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STUDIES IN SESQUITERPENES—XVI*

ZERUMBONE, A MONOCYCLIC SESQUITERPENE KETONE†

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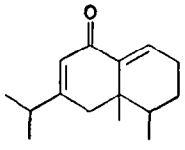
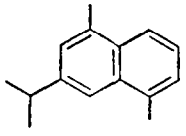
Abstract—The structure, previously assigned to zerumbone, has been found to be untenable. The ketone has been shown to be monocyclic containing three ethylenic linkages, and has been further correlated with humulene. Results from ozonolysis, and base-catalysed cleavage allow the compound to be formulated as 2,6,9,9-tetramethyl-2,6,10-cyclo-undecatrien-1-one.

THE isolation of a sesquiterpene ketone (m.p. 67–68°), $C_{15}H_{22}O$, from the rhizomes of *Zingiber zerumbet* (Sanskrit–Sthulagranthi; Hindi–Narkachur) was first described by Varier.[1] From another species (*Zingiber amaricans*; Lampoejang pait‡) of the same family van Romburgh[2] had earlier isolated a crystalline fraction, which was later studied in some detail by van Veen,[3] who declared it to be a mixture of ketones (m.p. 62–68°). From a comparison of several derivatives, it was suspected by Varier that the two products may be identical. Parihar and Dutt,[4,5] apparently, studied the ketone from *Zingiber zerumbet* in considerable detail and proposed the structure (I) for this new ketone, which was named zerumbone. The structure (I) rested chiefly on the selenium dehydrogenation of tetrahydrozerumbol to eudalene. Since no proof for the location of the carbonyl group had been given, it was decided to fix its position by dehydrogenation of a suitable precursor, when according to structure (I), 5-methyleudalene (II) should be obtained. As a matter of fact, no



I



II

picrate-forming material could be isolated from such a reaction and further, on repetition of dehydrogenation of tetrahydrozerumbol or its dehydration product we failed to detect the formation of eudalene.§ In view of this and other apparent

*Part XV: *J. Ind. Chem. Soc.* **34**, 255 (1957).

† A preliminary report appeared in *Chem. & Ind.* 1051 (1956).

‡ van Veen[3] states that according to K. Heyne 'Lampoejang pait' is *Zingiber amaricans* and not *Zingiber zerumbet* as described by van Romburgh.

§ This observation removed the apparent discrepancy between zerumbone and the ketone of van Veen, as he had shown earlier that his ketone does not belong to any naphthelenic system. This author carried out most of the reactions on the ketone fraction, m.p. 68°, and it is clear now that, at least, this particular fraction is identical with zerumbone.

[1] N. S. Varier, *Proc. Ind. Acad. Sci.* **A 20**, 257 (1944).
[2] P. van Romburgh, *Teysmannia* 561 (1902).
[3] A. G. van Veen, *Rec. Trav. Chim. Pays-Bas* **58**, 691 (1939).
[4] D. B. Parihar and S. Dutt, *Ind. Soap J.* **16**, 123 (1950).
[5] D. B. Parihar and S. Dutt, *Ind. Soap J.* **16**, 145 (1950).

contradictions in their own work, a systematic reinvestigation, ignoring the work of these authors* was undertaken.

The relevant features of the previous work carried out by van Veen[3] and Varier[1] may briefly be summarized as follows. With hydrogen sulphide in an ammonical ethanolic solution, zerumbone gave an addition compound and from this it was suspected[1] that zerumbone is an $\alpha\beta$-unsaturated ketone. On catalytic reduction it gave a tetrahydroketone.[1] van Veen on the other hand, on prolonged hydrogenation obtained a mixture of hydrogenation products from which a solid, m.p. 60°, and considered by him to have the formula $C_{15}H_{30}O$ (hence acyclic), could be isolated in a low yield. Wolff–Kishner reduction of zerumbone semicarbazone gave an impure sample of a monocyclic hydrocarbon.[3]

Zerumbone displayed its ultra-violet absorption peaks at 248 mμ (ε 8480) and 325 mμ (ε 250), a shoulder around 233 mμ (ε 8000) was also quite marked. The position of the *K*-band is in conformity with either an $\alpha\beta$-olefinic carbonyl[6] or a cross-conjugated dienone chromophore;[7] a decision in favour of the latter possibility could be made on the basis of the evidence described in the sequel. In the infra-red (in carbon tetrachloride) it showed bands at 1662 with slight shoulders around 1650 and 1635 cm^{-1} ($\alpha\beta$-unsaturated ketone and ethylenic linkage; possibly a conjugated dienone),[8] this band was broader and a little better resolved in Nujol (1658, 1650 and 1635 cm^{-1}); other bands at 1390 and 1370 (*gem*-dimethyl group), 970 (*trans-sym*-disubstituted ethylenic linkage) and 830 cm^{-1} (trisubstituted ethylenic linkage) were also prominent in both the spectra.

Lithium aluminium hydride reduction of zerumbone gave the corresponding alcohol (zerumbol), which regenerated the ketone on either manganese dioxide oxidation or Oppenauer oxidation. Sodium–alcohol reduction of zerumbone, produced a mixture of epimeric alcohols, separable via their 3:5-dinitrobenzoates into a liquid (α-epimer) and a crystalline (β-epimer) isomer. Pydridine–chromic acid oxidation of the α-alcohol gave tetrahydrozerumbone, described below. Catalytic reduction of zerumbone in alcoholic solution in the presence of Pd-$CaCO_3$ catalyst led to the uptake of two moles of hydrogen to give tetrahydrozerumbone (λ_{max}^{EtOH} 281 mμ, ε 39), which on lithium aluminium hydride reduction gave the same mixture of epimeric alcohols; reduction with aluminium isopropoxide in isopropanol gave the single crystalline β-epimer. It is clear from these observations that during the sodium–alcohol reduction of zerumbone, two ethylenic linkages, which must be conjugated with the keto group got reduced simultaneously to give tetrahydrozerumbols. These results, taken in conjunction with the ultra-violet data of zerumbone, establish the presence of a cross-conjugated dienone chromophore in the terpenoid; the position of the λ_{max} further indicated that the dienone chrompohore may have the di-transoid geometry.[9]

On treatment with alkali, zerumbone underwent reversal of aldol condensation to produce methyl ethyl ketone as the only volatile product, which together with the

* A report, containing the above results and also the evidence for its monocyclic nature was first made by the present author to the Council of the Indian Institute of Science, Bangalore, in 1951–55 (Forty-third Annual Report); however, the work could not be continued then for several reasons. Also cf. V. K. Balakrishnan, R. K. Razdan and S. C. Bhattacharyya, *Perf. and Essent. Oil Rec.* **47**, 274 (1956).

[6] R. B. Woodward, *J. Amer. Chem. Soc.* **63**, 1123 (1941); **64**, 70 (1942).
[7] L. Ruzicka, S. L. Cohen, M. Furter and F. Ch. van der Sluys-Veer, *Helv. Chim. Acta* **21**, 1735 (1938).
[8] L. J. Bellamy, *The Infrared Spectra of Complex Molecules*. Methuen, London (1954).
[9] G. G. Allan, M.B.E. Fayez, F. S. Spring and Robert Stevenson, *J. Chem. Soc.* 459 (1956).

information mentioned above, pointed to the probable occurrence of the unit (III) in the ketone.

Tetrahydrozerumbone and the two tetrahydrozerumbols still contain an olefinic linkage (yellow colour with tetranitromethane). On further catalytic hydrogenation in glacial acetic acid in the presence of Adam's catalyst, tetrahydrozerumbone took up one mole of hydrogen to provide a mixture of saturated ketones (no colour with tetranitromethane). By repeated crystallizations, one pure isomer of hexahydrozerumbone (λ_{max}^{EtOH} 288 mμ, ε 27·5) could be obtained. Thus zerumbone contains three ethylenic bonds and it follows, then, from its molecular formula ($C_{15}H_{22}O$) that it is monocyclic.

Since tetrahydrozerumbone gave a mixture of hexahydrozerumbones, the olefinic linkage must have at least one of its carbon atoms fully substituted. An asymmetric di-substituted ethylenic bond could hardly be expected to escape hydrogenation under the conditions of formation of tetrahydrozerumbone and hence, the olefinic bond in the tetrahydroketone must be at least trisubstituted. This is supported by the absence of any strong absorption around 890 cm^{-1} in the infra-red spectra of both zerumbone and its tetrahydro derivative. A decision between the trisubstituted and the tetrasubstituted ethylenic linkage could be made on the basis of the end-absorption[10–12] of this linkage in tetrahydrozerumbone and tetrahydrozerumbyl acetate (mixture of epimers). It is clear from the data (Table 1) that the double bond is trisubstituted.

TABLE 1. END ABSORPTION

	ε_{210}	ε_{215}	ε_{220}	ε_{225}
Tetrahydrozerumbone*	2740	1700	1145	820
Tetrahydrozerumbyl acetate	3195	1690	980	810
Trisubstituted olefinic linkage[10]	1400–4700	600–3500	250–1800	—
Tetrasubstituted olefinic linkage[10]	4400–10,000	3900–9200	3400–6700	—

* On Cary recording spectrophotometer it showed apparent λ_{max} 201 mμ, ε 4500.

This finding is further supported by the presence of bands in the infra-red spectrum (pure liquid) of tetrahydrozerumbone at 818 and 845 cm^{-1}.

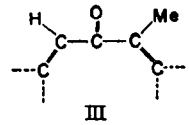
The C=O stretching frequency* for tetrahydrozerumbone (1700 cm^{-1}; liquid) and hexahydrozerumbone (1698 cm^{-1}; solid film) pointed to the interesting conclusion that the carbonyl group is situated in a ring which is possibly larger than seven-membered;[8],† a comparison with the C=O stretching frequencies in medium

* Determined precisely on a Perkin–Elmer Model 112 spectrophotometer (single beam) with a sodium chloride prism. Author is grateful to Mr. B. R. Lakshmanan for these measurements.

† Some cyclohexanones do exhibit their $\nu C=O$ in this range, but all such compounds are highly alkylated on both the carbon atoms flanking the carbonyl. It would be clear from the previous discussion that such a state does not prevail in the case of tetrahydro- and hexahydrozerumbone.

[10] P. Bladon, H. B. Henbest and G. W. Wood, *J. Chem. Soc.* 2737 (1952).
[11] T. G. Halsall, *Chem. & Ind.* 867 (1951).
[12] E. Lederer, *J. Chim. Phys.* **51**, D119 (1954).

rings[13,14] revealed that zerumbone may contain such a ring. This appeared to be further supported by the fact that tetrahydrozerumbone and tetrahydrozerumbyl acetate showed a depression of molecular refraction, a property characteristic of the medium ring-size.[13,15]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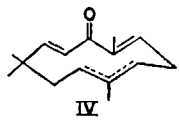
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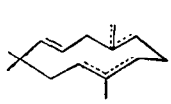
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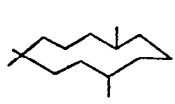
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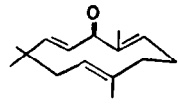

VII

Taking into consideration the above information and the biogenetic isoprene rule,[16] structure (IV) appeared attractive. The fact that humulene (V), in which the presence of an eleven-membered ring[17] is now well-established,[18] is an important constituent of the essential oil of *Zingiber zerumbet*, the working structure (IV) became all the more plausible. Clemmensen reduction of hexahydrozerumbone was carried out to yield the deoxy compound, which had properties virtually identical with those of humulane (VI) (Table 2). The identity of the two compounds was

TABLE 2. PHYSICAL PROPERTIES OF HUMULANE AND DEOXYHEXAHYDROZERUMBONE

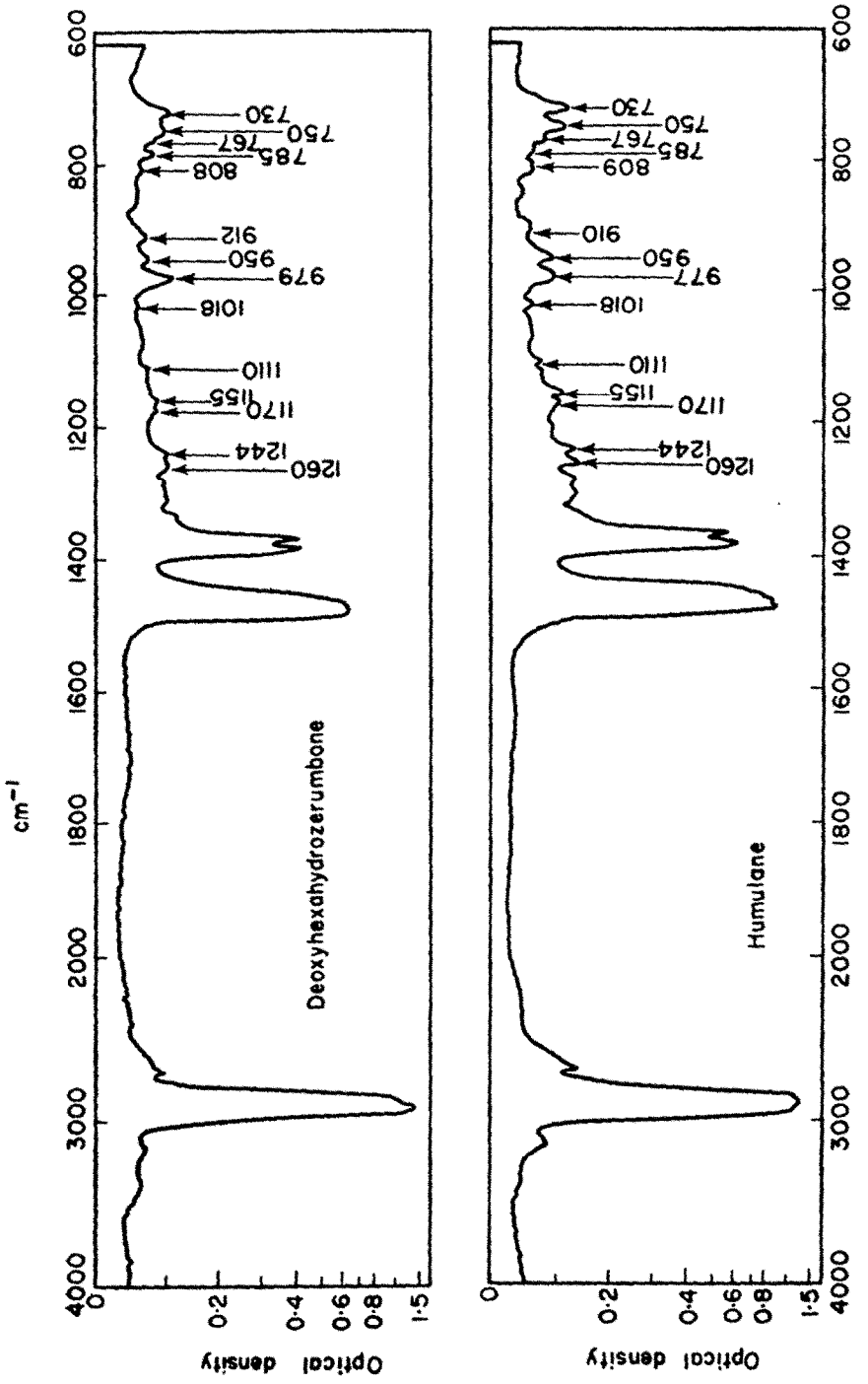
Sample	b.p./mm	$n_D/t°$	$d_4/t°$	M_D	EM_D
Deoxyhexahydrozerumbone	128–9/13	1·4720/25	0·8506/25	69·15	−0·12
Humulane*	128–9/13	1·4705/25	0·8500/25	69·00	−0·27
Humulane†	128/14	1·4720/20	0·8593/20	68·55	−0·72

* An authentic sample from humulene (*vide* Experimental).
† Data reported by F. Sorm *et al.*[18] for synthetic humulane.

confirmed by a comparison of their infra-red spectra (Figs. 1 and 2).[18,19] The small difference in the relative intensity of some of the peaks is attributable to the difference in the relative proportions of the two possible stereoisomers of 1,1,4,8-tetramethyl-cyclo-undecane; this is confirmed by the vapour-phase chromatography of the two samples (Fig. 3).

Taking humulane as the basic skeleton, the unit (III) and another unconjugated trisubstituted ethylenic linkage can be accommodated only in the structure (IV); this also accounts for the optical inactivity of the ketone. Ozonolysis of zerumbone

[13] V. Prelog, *J. Chem. Soc.* 420 (1950).
[14] F. Sorm, L. Dolejs and J. Pliva, *Coll. Czech. Chem. Comm.* **15**, 186 (1950).
[15] F. Sorm, M. Streibl, J. Pliva and V. Herout, *Coll. Czech. Chem. Comm.* **16**, 639 (1951).
[16] L. Ruzicka, *Experientia* **9**, 357 (1953).
[17] F. Sorm, M. Streibl, J. Pliva and V. Herout, *Chem. Listy* **45**, 308 (1951); **46**, 30 (1932); G. R. Clemo and J O. Harris, *Chem. & Ind.* 799 (1951); Sukh Dev, *Curr. Sci.* **20**, 296 (1951).
[18] F. Sorm, M. Streibl, V. Jarolim, L. Novotny, L. Dolejs and V. Herout, *Coll. Czech. Chem. Comm.* **19**, 570 (1954).
[19] J. Pliva, V. Herout and F. Sorm, *Coll. Czech. Chem. Comm.* **16**, 164 (1951).



FIGS. 1 and 2. The spectra were taken on pure liquid (smear film) and sodium chloride optics were employed.

was carried out to distinguish between the two possible alternatives depicted in IV, however, no identifiable product could be isolated.* On the other hand, ozonolysis of zerumbol proceeded smoothly to yield *as*-dimethylsuccinic acid and laevulinic acid. This finding fixes the structure of zerumbone as 2,6,9,9-tetramethyl-2,6,10-cyclo-undecatrien-1-one (VII). It is clear from the out-of-plane =CH deformation

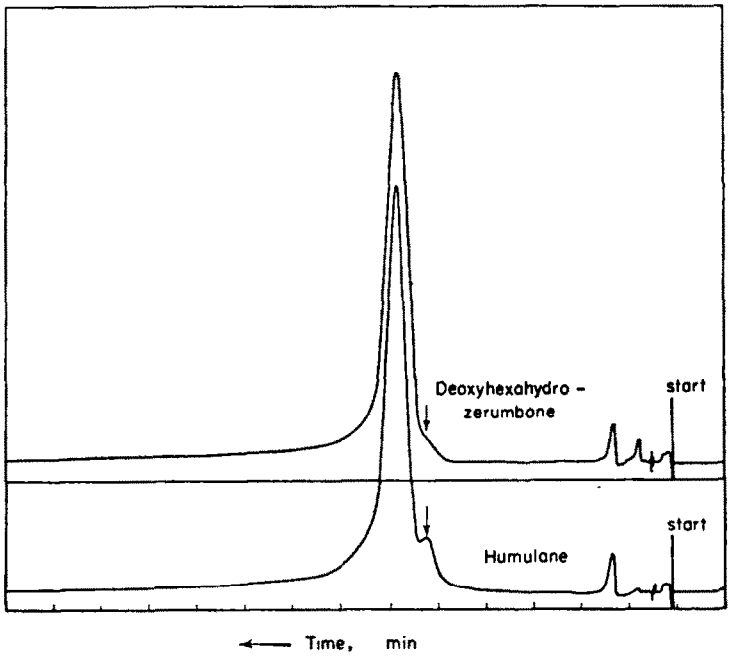


FIG. 3. The chromatography was run on a Perkin–Elmer Vapour Fractometer, Model 154B, using a 2 m column-C (Silicone oil-inert support) at 225°, with a column pressure of 28 lb/in² and flow rate of 5·0. Helium was used as the mobile phase and a 0·002 ml sample was employed in each case. This analysis was done at the Noyes Laboratories, University of Illinois, Urbana, and the author wishes to express his sincere thanks to Prof. E. J. Corey for these facilities.

vibration (970 cm^{-1}) of the C_{10}-C_{11} ethylenic linkage in zerumbone (VII) that this bond possesses the *trans*-configuration, the precise geometry of the remaining olefinic bonds must be considered as yet unsettled.

EXPERIMENTAL

All melting and boiling points are uncorrected. The ultra-violet spectra were measured in 95% ethanol (unless stated to the contrary) with a Beckman DU spectrophotometer. Infra-red spectra were (unless otherwise stated) determined with a Perkin–Elmer double-beam instrument. Pet ether refers to the fraction of b.p. 40–50°. Microanalyses were carried out by B. R. Seetharamia and D. P. Bose of this laboratory.

Isolation of zerumbone

Fully matured, raw wild ginger (*Zingiber zerumbet*) was procured from the "Kerala Soap Institute, Kozhikode" and after slicing it into thin pieces, was dried in the shade (loss of weight on drying amounted to 75%). This material on steam-distillation gave in a yield of 0·30 to 0·55% (based on the undried material) a dark oil, which almost completely crystallized out. The oil (100 g) was

* Zerumbone is a labile compound and undergoes polymerization on exposure to air to yield a gum.

taken up in pet ether (50 ml) and chilled to −5 to −10° and the solid (50 g, m.p. 60–62°) collected after 24 hr. The solid ketone was distilled (b.p. 137–141°/2·5 mm, yield 48 g) and the product crystallized once from pet ether and finally from dilute alcohol to give 40 g of colourless, flat needles (or stout prismatic rods), m.p. 66–67°.

The remaining portion of the essential oil, still containing some dissolved zerumbone, was reserved for investigation at a later date.

Zerumbone soon deteriorates at room temp (10–30 days) to give a gummy material, from which any unchanged zerumbone may be isolated by distillation; no fore-run is obtained and besides zerumbone only polymerized residue is left. The ketone is best stored as a saturated ethanolic solution in a refrigerator, where it will keep for years. In the solid state it can be preserved at 0° for a few months.

Oxime. This was prepared by the pyridine method and the product crystallized twice from dilute alcohol to yield colourless prisms, m.p. 178·5° (Lit. m.p.: 172–173°[1], 179°[8]) (Found: N, 6·3, $C_{15}H_{23}ON$ requires: N, 6·0%).

Semicarbazone was prepared by the pyridine method at room temp and was obtained in long, flat needles after two crystallizations from dil alcohol: m.p. 161·5–162·5° (Lit. m.p.: 163°[1], 155–160°[8]) (Found: N, 15·0. $C_{16}H_{25}ON_3$ requires: N, 15·3%).

Thiosemicarbazone was obtained by refluxing for 5 min a mixture of thiosemicarbazide (0·5 g), ketone (0·5 g), water (5 ml) and alcohol (10 ml). The product was collected after two days at room temp and recrystallized from dil alcohol to furnish white, feathery plates, m.p. 229·5–230·5° (efferv) (Found: N, 14·4. $C_{16}H_{25}N_3S$ requires: N, 14·4%).

2,4-*Dinitrophenylhydrazone.* The sulphuric acid method yielded a material (crude, m.p. 140–145°) which could be purified only with difficulty. It was best prepared by adding zerumbone (1·0 g) and two drops of conc HCl to a refluxing solution of 2,4-dinitrophenylhydrazine (0·9 g) in alcohol (75 ml). The clear, deep red solution, thus obtained, was left aside and the product collected after several hours (crude, m.p. 159–160°) and recrystallized twice from benzene–pet ether to give deep red prisms, m.p. 160·5–161°. (Found: N, 14·03. $C_{21}H_{26}O_4N_4$ requires: N, 14·06%).

Lithium aluminium hydride reduction of zerumbone to zerumbol

To a well-dispersed suspension of lithium aluminium hydride (0·285 g, 0·0075 mole) in anhydrous ether (25 ml), a solution of zerumbone (4·36 g, 0·02 mole) in ether (25 ml) was introduced, with cooling in an ice–salt bath, during 5 min. After stirring for 1 hr in the ice-bath, the reaction mixture was left aside as such overnight (13 hr). This was chilled in an ice–salt bath and with stirring, cautiously treated, first with 10 ml of water and then with 15 ml of 10% H_2SO_4. The ether layer was separated as soon as the complex had dissolved, and the aqueous phase extracted with pet ether (15 ml × 2). The combined extracts were washed with water, saturated aq. sodium bicarbonate solution and finally again with water and dried (sodium sulphate). The solvent was removed at room temp/suction, and the crystalline residue crystallized from pet ether at −5 to −10° to give white, prismatic needles, m.p. 77–78°, yield 2·0 g (91%). An analytical sample was crystallized once from dil alcohol and then from pet ether: m.p. 79–80° (Found: C, 81·90; H, 10·57. $C_{15}H_{24}O$ requires: C, 81·76; H, 10·98%)

3,5-*Dinitrobenzoate* was obtained as white lustrous leaflets from benzene–pet ether, m.p. 119–120° (Found: N, 6·7. $C_{22}H_{26}O_6N_2$ requires: N, 6·8%).

Oxidation of zerumbol to zerumbone

(i) *Oppenauer oxidation.* A mixture of the alcohol (220 mg), cyclohexanone (980 mg), aluminium t-butoxide (396 mg) and thiophene-free benzene (5 ml) was refluxed for 15 hr and then after cooling, treated with 5% HCl (10 ml). The benzene layer was washed once with ice-cold 5% HCl, then with water and dried. The solvent was removed and the residue fractionated and the fraction, b.p. 115–120°/0·3 mm directly converted into its 2,4-dinitrophenylhydrazone by the HCl-method. The derivative was obtained from benzene–pet ether as deep red prisms, yield 60 mg, m.p. and mixed m.p. with an authentic sample was 160–161°.

(ii) *Manganese dioxide oxidation.* A solution of zerumbol (660 mg) in dry pet ether (60 ml) was stirred with active manganese dioxide[20] (6 g) under nitrogen atmosphere, for 24 hr, at room temp

[20] J. Attenburrow, A. F. B. Cameron, J. H. Chapman, R. M. Evans, B. A. Hems, A. B. A. Jansen and T. Walker, *J. Chem. Soc.* 1104 (1952).

(24–26°). The manganese dioxide was removed by filtration and washed with ether. Removal of the solvent from the filtrate gave a crystalline residue (550 mg, m.p. 64–65°), which was recrystallized from dil alcohol, m.p. and mixed m.p. with a genuine sample of zerumbone was 65–66°.

Sodium–alcohol reduction of zerumbone to tetrahydrozerumbols

To an ice-cooled solution of zerumbone (5·0 g) in absolute ethanol (125 ml), sodium (12·0 g) cut into small pieces was added all at once. After the vigour of the reaction had subsided, the ice-bath was removed and the reaction allowed to proceed first at room temp and later on a water-bath (1 hr) so that the vigour of the reaction was maintained. The alcohol was removed by suction and the residue cooled and diluted with water till an oily layer separated. This was taken up in pet ether–ether mixture (1 : 1; 30 ml × 3) and washed with brine and dried. The solvent was flashed off and the residue fractionated to give the alcohols as a colourless, thick oil, b.p. 123°/0·5 mm, yield 4·0 g. With tetranitromethane in chloroform it gave a yellow colour.

The *acetates* were prepared by the acetyl chloride–pyridine procedure in benzene solution at room temp. The product was obtained as a colourless, viscous liquid: b.p. 156–159°/5 mm, n_D^{28} 1·4833, d_4^{28} 0·9649, M_D 78·77 (Calc.: 79·72, $E\Sigma_D$ −0·36) (Found: C, 76·3; H, 11·2. $C_{17}H_{30}O_2$ requires: C, 76·6; H, 11·3%).

Separation of epimers. 3,5-Dinitrobenzoyl chloride (5·07 g, 0·022 mole) was added all at once to a solution of the above alcohols (3·33 g, 0·015 mole) in benzene (30 ml). This was cooled to 0° and treated with anhydrous pyridine (1 ml × 2) with swirling. The reaction mixture was heated at 55–60° for 4 hr and then left aside as such for another 36 hr at room temp (26°). This was diluted with water (25 ml) and the product taken up in ether–benzene (1 : 1), washed with saturated aqueous sodium bicarbonate and dried (sodium sulphate). The solvent was removed and the oily residue treated with pet ether (50 ml) and set aside at 0° and the product collected after a day: m.p. 108–114°, yield 4·6 g.

The above mixture of benzoates was dissolved in benzene (10 ml) and diluted with n-hexane (40 ml) and allowed to crystallize at room temp (26°). The white crystalline nodules (500 mg, m.p. 133–136°) were collected after four days and the mother liquor further diluted with n-hexane (50 cc) and a second crop (200 mg, m.p. 120–123°) obtained after same period. The two crops were combined (product A). The final mother liquor was freed of the solvent and residue crystallized from dilute acetone to give crystals, m.p. 118–122°, yield 3·0 g (product B); the mother liquor was rejected.

Product A was crystallized twice from benzene–pet ether to give white, silky needles (200 mg), m.p. 146–147°, of *α-tetrahydrozerumbyl 3,5-dinitrobenzoate* (Found: N, 6·68. $C_{22}H_{30}O_6N_2$ requires: N, 6·69%). The *α-tetrahydrozerumbol* was regenerated from 100 mg of the pure 3,5-dinitrobenzoate in ethanol (5 ml), on heating to just boiling with a solution of sodium hydroxide (50 mg in 0·1 ml of water and diluted to 2 ml with ethanol) and leaving aside at room temp for 24 hr. This was extracted with pet ether (10 ml × 3), washed with brine and dried. On removal of the solvent 60 mg of an extremely viscous syrup remained, which failed to crystallize. This was taken up in pyridine (1 ml) and oxidized with pyridine–chromic acid complex[21] (from 2 ml of pyridine and 100 mg of chromic acid) at room temp (24–26°) for 24 hr. Usual work up gave a ketone, which was isolated as its oxime, white needles (dil alcohol), m.p. 130–132°, mixed m.p. with an authentic sample (m.p. 133–134°) of *tetrahydrozerumbone oxime* (*vide infra*) was 131–132°.

Product B was thrice crystallized from acetone, when white silky needles (1 g) of *β-tetrahydrozerumbyl 3,5-dinitrobenzoate* were obtained, m.p. 142–143°, mixed m.p. with α-tetrahydrozerumbyl 3,5-dinitrobenzoate was 120–135° (Found: N, 6·70. $C_{22}H_{30}O_6N_2$ requires: N, 6·69%). The ester (500 mg), on saponification as above, yielded *β-tetrahydrozerumbol* (250 mg, m.p. 65–68°) which, after two crystallizations from pet ether, was obtained in white, fine needles, m.p. 72°, mixed m.p. with the Meerwein–Ponndorf reduction product (*vide infra*) of tetrahydrozerumbone was undepressed.

Tetrahydrozerumbone

Zerumbone (10·9 g) was hydrogenated, at room temp and pressure, in alcohol (75 ml) over pre-reduced Pd–$CaCO_3$ catalyst[22] (4 g). The hydrogen uptake came to a close after absorption of 100% of two mole equivalents of the gas, during 40–60 min. The reduction also stopped at the tetrahydro stage when Adam's PtO_2 catalyst (100 mg) was employed in an alcohol medium. The

[21] G. I. Poos, G. E. Arth, R. E. Beyler and L. H. Sarett, *J. Amer. Chem. Soc.* **75**, 422 (1953)
[22] M. Busch and K. Schulz, *Ber. Dtsch. Chem. Ges.* **62**, 1458 (1929).

catalyst was removed by filtration and the filtrate diluted with water, and the product taken up in pet ether. Working up gave tetrahydrozerumbone as a colourless liquid, b.p. 130°/3 mm, n_D^{24} 1·4912, yield 10·2 g. An analytical sample had b.p. 113°/1·6 mm, n_D^{29} 1·4890, d_4^{29} 0·9378, M_D 68·36. (Calc. 68·84, $E\Sigma_D$ —0·22). (Found: C, 81·28; H, 11·79. $C_{15}H_{26}O$ requires: C, 81·09; H, 11·80%). The *oxime* crystallized from dil alcohol in fine needles, m.p. 133–134° (Found: N, 5·88. $C_{15}H_{27}ON$ requires: N, 5·9%). The *semicarbazone* was obtained by the pyridine method by heating on a steam-bath for 8 hr and was twice recrystallized from dil alcohol to yield flat needles, m.p. 197–197·5° (dec) (Found: N, 15·0. $C_{16}H_{29}ON_3$ requires: N, 15·1%). 2,4-Dinitrophenylhydrazone could not be obtained under the usual conditions.

Meerwein–Ponndorf reduction of tetrahydrozerumbone

Tetrahydrozerumbone (1·1 g, 0·005 mole), aluminium isopropoxide (5·1 g, 0·025 mole) and anhydrous isopropanol (25 ml) were placed in a flask, which was connected to a one-foot Vigreux column carrying a total condensation-type still-head. The reaction mixture was heated under total reflux for 1 hr and then the reflux removed at the rate of 1 drop/1–2 min till no more acetone was formed (2–5 hr). Another 10 ml of the alcohol were distilled off, the residue cooled, and poured into ice and HCl aq., when an oil separated, which slowly crystallized out on refrigeration. The product was collected and crystallized from dil alcohol at 0° to give needles (900 mg), m.p. 66–67°; two recrystallizations at 0 to −5° from pet ether gave white, fine needles, m.p. 72°. This gave a yellow colour with tetranitromethane in chloroform solution. (Found: C, 80·1; H, 12·3. $C_{15}H_{28}O$ requires: C, 80·3; H, 12·6%). The 3,5-*dinitrobenzoate* crystallized from a mixture of benzene and pet ether in silky needles, m.p. 144°, mixed m.p. with β-tetrahydrozerumbyl 3,5-dinitrobenzoate (*vide supra*) was 143–144°. (Found: N, 6·65. $C_{22}H_{30}O_6N_2$ requires: N, 6·69%).

Lithium aluminium hydride reduction of tetrahydrozerumbone

Tetrahydrozerumbone (1·1 g) in ether (20 ml) was reduced with a slurry of 100 mg of lithium aluminium hydride in 20 ml of ether, in a manner detailed above for zerumbone. The product was obtained as a colourless, very viscous liquid, b.p. 123–124°/0·5 mm, n_D^{25} 1·4990. (Found: C, 80·0; H, 12·5. $C_{15}H_{28}O$ requires: C, 80·3; H, 12·6%). The crude 3,5-dinitrobenzoate had m.p. 85–95° and further purification showed it to be a mixture of tetrahydrozerumbyl 3,5-dinitrobenzoates (*vide supra*).

Base-catalysed cleavage of zerumbone

To a solution of 1 g of potassium hydroxide in 3 ml of water and 17 ml of aldehyde-free ethanol, zerumbone (1 g) was added, and the mixture heated on a steam-bath for 6 hr under total reflux, in a flask attached to a one-foot Vigreux column carrying a total condensation-type still-head. After the above period, first 5 ml of the distillate were collected and treated with 2,4-dinitrophenylhydrazine sulphate reagent to give an orange-yellow precipitate (m.p. 95–100°), which was thrice recrystallized from dil alcohol to furnish orange-yellow needles, m.p. 113–114°, mixed m.p. with an authentic sample of methyl ethyl ketone 2,4-dinitrophenylhydrazone (m.p. 113–114°) was undepressed (Found: N, 22·00, 22·10. $C_{10}H_{12}O_4N_4$ requires: N, 22·22%).

Hexahydrozerumbones

Tetrahydrozerumbone (16·65 g, 0·075 mole) was further hydrogenated over 300 mg of pre-reduced PtO_2 catalyst in 75 ml of gl acetic acid. The absorption of hydrogen ceased after 12 hr, when 1990 ml of the gas at 25°/684 mm had been consumed (Calc. for 1 mole of hydrogen: 2030 ml). The catalyst was removed and the filtrate diluted with water (150 ml), extracted with pet ether (20 ml × 3), washed with brine and dried (sodium sulphate). Removal of the solvent gave a mixture of crystals and an oil, which was recrystallized as such from dil alcohol at —10° to give crystals (11 g), m.p. 50–54°. This on two further recrystallizations at —15° from pet ether gave white needles, m.p. 62·5–63°, yield 4·8 g; no colour with tetranitromethane. (Found: C, 80·5; H, 12·5. $C_{15}H_{28}O$ requires: C, 80·3; H, 12·6%). The mother liquors were worked up to give a mixture of stereoisomers, as a colourless liquid, b.p. 115–116°/1 mm, n_D^{24} 1·4820, yield 10·5 g; this was not studied further.

The *oxime* (crude, m.p. 106–107°) was crystallized from dil alcohol to give long, flat needles, m.p. 107–107·5°. (Found: N, 6·1. $C_{15}H_{29}ON$ requires: N, 5·9%). The *semicarbazone* (crude,

m.p. 178–180°) separated from dil alcohol in white needles, m.p. 182–182·5° with effervescence. (Found: N, 15·0. $C_{16}H_{31}ON_3$ requires: N, 14·9%). 2,4-Dinitrophenylhydrazone could not be prepared.

Deoxyhexahydrozerumbone

A mixture of pure hexahydrozerumbone (0·7 g), amalgamated zinc wool (prepared from 3·6 g of zinc and 0·3 g of mercuric chloride in the presence of HCl), acetic acid (3·6 ml) and conc HCl (12·4 ml) was gently refluxed for 15 hr. The refluxing was continued for another 5 hr after adding 5 ml HCl. The reaction mixture was cooled, diluted with water (20 ml) and the hydrocarbon taken up in pet ether (10 ml × 3), the extracts washed with brine and dried. Removal of the solvent, followed by fractionation over sodium gave the desired product as a colourless liquid with properties recorded in Table 2; no colour with tetranitromethane. (Found: C, 85·9; H, 14·1. $C_{15}H_{30}$ requires: C, 85·7; H, 14·3%).

Humulane

A 2·04 g sample of humulene (b.p. 114–115°/5 mm, n_D^{25} 1·5015, $[\alpha]_D^2$ −1·0) isolated from the essential oil of wild ginger[4,17C] was hydrogenated in 1 g acetic acid over Adam's catalyst when 98·9% of the theoretical quantity of hydrogen was absorbed at room temp and pressure. The reaction mixture was worked up to give 1·2 g of humulane of characteristics given in Table 2; no colour with tetranitromethane.

Ozonolysis of zerumbol

A solution of 2·2 g of zerumbol in purified ethyl acetate (100 ml) was ozonised at −20° with a current of ozonized oxygen (15 mg/min) till no more of ozone was absorbed (2 hr; potassium iodide–boric acid test). The solvent was removed under suction at room temp and the residual colourless syrup taken up in 20 ml of acetic acid. After adding 15 ml of 20% hydrogen peroxide, the clear mixture was heated over the steam-bath for 3 hr and then left aside at room temp overnight. The aqueous acetic acid was removed from a steam-bath/suction and the residue treated with a saturated aqueous sodium bicarbonate solution till alkaline. This was washed with ether to remove a negligible amount of neutral material. The alkaline solution was acidified with conc phosphoric acid and after saturating with ammonium sulphate, was continuously extracted with ether for 24 hr. The solvent was removed to give 1·8 g of a syrup which partially crystallised. This was taken up in carbon tetrachloride (10 ml) and ethanol (5 ml), and after adding 200 mg of sulphosalicylic acid, was gently refluxed in an apparatus permitting continuous removal of the azeotrope. When no more of the lighter phase separated, the product was worked up into sodium bicarbonate soluble (400 mg; half ester of *gem*-dimethylsuccinic acid, *vide infra*) and insoluble portion (1·6 g). The neutral product was further separated by Girard P reagent into a reactive (0·6 g) and non-reactive fraction (0·6 g). The Girard P reactive portion gave a positive test for iodoform and was converted into its 2:4-dinitrophenylhydrazone which after three crystallizations from dil alcohol was obtained in soft, yellow needles (500 mg), m.p. 100–101°, mixed m.p. with an authentic sample of 2:4-*dinitrophenylhydrazone of ethyl laevulinate* (m.p. 100–101°) was undepressed. (Found: N, 17·7. $C_{13}H_{16}O_8N_4$ requires: N, 17·3%).

The acidic material (400 mg) was mixed with the Girard P non-reactive fraction and hydrolysed by heating with conc HCl (15 ml) on the steam-bath for 8 hr. Removal of the aqueous acid gave a crystalline residue (0·75 g, m.p. 125–130°), which was thrice recrystallized from acetone–benzene to give prisms (250 mg), m.p. 136–137°, mixed m.p. with a genuine sample of *gem-dimethylsuccinic acid* (m.p. 140–141°) was 137–139°. (Found: C, 49·2; H, 6·9. $C_6H_{10}O_4$ requires: C, 49·3; H, 6·9%).