Conformation of the Sesquiterpenoid Zerumbone: *X*-Ray Crystallographic Analysis of Zerumbone 2,4-Dinitrophenylhydrazone

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The molecular geometry of the title compound, $C_{15}H_{22}O$, has been determined by *X*-ray diffraction. The double bonds in the 2,6,9,9-tetramethylcycloundeca-2,6,10-trienone ring have *trans*-stereochemistry. The conformation of the macrocycle differs from that found in several derivatives of humulene, $C_{15}H_{24}$, and is related to one of the low-energy conformations of cycloundecane. Force-field calculations indicate that this zerumbone conformation is of lower energy than the alternative humulene-like conformation. Crystallographic data are a = 12.619(2), b = 7.290(3), c = 23.422(3) Å, β = 98.06(1)°, Z = 4, space group $P2_1/c$. Diffractometer intensity measurements were made with Cu-K_α radiation and least-squares adjustment of the atomic parameters converged at R 0.046 for 3 222 $|F_o|$ values.

ZERUMBONE, $C_{15}H_{22}O$, a sequiterpenoid ketone from *Zingiber zerumbet*, was assigned structure (1) (Table 2) on the basis of chemical and spectroscopic investigations.[1] In view of the compound's close structural similarity to humulene (2),[2] the double bonds in zerumbone are believed to have *trans*-stereochemistry.

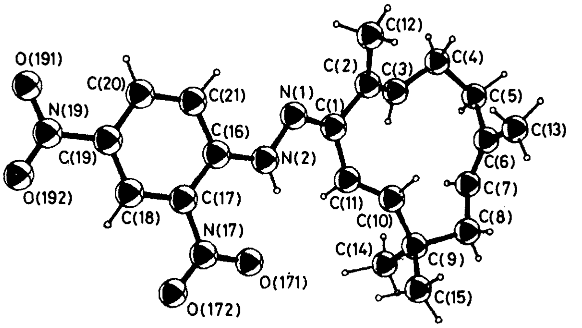
X-Ray studies of the bis(silver nitrate) adduct of humulene [2] and of humulene di- [3] and tri-epoxide [4] disclosed a common conformation for the eleven-membered rings in these compounds. Moreover, the stereochemistries of other sequiterpenoids (*e.g.* illudol) are consistent with biogenesis from humulene-like precursors with this type of conformation.[5] We intended to undertake an *X*-ray analysis of zerumbone to define the stereochemistry and to compare the conformation with that of humulene derivatives but failed to obtain good crystals; we therefore prepared and studied the 2,4-dinitrophenylhydrazone (3).

TABLE 1

Fractional atomic co-ordinates (× 10^4) with standard deviations in parentheses

Atom	*x*	*y*	*z*
C(1)	11 464(1)	0 166(2)	−1 487(1)
C(2)	11 149(1)	−0 552(2)	−2 078(1)
C(3)	11 849(1)	−0 426(3)	−2 451(1)
C(4)	11 814(2)	−1 335(4)	−3 025(1)
C(5)	12 953(2)	−1 959(4)	−3 109(1)
C(6)	13 516(2)	−2 919(3)	−2 583(1)
C(7)	14 292(2)	−2 047(4)	−2 236(1)
C(8)	14 786(2)	−2 623(4)	−1 642(1)
C(9)	14 437(1)	−1 401(4)	−1 153(1)
C(10)	13 234(1)	−1 228(3)	−1 282(1)
C(11)	12 626(1)	0 234(3)	−1 266(1)
C(12)	10 063(2)	−1 410(3)	−2 218(1)
C(13)	13 075(2)	−4 744(4)	−2 458(1)
C(14)	14 984(2)	0 467(5)	−1 132(1)
C(15)	14 734(2)	−2 380(6)	−0 573(1)
C(16)	10 421(1)	1 838(2)	−0 293(1)
C(17)	10 740(1)	2 301(2)	0 298(1)
C(18)	10 049(1)	3 149(2)	0 620(1)
C(19)	9 029(1)	3 542(2)	0 372(1)
C(20)	8 666(1)	3 061(2)	−0 197(1)
C(21)	9 341(1)	2 230(2)	−0 520(1)
N(1)	10 718(1)	0 613(2)	−1 189(1)
N(2)	11 084(1)	1 103(2)	−0 627(1)
N(17)	11 806(1)	1 920(2)	0 584(1)
N(19)	8 334(2)	4 549(2)	0 708(1)
O(171)	12 456(1)	1 169(2)	0 317(1)
O(172)	12 027(1)	2 329(3)	1 093(1)
O(191)	7 476(1)	5 083(2)	0 457(1)
O(192)	8 642(2)	4 851(2)	1 217(1)

The crystal structure was elucidated by direct-phasing procedures and the atomic parameters were adjusted by least-squares calculations that converged at R 0.046 for 3 222 reflections. The atomic co-ordinates are listed in Table 1. The Figure shows the molecular structure and confirms that all three double bonds have *trans*-stereochemistry.



Molecular structure of zerumbone 2,4-dinitrophenylhydrazone. The thermal ellipsoids are drawn at the 50% probability level

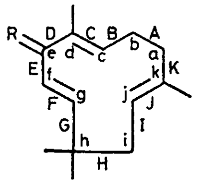
The torsion angles around the carbon-carbon bonds of the eleven-membered ring in (3) are given in Table 2 (column *Z*) together with the values for humulene (2) in its silver nitrate complex (column *H*). The correspondence for most of the results is evident, but the conformations differ in the region of the phenylhydrazone group of the zerumbone derivative.

The cycloundecatriene conformation in (3) has approximate C_2 symmetry, the only notable departure being evident in the torsion angles around bonds C(1)–C(2), −26°, and C(1)–C(11), −52°. The larger angle of this pair probably arises from the need to keep the 11-H and NH hydrogen atoms apart (H ··· H 2.31 Å).

The conformational difference between (2) and (3) may arise from the replacement of the sp^3-carbon atom of a CH_2 group by the sp^2-carbon atom of a C=R group, from the effect of Ag^+ ions and epoxide oxygen atoms on humulene, or from the crystal environment associated with the dinitrophenylhydrazone moiety. In order to decide among these alternatives, we calculated steric energies and equilibrium geometries for humulene (2) and its methylene derivative (4), each in conformations *Z* and *H* of Table 2; these calculations employed the hydrocarbon force field developed by White and Bovill[6] with a full-matrix procedure for minimization of energy.[7] We find for the methylene derivative (4) that conformation of type *Z* is of lower energy than that of type *H* by 23.0 kJ mol^{-1} while for humulene the conformation of type *Z* is also the more stable though by only 4.8 kJ mol^{-1} in this case. Since the methylene compound (4) should be a good analogue for zerumbone in force-field calculations (*cf.* force-field calculations for cycloheptanone[8] and methylenecycloheptane[9]) we conclude that the dinitrophenylhydrazone group has not influenced the conformation of the macrocycle in (3). There is a large measure of correspondence between conformations *H* and *Z*, and the indication that the energetically favoured conformation of humulene may be of type *Z* rather than type *H* does not require any revision of previous proposals that the stereochemistries of various sesquiterpenoids are consistent with biogenesis from humulene-like precursors.

Table 2

Conformational comparisons: *X*-ray observations and force-field calculations. The columns headed *H*(obs) and *Z*(obs) are *X*-ray results for compounds (2) and (3), respectively, and the columns headed *F*(calc) are force-field results for compound (4). The column headed *E*(obs) lists *X*-ray results for cycloundec-1-enecarboxylic acid and that headed *A*(calc) lists Anet's force-field calculations for the [12314] conformation of cycloundecane



(1) R = O
(2) R = H_2
(3) R = $NNHC_6H_3(NO_2)_2$
(4) R = CH_2

Torsion angles (°)

	(2) *H*(obs)	(3) *Z*(obs)	(4) *F*(calc)	*E*(obs)	*A*(calc)
A	35	46	48	63	65
B	77	−141	−127	−90	−92
C	−162	168	170	155	168
D	95	−26	−48	−80	−82
E	−94	−52	−43	−70	−70
F	156	172	169	155	129
G	−102	−136	−129	−94	−86
H	55	48	42	54	79
I	−126	−107	−110	−116	−153
J	172	167	172	178	160
K	−109	−105	−102	−111	−86

Bond angles (°)

	(3) *Z*(obs)	(4) *F*(calc)
a	111.9	112.6
b	109.6	110.0
c	128.5	128.4
d	118.3	118.3
e	117.4	114.8
f	120.9	120.5
g	129.4	127.3
h	106.3	107.6
i	113.3	112.8
j	127.0	126.7
k	119.8	120.3

The conformation found for the eleven-membered ring in (3) is quite different from that characterized in a low-temperature *X*-ray study of cycloundecanone;[10] on the other hand, it resembles a conformation we have found for cycloundec-1-enecarboxylic acid (see column *E* in Table 2).[11] Anet and Rawdah have reported force-field calculations leading to six low-energy conformations for cycloundecane;[12] the [12314] conformation (column *A* in Table 2) has the same pattern of torsion angle signs as conformations *Z* and *E*. Conformation *H*, however, does not correspond to any of the six low-energy cycloundecane conformations. These results suggest that a full understanding of the conformational inter-relationships of eleven-membered rings may be obtained by further crystallographic and force-field investigations.

The four C–C(sp^3)–C angles in the eleven-membered ring in (3) range from 106.3 to 113.3° and the six C–C=C angles range from 118.3 to 129.4°, indicating some degree of steric strain. The force-field calculations for the *Z*-conformation of (4) reproduce these variations in a most satisfactory manner (Table 2). The *trans* double bonds have torsion angles (167—172°) that differ appreciably from the ideal value of 180° and these departures from planarity are also reproduced by the force-field calculations (Table 2).

EXPERIMENTAL

The 2,4-dinitrophenylhydrazone derivative of zerumbone was prepared by a standard procedure[13] and crystallised from ethanol.

Crystal Data.—$C_{21}H_{26}N_4O_4$, $M = 398.50$. Monoclinic, $a = 12.619(2)$, $b = 7.290(3)$, $c = 23.422(3)$Å, $\beta = 98.06(1)°$, $U = 2133.4$ Å^3, $D_c = 1.24$ g cm^{-3}, $Z = 4$, $F(000) = 848$, μ(Cu-K_α) = 7.2 cm^{-1}, space group $P2_1/c$.

Crystallographic Measurements.—Cell dimensions were derived from least-squares treatment of the setting angles for 25 reflections measured on an Enraf-Nonius CAD4 diffractometer with Cu-K_α radiation. For intensity measurements, 4 856 reflections *hkl* and *hkl* were surveyed in the range $\theta \leqslant 72°$ and 3 222 reflections satisfied the criterion $I > 2.5\sigma(I)$.

Structure Analysis.—The crystal structure was solved by a version of MULTAN[14] adapted for the Glasgow University ICL 2976 computer by Dr. C. J. Gilmore.

The co-ordinates and thermal parameters of the C, N, and O atoms were adjusted by full-matrix least-squares calculations with unit weights and these calculations converged at *R* 0.10. The hydrogen atoms were then located in a difference electron-density distribution and included in the least-squares calculations with isotropic thermal parameters. The weighting scheme was changed to $w = 1/\sigma^2(F)$ and R converged to 0.046, R_w 0.052.

Fourier and least-squares calculations were performed with the SHELX series of programs,[15] and the molecular diagram was prepared with ORTEP.[16]

Observed and calculated structure amplitudes, thermal parameters, hydrogen atom positions, and full details of bond lengths and angles are listed in Supplementary Publication No. SUP23222 (29 pp.).*

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* For details of Supplementary Publications see Notice to Authors No. 7 in *J. Chem. Soc., Perkin Trans. 2*, 1981, Index Issue.

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