The Structure and Stereochemistry of α- and β-Cubebene from the Crystal Structure of Norcubebanone, C₁₄H₂₂O*

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The crystal structure of norcubebanone, $C_{14}H_{22}O$, a conjugated cyclopropyl ketone, has been solved by direct phase-determining methods. The ketone crystallizes in the orthorhombic system with $a = 8.480$ (2), $b = 23.502$ (5), $c = 6.314$ (1) Å, space group $P2_12_12_1$, with four molecules in the unit cell. The structure was refined by full-matrix least-squares methods to a final $R(F) = 0.044$ on 1494 reflections whose intensities were measured to be greater than their estimated standard deviations on a Picker automatic diffractometer with Cu $K\alpha$ radiation. The observed molecular structure, 7(S)-isopropyl-10(R)-methyl-(5R,6R)-tricyclo[4.4.0.0¹,⁵]decan-4-one, establishes the structures of the natural products from which it was derived and provides a precise molecular geometry of the conjugated system.

Introduction

At the time this work was initiated, α- and β-cubebene, isomeric hydrocarbons from the oil of *Piper cubeba* L., had been assigned structures I and II (Fig. 1), respectively, by Ohta, Sakai & Hirose (1966). The chemical evidence adduced by these workers did not establish the stereochemistry at the centers indicated by wavy lines in Fig. 1, nor did it rule out alternative structures of type III (Fig. 2). In order that a rational synthetic scheme for these natural products may be devised, an experiment distinguishing among these structural possibilities was deemed necessary.

Degradation work on the cubebenes is complicated at the outset by the difficulty of separating the α and β

isomers. Ozonolysis of the hydrocarbon mixture followed by treatment with hydrogen peroxide gives, after separation of the acidic products derived from α-cubebene, the norketone IV (Fig. 1) derived from β-cubebene. This crystalline ketone can be reconverted in good yield to β-cubebene by reaction with triphenylphosphinemethylene, demonstrating that no rearrangement has occurred in the ozonolysis.† Crystal structure analysis of the norcubebanone was therefore undertaken to ascertain the structures of the natural products and to determine the accurate molecular geometry of a conjugated cyclopropyl ketone system. The spectral characteristics of norcubebanone given in Fig. 1 indicate some degree of electronic interaction between the three-membered ring and the carbonyl group. A detailed description of the molecular geometry is given in the final section of this paper. A description of the structure solution, which was not straightforward, is also given.

While this work was in progress, structures I, II, and IV were established by a synthesis (Tanaka, Uda &
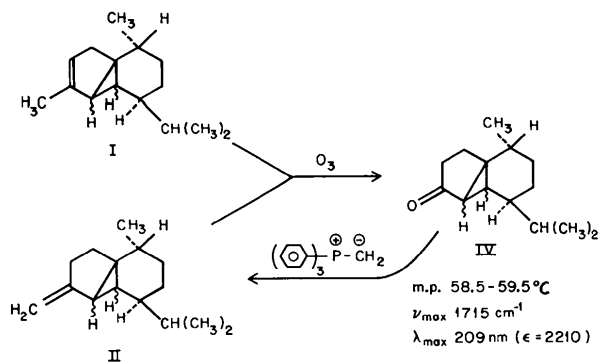
Fig. 1. Structural relationships between α- and β-cubebene and norcubebanone.
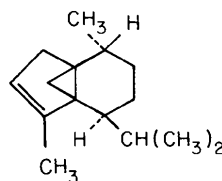
Fig. 2. An alternative structure for α-cubebene.

Yoshikoshi, 1969; Tanaka, Tanaka, Uda & Yoshikoshi, 1972) which produced both possible stereoisomers (note that the ring system constrains the two H atoms in question to be *trans*). Stereochemistry at these centers was then assigned through an interpretation of the circular-dichroism spectra of the two isomeric ketones (IV). The results reported here corroborate that assignment.

Experimental

Preliminary Weissenberg photographs displayed systematic absences ($h00$, $0k0$, $00l$ absent for odd indices) and symmetry uniquely consistent with the orthorhombic space group $P2_12_12_1$. The tendency of the crystalline ketone to sublime at an appreciable rate at room temperature was first noted at this stage. Consequently, a sphere approximately 0·35 mm in diameter, having been selected from several which had been ground from single crystals, was coated with a thin film of white glue (Wilhold's 'Glu-Bird') prior to being mounted on the Picker automatic diffractometer.* A least-squares fit of angle data from 14 reflections ($t = 24\,^\circ C$) yielded the following cell dimensions (on the assumption that $\lambda = 1\cdot54051$ Å for Cu $K\alpha_1$ radiation): $a = 8\cdot4800$ (16), $b = 23\cdot5020$ (54), $c = 6\cdot3138$ (10) Å.

Intensity data for 1597 reflections accessible with Cu $K\alpha$ radiation below $2\theta = 160^\circ$ were measured with the diffractometer in automatic mode by the $2\theta–\theta$ scan technique. Nickel-filtered radiation was used with a scintillation detector and pulse-height analyzer counting device. The count rate was kept below 10^4 counts s^{-1} with an automatic attenuator mechanism. Each scan extended in 2θ from 0·85° below the α_1 peak to 0·85° above the α_2 peak. The scan speed was 1° min^{-1} and background was measured for 40 s at each end of the scan with crystal and counter stationary. Standard deviations, $\sigma(I)$, were calculated (Stout & Jensen, 1968) using an instrumental instability factor of 0·03. The intensities of standard reflections decreased steadily with time, showing that the attempt to prevent sublimation was not entirely successful. This loss of intensity was nearly linear, the final standard measurement showing 58% of the initial intensity. A decay correction employing linear interpolation between successive standards was applied along with Lorentz and polarization corrections. No absorption correction was attempted in view of the uncertainty of the shape of the crystal as it evaporated.

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* The intensity data were collected at the University of California, Davis, in the laboratory of Professor Håkon Hope.

Solution and refinement of the structure

The observed structure factors were put on an absolute scale and corrected by an average isotropic temperature factor by the use of a Wilson-plot program (Dewar & Stone, 1966) to give normalized structure factors E_h. Four zonal reflections of proper parity (Karle & Hauptman, 1956) were chosen from among those with the largest values of E_h for arbitrary phase assignments to define origin and enantiomorph (Table 1). In addition, one general reflection (364) was allowed to take on initial values from 0 to $7\pi/4$ in steps of $\pi/4$ in order to begin the phase determination for the 125 reflections with $E_h > 1\cdot62$ by the tangent formula (Karle & Hauptman, 1956; Karle & Karle, 1966),

$$\tan \varphi_h \simeq A/B,$$

where

$$A = \sum_k |E_k E_{h-k}| \sin(\varphi_k + \varphi_{h-k}),$$

and

$$B = \sum_k |E_k E_{h-k}| \cos(\varphi_k + \varphi_{h-k}).$$

Of the eight sets of phases produced in this way, the four in which φ_{364} had been originally set to a cardinal point (0, π, or $\pm\pi/2$) had values of the inconsistency index

$$Q = \sum_h |E_h|(1 - t_h)/\sum_h |E_h|,$$

where

$$t_h = (A^2 + B^2)^{1/2}/\sum_k |E_k E_{h-k}|,$$

of 0·32 to 0·33. The other four had Q greater than 0·37.

Only one of four of the most self-consistent phase sets is in complete agreement with the Σ_1 predictions listed in Table 1. An E map was accordingly calculated from this set. Of the six strongest peaks in this map, five made up a very plausible arrangement consisting of the expected cyclopropane ring with two more atoms connected to one apex at reasonable distances

Table 1. *Initial values of phases assigned to reflections with large normalized structure amplitudes*

To specify origin and enantiomorph					From Σ_1					
h	k	l	E	φ	h	k	l	E	φ	P_1
1	29	0	3·41	$\pi/2$	0	18	0	2·60	0	0·96
0	9	2	2·90	$\pi/2$	0	28	0	2·30	π	0·19
0	19	1	1·96	$\pi/2$	0	6	6	2·30	π	0·16
10	11	0	2·13	0	2	28	0	1·74	0	0·80

and angles. Fourier methods, using the Sim (1961)/Woolfson (1956) weighting scheme, and refinement of phases by the method of Karle (1968) led to chemically reasonable positions for 12 atoms but also produced obviously spurious peaks. No placement of the remaining atoms from chemical reasoning or from analysis of the Patterson map was found which led to even an approximate agreement of observed and calculated structure factors.

Phase determination of the 193 reflections with $E_h \geq$ 1·47 was therefore attempted, allowing φ_{364} to take values from 0 to $19\pi/10$ in increments of $\pi/10$. These sets converted in 18 to 30 cycles of tangent-formula refinement; and of the three most nearly self-consistent

Table 2. *Final atomic parameters*

(*a*) Positional parameters ($\times 10^4$) for the non-hydrogen atoms

	x	y	z
C(1)	2284 (3)	1631 (1)	4246 (4)
C(2)	2361 (3)	2244 (1)	5047 (5)
C(3)	2795 (3)	2610 (1)	3128 (5)
C(4)	3579 (3)	2205 (1)	1594 (4)
C(5)	3060 (3)	1623 (1)	2075 (4)
C(6)	1277 (3)	1545 (1)	2340 (4)
C(7)	565 (3)	961 (1)	1827 (4)
C(8)	432 (4)	608 (1)	3844 (6)
C(9)	2009 (3)	581 (1)	4965 (6)
C(10)	2519 (3)	1158 (1)	5844 (5)
C(11)	4201 (4)	1136 (2)	6668 (6)
C(12)	-981 (3)	1027 (1)	580 (5)
C(13)	-2301 (4)	1294 (2)	1835 (8)
C(14)	-1503 (5)	469 (2)	-392 (7)
O(15)	4530 (3)	2338 (1)	242 (4)

(*b*) The final parameters ($\times 10^3$) of the isotropically refined atoms

	x	y	z
H(021)	332 (4)	228 (1)	614 (5)
H(022)	138 (4)	238 (1)	569 (6)
H(031)	351 (3)	292 (1)	346 (5)
H(032)	188 (4)	278 (1)	236 (5)
H(051)	365 (3)	128 (1)	159 (4)
H(061)	67 (3)	187 (1)	178 (4)
H(071)	130 (3)	76 (1)	88 (5)
H(081)	7 (4)	24 (1)	357 (6)
H(082)	-45 (4)	80 (1)	486 (6)
H(091)	291 (4)	44 (1)	386 (6)
H(092)	195 (4)	31 (1)	610 (6)
H(101)	186 (4)	126 (1)	708 (6)
H(111)	445 (5)	151 (2)	734 (8)
H(112)	436 (4)	80 (1)	773 (6)
H(113)	489 (4)	105 (2)	543 (7)
H(121)	-74 (4)	129 (1)	-57 (6)
H(131)	-199 (5)	167 (2)	252 (8)
H(132)	-324 (5)	136 (2)	92 (8)
H(133)	-260 (4)	102 (2)	290 (6)
H(141)	-179 (5)	15 (2)	67 (8)
H(142)	-241 (4)	53 (2)	-136 (7)
H(143)	-64 (5)	25 (2)	-125 (7)

sets, two were very similar and had the predicted values for those phases known from Σ_1 (Table 1), but the arbitrary starting value for $\varphi_{1,29,0}$ had been changed from $\pi/2$ to $-\pi/2$, indicating that an important Σ_2 relationship ($\bar{1},29,0$, $3,\bar{15},6$, $2,14,6$) used early in the phasing had a phase-angle sum near π. An E map calculated from the slightly more nearly self-consistent of these two sets revealed positions for 14 of the 15 nonhydrogen atoms among the 21 strongest peaks. One of the methyl C atoms of the isopropyl group was missing but was revealed by a subsequent Fourier synthesis based on all reflections.

Full-matrix least-squares refinement of these atom positions, together with isotropic and then anisotropic temperature factors, reduced $R(F)$ to 0·11. The atomic form factors for nonhydrogen atoms were those given by Hanson, Herman, Lea & Skillman (1964). Those for H were taken from Stewart, Davidson & Simpson (1965). A difference Fourier map showed peaks corresponding to calculated positions for all 22 H atoms. Further refinement (keeping H atoms isotropic) reduced $R(F)$ to 0·053 and showed clearly that the strongest reflections suffered from extinction. An isotropic extinction correction was applied; the value of the extinction parameter, g, was treated as a variable in the refinement (Zachariasen, 1967).

The function minimized was $\Sigma\, w(|F_o|^2 - yK^2|F_c|^2)^2$, where K is a scale factor, $y = (1 - gy|F_c|^2)^{-1/2}$, y is defined in the appendix of Coppens & Hamilton (1970) with the mean path length $\bar{T}$ taken as 0·2 mm for all reflections and $w = 1/\sigma^2(|F_o|^2)$ if $\sigma(|F_o|^2) \leq |F_o|^2$ and $w = 0$ otherwise. This removal of unobserved reflections from the refinement was a precaution adopted because the shutter did not always operate properly during the data collection. Inspection of the final observed and calculated structure factors indicates that between 10 and 14 reflections may have been affected by this systematic error. The $R(|F|)$ on all data was 0·0490, compared with 0·0437 for those included in the refinement. The corresponding values of $R(|F|^2)$ were 0·0467 and 0·0459 respectively.[*][†] The final positional parameters are listed in Table 2.

Comparison of the final structure with the partial false structure found earlier revealed that C(1), C(5) and C(6), which comprise the three-membered ring and have approximately the same y coordinates, are inverted through a point in the false structure to give another grouping having nearly the same set of interatomic vectors. The rest of the false structure is then made up of correct interatomic vectors springing from the incorrect positions.
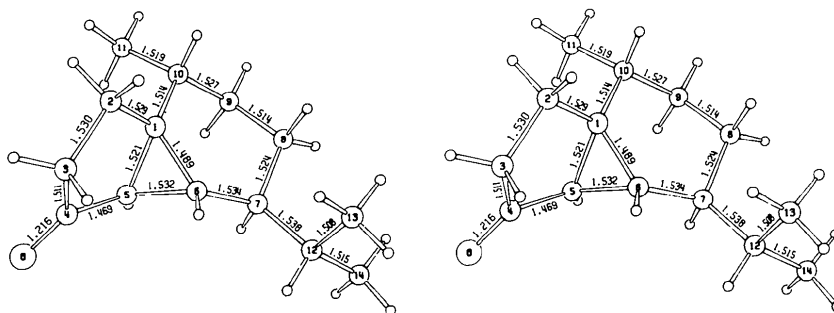
Fig. 3. Stereoscopic view of the norcubebanone molecule. Bond lengths (Å) are uncorrected for thermal motion and have standard errors of about 0·004 Å.

Description of the structure

The final structure corroborates the gross structure of Ohta, Sakai & Hirose (1966) and confirms the stereochemistry which had been inferred from spectral data (Tanaka, Tanaka, Uda & Yoshikoshi, 1972). The absolute configuration indicated is correct, since it has been shown (Ohta, Sakai & Hirose, 1966) that treatment of α-cubebene with dry HCl in ether yields (—)-cadinene hydrochloride, the absolute configuration of which is known.

The conjugation in the cyclopropyl ketone moiety inferred from spectral observations is strikingly verified in the geometry of the molecule (Figs. 3 and 4): (1) The length of the bond C(4)—C(5) connecting the cyclopropane ring to the carbonyl C atom is 1·469 Å, as short as the corresponding bond in α,β-unsaturated
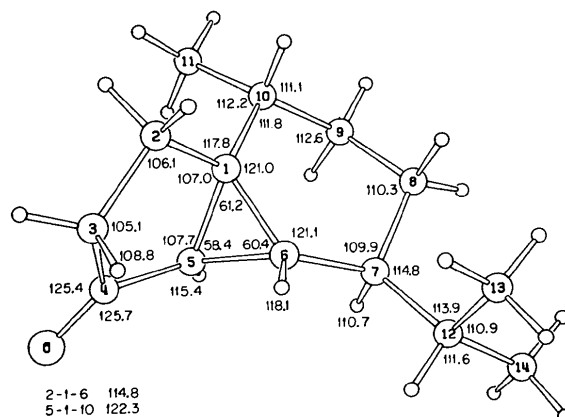
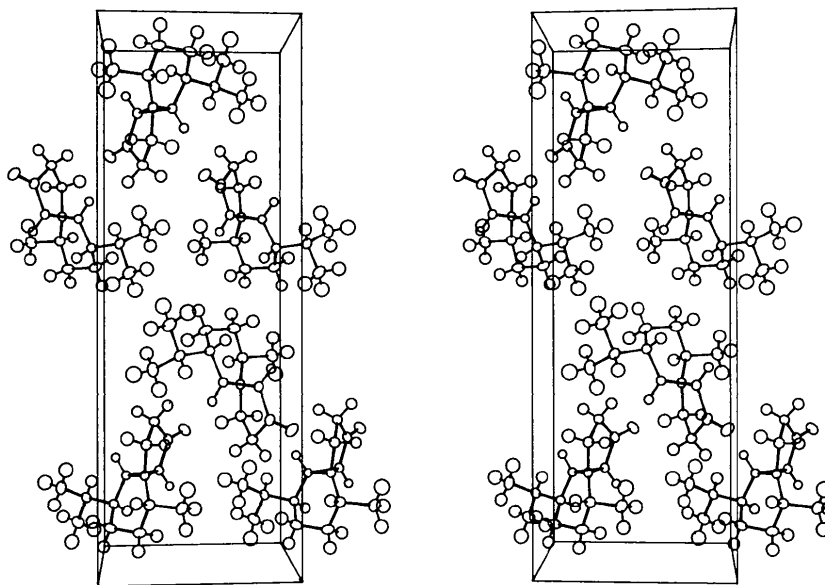

Fig. 4. Valence angles (°) in the norcubebanone molecule.

Fig. 5. Packing diagram viewed in the c direction. The origin is at the lower left-hand rear corner; a is horizontal and b is vertical.

ketones and much shorter than the typical sp^3–sp^2 bond, C(3)–C(4) 1·511 Å, on the other side of the carbonyl. (2) The two bonds of the three-membered ring involved in conjugation, C(1)–C(5) and C(5)–C(6) (1·521 and 1·532 Å), are appreciably longer than C(1)–C(6), 1·489 Å, which is not involved. (3) The five-membered ring is, of course, not planar but puckered; that is, C(3) is out of the plane of the other atoms to avoid the eclipsing of the H atoms connected to C(2) and C(3). The direction of the puckering is puzzling at first glance – the distance between the H pointing forward from C(3) (Fig. 3) and the H on C(6) is 2·40 Å, fully 0·1 Å shorter than any intermolecular H–H contact in the structure, whereas if C(3) had puckered the other way, no apparent disruption of the packing (Fig. 5) would have resulted. Fig. 6 is a Newman projection looking down the C(5)–C(4) bond. Of the two possible puckering directions depicted, the one actually observed (a) tends toward a situation in which the carbonyl bisects the three-membered ring, whereas the alternative (b) tends away from this geometry. Electron diffraction studies of cyclopropanecarboxaldehyde (Bartell & Guillory, 1965), cyclopropyl methyl ketone, and cyclopropanecarboxylic acid chloride (Bartell, Guillory & Parks, 1965) show that the favored conformations are those in which the carbonyl does bisect the ring to maximize conjugation. Evidently the H–H contact costs less energy than is gained by increased orbital overlap.
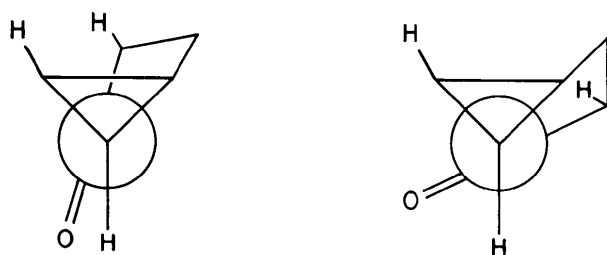
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Fig. 6. Newman projections showing the two possible conformations of the five-membered ring.