ adduct could be realized, though to a limited extent.

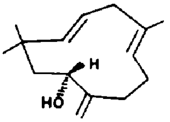
Stereochemistry of oxides

Based on X-ray studies[12] of humulene–$AgNO_3$ adduct, the three olefinic linkages of humulene have been assigned the all-*trans* geometry (III). Since in an epoxidation reaction, using a peracid, no change in the configuration of an ethylenic linkage is expected, the two ethylenic linkages in humulene monoepoxides, the racemic modifications of which are obtainable through monoepoxidation as demonstrated above, must be *trans*. Furthermore, since the epoxidation reaction involves a *cis*-addition of the epoxy oxygen,[22] without disturbing the configuration of the original double bond, the only remaining point about the stereochemistry of humulene monoepoxides is their absolute stereochemistry.

In connection with the structure and stereochemistry of (+)-humulenol-II (VI), stereospecific ring opening of the epoxy ring in humulene epoxide-II and humulene epoxide-I to the allylic alcohols VI and VII respectively, on Al_2O_3[2,*] has been carried out. This work is described in the accompanying paper,[23] which also includes the determination of the absolute stereochemistry of these alcohols, as shown in VI and VII, by Horeau's method.[24] Thus, both humulene epoxide-I and humulene epoxide-II can be assigned the R, R chirality[25] at the asymmetric centres as depicted in the absolute stereostructures I and II respectively.[†]

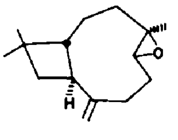


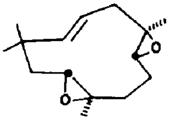
VI



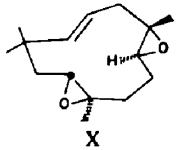
VII

Both (−)-humulene epoxide-I and (−)-humulene epoxide-II on further controlled epoxidation give the same (IR) humulene dioxide (V), m.p. 98–101°, but the two preparations are essentially antipodal showing $[\alpha]_D$ +1·42° and −0·76° respectively. This information uniquely suffices to fix the absolute stereostructure of humulene

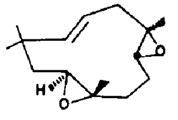




IX



X



XI

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[*] Systematic work on alumina-induced oxirane ring-fission has been carried out in our Laboratory and the results clearly demonstrate that the cleavage of the oxirane ring proceeds with retention of configuration. These results will be published shortly.

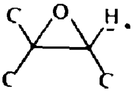
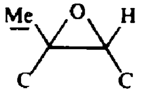
[†] It may be pointed out that (−)-caryophyllene oxide (VIII) which is another component of *Zingiber zerumbet*[1] has also the same absolute stereochemistry (R,R) at the oxirane ring.

diepoxide. Humulene dioxide derived from (−)-humulene epoxide-I (I) can have either of the structures IX and X. Likewise the diepoxide derived from (−)-humulene epoxide-II (II) can be either IX or XI. However, since the two preparations of humulene diepoxide are antipodal, X and XI must correctly represent (+)- and (−)-humulene diepoxides respectively.

Some PMR data

It is well-recognized that an oxirane ring proton is considerably shielded as compared to the frequencies of α-protons in other cyclic and acylic ethers.[26] This has been attributed to the anisotropy of the oxirane ring.[27,28] Table 2 lists the signals observed for the oxirane ring protons in the present series of compounds, the chemical shifts being in the expected range.[26] It was of interest to note if the shielding influence of the 3-membered ring is felt by the α-methyl protons. As can be seen from the data given in Table 2, practically no shielding occurs (cf. e.g. the methyl protons in diethyl ether, which occur centred at 70 c/s).

TABLE 2. CHEMICAL SHIFTS OF PROTONS AND METHYL PROTONS ON THE OXIRANE RING

Compound			
	Signal (c/s)*	multiplicity†	Signal (c/s)‡
Humulene epoxide-I (I)	135 (1H)	t (J = 2·5 c/s)	72
Humulene epoxide-II (II)	149 (1H)	dd (J_1 = 10 c/s, J_2 = 2·5 c/s)	73
Dihydro humulene epoxide-I	145 (1H)	dd (J_1 = 5 c/s, J_2 = 2·5 c/s)	66
Dihydro humulene epoxide-II	155 (1H)	dd (J_1 = 10 c/s, J_2 = 2 c/s)	68
Humulene diepoxide (V)	143–176 (2H)	m	78, 78
Humulene trioxide (IV) (in $CDCl_3$)	134–175 (4H)	m	82, 82
Caryophyllene oxide (VIII)	162 (1H)	dd (J_1 = 10·5 c/s, J_2 = 3·5 c/s)	69

* Unless the range is given, the position given is the centre of the multiplet.

† t = triplet, dd = a pair of doublets, m = multiplet.

‡ All 3H singlets.

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.

*Dihydrohumulene epoxide-*I

Humulene epoxide-I[1] (320 mg) was hydrogenated in 95% EtOH (15 ml) in presence of prereduced PtO_2 catalyst (44 mg) at 25° and 708 mm press, when 40·5 ml (1·02 mole equiv) of H_2 was consumed. The catalyst was filtered off and the alcoholic soln diluted with water (60 ml) and worked up with pet. ether in the usual manner to give the product (313 mg) as an oil, which was filtered through Al_2O_3/II (10 g) with pet. ether and distilled: b.p. 102–103°/1 mm, n_D^{30} 1·4870, $[\alpha]_D$ −26·1°. IR spectrum: oxirane ring 860, 1250 cm^{-1}; —C═CH— 815 cm^{-1}. PMR spectrum: quaternary Me's 50, 62, 66 c/s; vinylic Me 3H d at 100 c/s, J = 0·5 c/s; olefinic proton, m centred at 308 c/s. (Found: C, 80·72; H, 11·48. $C_{15}H_{26}O$ requires: C, 81·02; H, 11·79%).

Dihydrohumulene epoxide-II

(i) *From* (−)-*humulene epoxide*-II. (−)-Humulene epoxide-II[1] (800 mg) was hydrogenated in 95% EtOH (15 ml) over prereduced PtO_2 catalyst (86 mg) exactly as above; the H_2 uptake came to a close after absorption of 1·1 mole equiv of H_2. The crude product (800 mg), which was semisolid, was twice crystallized from pet. ether at ~0° to give colourless plates (280 mg), m.p. 69–69·5°, $[\alpha]_D$ −0·28 (*c*, 205%, CCl_4); the m.p. was not depressed on admixture with the sample described below: IR spectrum : oxirane ring 778, 795, 1239 cm^{-1}; —C=CH— 835 cm^{-1}. PMR spectrum: quaternary Me's 52, 57, 69 c/s; vinylic Me 95 c/s; olefinic proton, a pair of broad singlets centred at 308 c/s, J = 10 c/s. (Found: C, 80·83; H, 11·76. $C_{15}H_{26}O$ requires: C, 81·02; H, 11·79%).

The liquid residue from the above mother liquors was distilled: b.p. 113–114°/2 mm, n_D^{30} 1·4851, $[\alpha]_D$ −32·5° (*c*, 5·1%). (Found: C, 81·9; H, 12·02. $C_{15}H_{26}O$ requires: C, 81·02; H, 11·79%).

(ii) *From* (±)-*humulene epoxide*-II. (±)-Humulene epoxide-II[19] (*vide infra*) (1·04 g) on hydrogenation and work-up as above gave the (±)-derivative (0·8 g), m.p. 68–69° (pet. ether) (Lit.[19] m.p. 70°).

Humulene trioxide (IV)

(i) *From* (−)-*humulene epoxide*-I. An ice-cold $CHCl_3$ soln of PBA (0·343N, 10 ml) was added to (−)-humulene epoxide-I (64·8 mg) and the mixture left aside at ~5°. In 70 hr, 2 mole equivalent of per acid had been consumed, when the reaction mixture was diluted with $CHCl_3$ (25 ml), washed with Na_2CO_3aq (5%, 15 ml × 4) and water and dried. Solvent was removed to give a product (80 mg), which crystallized on dilution with a few drops of pet. ether and chilling. The crystalline material (33 mg, m.p. 108–112°) was twice recrystallized from pet. ether to afford colourless needles (18 mg), m.p. 114–117°, $[\alpha]_D$ −4·4° (*c*, 0·6%); mixed m.p. with authentic (±)-humulene trioxide (m.p. 121–122°) was 116–118°.

(ii) *From* (−)-*humulene epoxide*-II. A sample of (−)-humulene epoxide-II (273 mg) was treated (72 hr) with a $CHCl_3$ soln of PBA (0·252N, 30 ml) as above and worked up to give a semi-solid product (378 mg), which after three crystallizations from pet. ether gave colourless needles (100 mg), m.p. 121–122°, $[\alpha]_D$ +0·57 (*c*, 0·7%); mixed m.p. with (±)-humulene trioxide remained undepressed.

Humulene dioxide (V)

(i) *From* (−)-*humulene epoxide*-I. (−)-Humulene epoxide-I (117·6 mg) was treated with one mole equiv of PBA in $CHCl_3$ (0·454N, 2·6 ml) at ~5° for 24 hr (all PBA had been consumed by this time) and worked up as above to give a product (132 mg) which after two crystallizations from pet. ether gave colourless needles (35 mg), m.p. 97–101°, $[\alpha]_D$ +1·42 (*c*, 1%); mixed m.p. with "natural" humulene dioxide[1] (m.p. 106–106·5°, $[\alpha]_D$ −0·129) was 103–105°.

(ii) *From* (−)-*humulene epoxide*-II. (−)-Humulene epoxide-II (157·6 mg), when treated with PBA, exactly as above, gave a product (195 mg), which was twice recrystallized from pet. ether to give colourless needles (74 mg), m.p. 98–101°, undepressed by the dioxide described under (i), $[\alpha]_D$ −0·76 (*c*, 1%).

Ozonolysis of humulene epoxide-II

A stream of ozonized O_2 (~180 mg O_3/hr) was bubbled through a solution of (±)-humulene epoxide-II (1·21 g) in dry EtOAc (60 ml), chilled to −15°, till O_3 was no longer absorbed (~3 hr). Solvent was removed under suction at room temp and the viscous residue treated with H_2O_2aq (30%, 2 ml) and Na_2CO_3aq (10%, 12 ml), first at 60° (1 hr) and thereafter on a steam-bath (2 hr). The reaction mixture was diluted with water (10 ml) and extracted with pet. ether (15 ml × 3) to remove neutral material (46 mg), which was rejected. The alkaline aqueous soln was charcoaled and acidified with H_3PO_4-aq (1:1), saturated with ammonium sulphate and extracted exhaustively with ether, to yield after solvent removal, a brown gum (900 mg), which slowly crystallized. Repeated recrystallizations from acetone–pet. ether gave colourless needles (157 mg), m.p. 138–139°, undepressed by authentic *as*-dimethylsuccinic acid (m.p. 139–140°). (Found: C, 49·37; H, 6·95. $C_6H_{10}O_4$ requires: C, 49·31; H, 6·90%).

Epoxidation of humulene with one mole of oxidant

(i) *Pervanadic acid in acetone*. To V_2O_5 (50 mg), a few drops of 25% H_2O_2 were added and, after the effervescence had subsided, it was diluted with acetone (50 ml) to give a dark-brown soln. This product was chilled (0°) and a soln of freshly distilled humulene (10·03 g, 0·05 mole) in acetone (10 ml) was added. A soln of H_2O_2 (25%, 10 ml, ~0·07 mole) in acetone (10 ml), precooled in ice, was slowly (15 min) introduced with shaking and cooling, into the above humulene-pervanadic acid soln. The reaction mixture was left in ice for 4 hr and thereafter first at 1–2° for 12 hr and later at ~25° for 12 hr when the colour had changed to a clear greenish brown from the original reddish brown. Acetone was stripped off under suction, the residue mixed with water (150 ml) and extracted with pet. ether (50 ml × 5). Evaporation of solvent furnished a pale yellow oil (10·5 g), which was diluted with pet. ether (10 ml) and chromatographed on Al_2O_3/II (4·2 cm × 23 cm):

Fraction 1	Pet. ether	3 × 200 ml	34 mg, rejected
Fraction 2	Pet. ether	29 × 200 ml	4·33 g of pure (GLC) (±)-humulene epoxide-II
Fraction 3	Pet. ether–25% C_6H_6	10 × 200 ml	1·33 g of pure (GLC) (±)-humulene epoxide-II
Fraction 4	Pet. ether–25% C_6H_6	2 × 400 ml	24 mg, rejected.
Fraction 5	Pet. ether–50% C_6H_6	7 × 400 ml	1·51 g, m.p. 102–105° humulene dioxide.
Fraction 6	C_6H_6	11 × 200 ml	0·47 g, liquid.
Fraction 7	C_6H_6–3% MeOH	5 × 200 ml	1·72 g, liquid.

Fractions 2 and 3 were mixed and distilled: b.p. 105–106°/1·5 mm, n_D^{30} 1·4958, d_4^{30} 0·9477. (Found: C, 81·41; H, 11·3. $C_{15}H_{24}O$ requires: C, 81·76; H, 10·98%). IR and PMR spectra were indistinguishable from those of (−)-humulene epoxide-II (II).

Fraction 5 was recrystallized from pet. ether to give colourless needles, m.p. 105–106°, identified (IR) as (±)-humulene dioxide (V).

(ii) *Perbenzoic acid in chloroform.* To a soln of humulene (319 mg) in $CHCl_3$ (20 ml), prechilled in ice–salt, was added ice-cold PBA (0·356N, 8·4 ml, one mole equiv) in $CHCl_3$. The mixture was left aside at −6° to −10° for 6 hr and then at ~5° for 18 hr, when all PBA had been consumed. The usual work-up gave a liquid, which was distilled: b.p. 107–108°/1·4 mm, n_D^{30} 1·4961, yield 287 mg. TLC, GLC (for conditions see footnote to Table 1) showed it to consist of essentially II with less than 5% of I. The IR spectrum was virtually identical with that of II.

(iii) *Perbenzoic acid in benzene–pet. ether.* When in the above experiment $CHCl_3$ was replaced by a 1:1 mixture of C_6H_6–pet. ether identical results were obtained.

(iv) *Epoxidation of humulene–*$AgNO_3$ *adduct.* Freshly distilled humulene (540 mg, 0·0026 mole) in pet. ether (1 ml) was added to a stirred suspension of 10% $AgNO_3$–SiO_2 gel (TLC grade;[6] activated at 120° for 3 hr) in pet. ether (25 ml) with cooling (0°). To this a PBA solution in 1:1 C_6H_6–pet. ether (0·526N, 10 ml, 0·0026 mole) precooled to 0°, was introduced dropwise with stirring (1 hr) and cooling. After stirring for another 0·5 hr, no more of unreacted PBA remained, when it was diluted with water (150 ml) and extracted with pet. ether (50 ml × 3). The combined extracts were washed with Na_2CO_3 aq (5%, 20 ml × 3), water and dried. Removal of solvent gave a product (532 mg), TLC (10% $AgNO_3$–SiO_2 gel;[6] solvent: pet. ether–$CHCl_3$–EtOAc, 4:2:1) of which showed the presence of unchanged humulene, I, II, V and traces of humulene epoxide-III.

When the above experiment was carried out at −10°, identical results were obtained. In another experiment humulene was first adsorbed on a $AgNO_3$–SiO_2 gel column, which was washed with pet. ether and treated with PBA as above. This also gave identical results.

The crude epoxidation production (2·6 g) obtained in the above experiment, was first chromatographed over Al_2O_3/II (1·5 cm × 39 cm) so as to effect a broad separation (monitoring with TLC on $AgNO_3$–SiO_2 gel):

Fraction 1	Pet. ether	10 × 20 ml	0·84 g of humulene (IR)
Fraction 2	Pet. ether–30% C_6H_6	2 × 200 ml	1·22 g of mono-epoxides
Fraction 3	Pet. ether–30% C_6H_6	6 × 200 ml	0·494 g, m.p. 101–104° humulene dioxide
Fraction 4	C_6H_6–3% MeOH	4 × 150 ml	98 mg, hydroxylic material

Fraction 3 was recrystallized from pet. ether at 0° to give colourless needles, m.p. 101–104°. IR spectrum was identical with that of humulene dioxide and mixed m.p. with an authentic sample (m.p. 106–106·5°) was 105–106°.

The monoepoxide mixture (Fraction 2, 1·0 g) was separated by inverted dry column chromatography[29] (10% $AgNO_3$–SiO_2 gel, activated at 120–130° for 6 hr; 110 g packed in a tube 3·3 cm × 25 cm up to 16 cm, the rest being packed with Al_2O_3/III; solvent: pet. ether–$CHCl_3$–EtOAc, 4:2:1), The column after development was divided into 34 equal segments, which were separately scooped. Each cut was extracted with $CHCl_3$–10% EtOAc and screened by TLC and like fractions combined and identified (TLC, GLC, IR):

Cut	Wt. (mg)	b.p. (bath)/mm	n_D^{30}	Remarks
1–5	117	130–135°/1·5	1·4936	Humulene epoxide-I
6–14	532	—	—	Mixture of I and II
15–18	257	140–145°/2	1·4957	Humulene epoxide-II
19–20	41	130–135°/1·5	1·4968	Humulene epoxide-III
21–34	—	—	—	—

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