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THE STRUCTURE AND ABSOLUTE CONFIGURATION OF CHONDROCOLACTONE, A HALOGENATED MONOTERPENE FROM THE RED ALGA CHONDROCOCCUS HORNEMANNI, AND A REVISED STRUCTURE FOR CHONDROCOLE A

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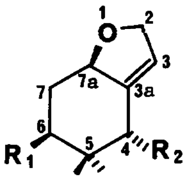
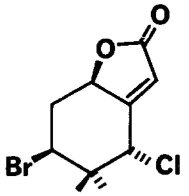
In an investigation of volatile compounds from Hawaiian marine algae,[2] we found that a cyclic halogenated monoterpene, chondrocole A, is a major constituent in the essential oil of a Chondrococcus hornemanni found in the vicinity of the Halona Blowhole, Oahu. From spectral evidence, mainly PMR and mass spectral data, we assigned structure 1 to chondrocole A.[3] Further study, however, in particular an X-ray crystallographic analysis of a closely-related metabolite, chondrocolactone (2), has now shown that this structure is incorrect and that chondrocole A has structure 3.



1 $R_1 = Cl, R_2 = Br$
3 $R_1 = Br, R_2 = Cl$



2

Chondrocolactone (2) was isolated from the CH_2Cl_2 extract of the alga, using conventional silica gel chromatography (elution with 1:1 CH_2Cl_2-hexane), as colorless needles, mp 107-108° (recrystallization from CH_2Cl_2-hexane); $[\alpha]_D^{24}$ -48° (CH_2Cl_2, c 0.62). The PMR spectrum of 2 (Table 1) was similar to that of 3 except that the signal for the C-2 protons was missing. The presence of an oxo group on C-2 (α,β-unsaturated γ-lactone functionality) was indicated by the

Table I. NMR Data for Chondrocole A (3) and Chondrocolactone (2) in $CDCl_3$

3	2			
^{13}C δ[a]	Carbon No.	^{13}C δ[a]	^{1}H δ[a]	Multiplicity; J(Hz)
75.4	2	171.0		
122.3	3	115.4	6.97	d; $J_{3,7a} = 2$
137.6	3a	164.4		
63.8[b]	4	60.8	4.78	s
41.7	5	42.3		
54.4[b]	6	51.0	4.40	dd; $J_{6,7ax} = 13$, $J_{6,7eq} = 4$
41.7	7	40.0	1.95(ax) 2.94(eq)	ddd; $J_{6,7ax} = 13$, $J_{7ax,7eq} = -12$, $J_{7a,7ax} = 11$ ddd; $J_{6,7eq} = 4$, $J_{7ax,7eq} = -12$, $J_{7a,7eq} = 6$
80.7	7a	76.9[c]		ddd; $J_{3,7a} = 2$, $J_{7a,7eq} = 6$, $J_{7a,7ax} = 11$
21.0, 27.6	10, 11	20.5, 26.9	1.07 1.32	s s

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[a] In ppm using TMS as an internal reference (δ=0). [b] ^{13}C-^{1}H correlation based on single frequency off resonance decoupling (SFORD) experiments; C-4 and C-6 protons for 3 are at δ 4.64 and 4.45, respectively (see ref. 3). [c] Coincidental with $CDCl_3$ signal in proton noise decoupled (PND) spectrum; signal observed as doublet in SFORD spectrum (decoupler at δ14).

UV [λ_{max}^{EtOH} 229.5 (ε 3900)], IR (ν_{max}^{nujol} 1760 cm^{-1}), and CMR (δ 171.0) spectra. The mass spectrum of 2 showed a small 1:1.5:0.4 molecular ion cluster at m/e 278, 280, 282 ($C_{10}H_{12}BrClO_2$) and, similar to the mass spectrum of 3,[3] an intense 3:1 fragment ion cluster at m/e 199 (base peak), 201 for loss of bromine from the molecular ion. Oxidation of 3 with chromic acid gave 2, identical in all respects including optical rotation, $[\alpha]_D^{24}$ -50° (CH_2Cl_2, c 1.2), with natural 2

Preliminary X-ray photographs of 2 showed that the crystals belonged to the orthorhombic crystal class. Accurate cell constants, determined by least squares refinement of fifteen moderate angle reflections, were $\underset{\sim}{a}$ = 7.111(5), $\underset{\sim}{b}$ = 11.547(7) and $\underset{\sim}{c}$ = 13.821(12) Å. Systematic extinctions and the known chirality indicated space group $P2_12_12_1$. A calculated (z=4) and observed density of ∿1.0 g/cc indicated one molecule formed the asymmetric unit. All unique diffraction maxima with $2\theta \leq 114°$ were collected on a fully automated four circle diffractometer using graphite monochromated CuKα (1.54178 Å) radiation and a variable speed ω-scan. Periodically monitored check reflections showed an ∿10% decline during data collection. No allowance for this presumed crystal decomposition has been made. A total of 911 reflections were surveyed in this manner and after correction for Lorentz, polarization and absorption effects, 747 (81%) of these were judged observed ($I \geq 3\sigma(I)$).

The structure was solved by conventional heavy atom techniques. A three-dimensional Patterson synthesis[4] was deconvoluted to determine the bromine position and the remaining nonhydrogen atoms were located on successive F_o-syntheses. Most of the hydrogens were located on a final difference synthesis but some were put in at calculated positions. Full matrix least-squares refinements with anisotropic temperature factors for all nonhydrogen atoms and isotropic hydrogens converged smoothly. Anomalous scattering factor corrections for the bromine and chlorine were introduced and refinement continued. The final crystallographic residual for the structure was 0.071 for the observed reflections and a significantly higher[5] 0.076 for the enantiomer. The temperature factors of the hydrogens were held fixed during the final cycles.

Figure 1 shows a computer generated perspective drawing of the final X-ray model.[1] Hydrogen atoms are omitted for clarity. There were no abnormally short intermolecular contacts or substantial electron density in a final difference synthesis. In general the metric details agree well with accepted values. The three chiral centers have the following absolute configurations: 4(_S_), 6(_S_) and 7a(_R_). The unsaturated γ-lactone ring is planar; the largest deviation from the least squares plane is 0.01 Å. The cyclohexane ring is in a slightly distorted chair conformation. The chlorine at C(4) is in an axial orientation and the bromine at C(6) is equatorial.

Chondrocole A therefore has the structure and absolute configuration depicted in **3**. Our error in originally concluding structure **1** was due to a mass spectral misinterpretation whereby we assigned the bromine to the allylic C-4 position on the basis of an intense M-Br peak. A similar mass spectral misinterpretation led to an incorrect structure for violacene-1, and this structure was subsequently revised after an X-ray study.[6] In our case the positions of the bromine and chlorine could have been decided from correlating the C-4 and C-6 PMR and CMR signals (Table 1). In some cases, however, CMR data has not provided an unambiguous answer.[7]

REFERENCES AND NOTES

1. Address any correspondence to this author to the Department of Chemistry, Cornell University, Ithaca, NY 14853. Additional crystallographic details, i.e. tables of fractional coordinates and thermal parameters, bond distances, bond angles, and observed and calculated structure factors, are available on request.

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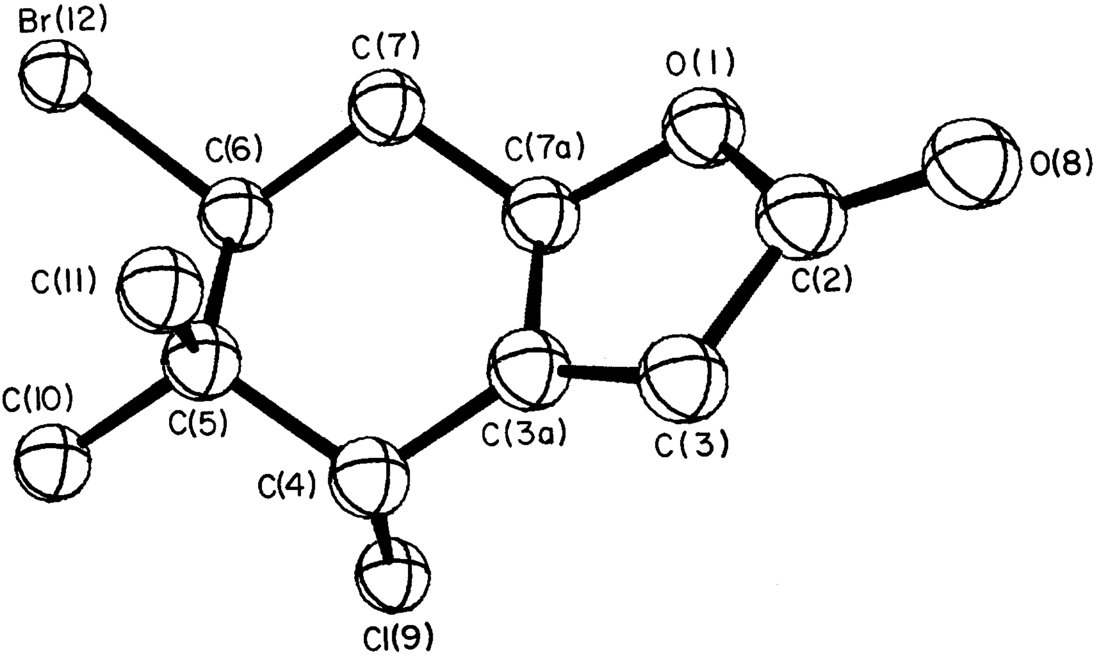

FIGURE 1