Tetrahedron Letters No.24, pp. 1977-1981, 1965. Pergamon Press Ltd.
Printed in Great Britain.

STEREOCHEMISTRY OF ZERUMBONE*

N.P. Damodaran and Sukh Dev
National Chemical Laboratory, Poona (India)

(Received 15 April 1965)

While reporting[1] on the structure of zerumbone (I), it was stated that whereas the C_9-C_{10} ethylenic linkage has the trans-configuration (strong $\delta^{=CH}$ band at 970 cm^{-1}), the precise geometry of the remaining two olefinic linkages must be considered as yet unsettled. We now report on the fine structure of zerumbone.

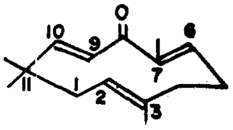
Humulene[2,3] and zerumbone[1] are, apparently, related by an oxidation-reduction system[2]. Since, the stereochemistry of humulene has recently been shown[4,5,+] to be II,

---

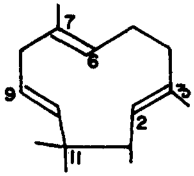
*Communication No. 775 , National Chemical Lab., Poona.

+We endeavoured to solve this problem by a study of the rates of per-acid epoxidation of humulene, humulene epoxide-I, humulene epoxide-II, dihydroepoxides, caryophyllene and dihydroisocaryophyllene. According to our results, Δ^6-olefinic linkage of humulene reacts several times faster than the Δ^2-ethylenic bond, the rate difference being similar to that observed in the case of caryophyllene and dihydroisocaryophyllene. This had led us to conclude that the Δ^6- and Δ^2-olefinic linkages (which are identically substituted and are essentially unhindered) must have different geometry[6]. However, since the X-ray work has shown humulene to be all-trans, one is forced to the conclusion that peracid kinetics method for distinguishing the configuration of olefinic linkages must be treated with reserve.

zerumbone may also be expected to possess the all *trans-*geometry, and we now present evidence in favour of this.



I



II

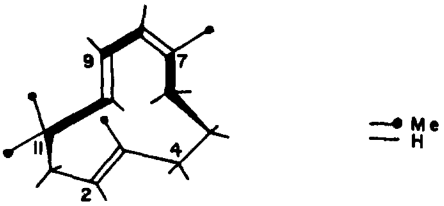
Zerumbone semicarbazone on being refluxed (70 hr) with dry KOBu^t in toluene[7] furnished, in 70-80% yield, a mixture of hydrocarbons* (five components; two major: 30 and 53%) from which humulene (30%) could be readily isolated by extraction with aq. silver nitrate[8] and identified by standard methods (b.p., n_D, GLC, IR, m.p. of $AgNO_3$-adduct). The humulene-free material on chromatography over

---

*The conventional Wolff-Kishner reduction failed to give more than a trace of humulene. Likewise, hydrogenolysis of zerumbyl bromide or tosylate, under a variety of conditions, was unsuccessful.

Oxidation of humulene to zerumbone by several methods [$Na_2Cr_2O_7$-AcOH, t-butyl chromate, MnO_2, $Pb(OAc)_4$ enzymatic, *via* allylic hydroperoxidation[10]] has not been successful so far. In this connection it may be mentioned that both $Na_2Cr_2O_7$-AcOH and t-butyl chromate furnished humulene epoxide-II and humulene dioxide[9] in good yields, as products of oxidation.

AgNO$_3$-SiO$_2$ gel[9] yielded the second major (53%) component: $C_{15}H_{24}$, b.p. 82-83°/2.5 mm, n_D^{30} 1.5108, λ_{max}^{EtOH} 236-238 mμ (ε, 9625), $\delta^{=CH}$ 969 cm^{-1}. This on quantitative hydrogenation consumed three moles of hydrogen to give humulane. Its PMR[*] spectrum showed the presence of two quaternary methyls (6H signal at 67 cps), two vinylic methyls (3H doublets centred at 74 and 101 cps; J = 1.5 cps in each case), four olefinic protons (located between 290 and 373 cps, an ABC pattern is discernible) and the absence of 143, 149 cps signals (2H) characteristic of $=C-CH_2-C=$ protons in humulene[2,9]. These data are consistent with the formulation of this compound as III.[**] [+]



III

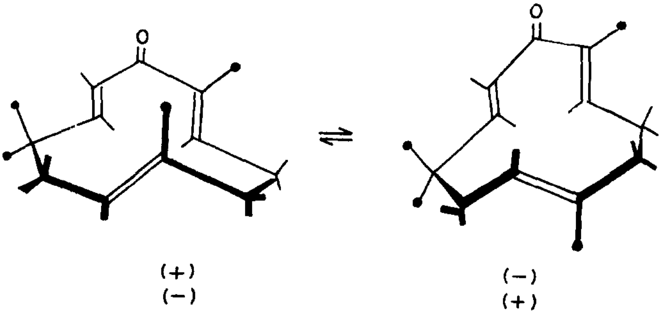
---

[*] Spectra were taken on ~ 20% solution in CCl_4 on a Varian A-60 spectrometer; the signals are recorded in cps from tetramethylsilane as zero.

[**] The rearrangement of an olefinic linkage during Wolff-Kishner reduction of $\alpha\beta$-unsaturated ketones or aldehydes is well-recognised[11].

[+] *Cis*-Geometry of the Δ^7-olefinic linkage in III is preferred to the alternate *trans*-configuration, as *trans*-*trans*-configuration in a C_{11}-cycle appears (as judged from models) to be highly strained, if not prohibitive. The conformation shown appears to explain best the PMR (note the shielding of one of the vinylic methyls) and UV spectral data.

Since zerumbone and humulene, both, have the ethylenic linkages in the same position in the humulane skeleton, it follows that in the formation of humulene from zerumbone by the Wolff-Kishner reduction, no reshuffling[*] of the ethylenic linkages is involved and hence the olefinic linkages of zerumbone must have the same geometry as those of humulene i.e. all-trans. Thus, zerumbone may be represented by the stereostructure IV. The conformation shown would fit best the PMR (shielding of the β,β'-protons of the αβ, α'β'-dienone chromophore) and UV (ditransoid geometry of the chromophore[1]) spectral data.



IV

---

[*] Humulene is recovered unchanged after refluxing with KOBu^t in toluene under the conditions of Wolff-Kishner reduction. This ensures that humulene and III are not products of equilibration. Had this not been the case, no conclusion about the stereochemistry of zerumbone could have been possible from its conversion into humulene.

REFERENCES

1 Sukh Dev, Tetrahedron 8, 171 (1960).

2 Sukh Dev, Tetrahedron Letters No.7, 12 (1959); Tetrahedron 9, 1 (1960).

3 R.P. Hildebrand, M.D. Sutherland and O.J. Waters, Chem. and Ind. 489 (1959); M.D. Sutherland and O.J. Waters, Aust. J. Chem. 14, 596 (1961).

4 A.T. McPhail, R.I. Reed and G.A.Sim, Chem. and Ind. 976 (1964).

5 J.A. Hartsuck and I.C. Paul, Chem. and Ind. 977 (1964).

6 e.g. see: V. Prelog, K. Schenker and W. Küng, Helv. Chim. Acta 36, 471 (1953); V. Prelog, K. Schenker and H.H. Gunthard, Helv. Chim. Acta 35, 1598 (1952); A.Aebi D.H.R. Barton and A.S. Lindsey, J. Chem. Soc. 3124 (1953).

7 M.F. Grundon, H.B. Henbest and M.D.Scott, J. Chem. Soc. 1855 (1963).

8 R.P. Hildebrand and M.D.Sutherland, Aust. J. Chem. 14, 272 (1961).

9 N.P. Damodaran and Sukh Dev, Tetrahedron Letters No.28, 1941 (1963).

10 M.S. Kharasch, G. Sosnovksy and N.C.Yang, J. Amer. Chem. Soc. 81, 5819 (1959); M.S.Kharasch and A. Fono, J. Org. Chem. 23, 324, 325 (1958).

11 G. Lardelli and O. Jeger, Helv. Chim. Acta 32, 1817 (1949); R. Fischer, G. Lardelli and O. Jeger, Helv. Chim. Acta 33, 1335 (1950); 34, 1577 (1951); R. M. Dodson and P. Sollman, J. Amer. Chem. Soc. 73, 4197 (1951).