Molecular Structure of Guayulin A

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MOLECULAR STRUCTURE OF GUAYULIN A

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Guayulin A (**1**) is a principal component of the resin of the Mexican rubber plant, guayule [*Parthenium argentatum* (Gray)], a common desert shrub in the southwestern United States. Guayule was the main source of rubber in the U.S. during the early part of this century, before being supplanted by rubber from Asian rubber-tree plantations and later by synthetic rubbers. The projected future of natural rubber needs, production, and prices, as well as national security considerations, have promoted a concerted program, sponsored by both government and industry, to reestablish a domestic U.S. rubber industry based on guayule (1). Annual production of guayule rubber is expected to be 500-1500 million pounds by the year 2000 (2,3). Guayulin A comprises 8-10% of the resin (4,5) which is obtained as a by-product in about equal weight with rubber (6). At the predicted levels of guayule rubber production, guayulin A will conceivably be available in amounts of 40-150 million pounds per year. It thus has potential as a source of chiral synthons obtainable in industrial quantities. Preliminary studies in our laboratories indicate potential biocidal uses of certain derivatives of guayulin A.

Guayulin A was first isolated in 1911 (7) and was later assigned an incorrect structure along with the name "partheniol" for the sesquiterpene alcohol (8). A correct structure was determined by Romo and co-workers (9), who gave the compound its present common name. It has recently been found to be a potent contact allergen (10).

The chemistry and potential applications of guayulin A have not been extensively studied. Configuration at chiral centers and conformation of the decadiene ring (**2**) have remained uncertain. Both the transannular cyclization and the Cope rearrangement of cyclodeca-1,5-dienes require a specific geometry in regard to the endocyclic double bonds, with different conformations leading to various derivatives (11,12). Because of its biological activity and its potential value as a precursor for stereospecific specialty chemicals, we have eliminated structural uncertainties by an X-ray crystal structure determination.
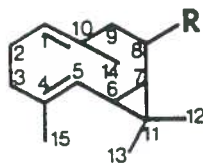
1   R = −OOCCH=CHC$_6$H$_5$
2   R = −H

Guayulin A was isolated from the Me$_2$CO extract of dried aerial parts of guayule plants obtained from the University of California, Riverside, Guayule Breeding Program. A clear, pale yellow crystal grown from CHCl$_3$ solution, measuring $0.28 \times 0.44 \times 0.66$ mm, was used for data collection at 21° on an Enraf-Nonius CAD4 automatic diffractometer with CuKα radiation

($\lambda = 1.54184$ Å) and a graphite monochromator.

A preliminary survey revealed the crystal system to be tetragonal, and systematic absences ($00\ell. \ell \ne 4n$; h00:h $\ne$ 2n) indicated the space group to be one of the enantiomorphous pair $P4_12_12$ or $P4_32_12$. The latter was assumed in order that the absolute configuration be consistent with that of known germacranolide sesquiterpenes from higher plants (13, 14). Cell dimensions, determined by a least squares fit of setting angles of 24 reflections having $68° < 2\theta < 72°$, are: $a = 10.426(1)$, $c = 38.749(5)$Å, $V = 4214.1(8)$Å^3, D (calcd) $= 1.105$ g cm^{-3}, $Z = 8$, μ(CuKα) $= 5.4$ cm^{-1}. Intensity data were collected by ω-2θ scans from one unique hexadecant: $0 \le k \le 12$, h $\le$ k, $0 \le \ell \le 47$, $4° < 2\theta < 140°$. Three standard intensities were periodically remeasured, on the basis of which a 4% linear decay correction was applied. Several ψ scans indicated absorption effects to be insignificant. A total of 2365 unique intensities was measured, of which 2221 with I>0 were used in the refinement.

The structure was solved using direct methods program RANT (15) and refined by full-matrix least squares using the Enraf, Nonius SDP (16). Carbon and oxygen atoms were treated anisotropically; hydrogen atoms were located from difference maps, and except for those on

C6 and C7, were included as fixed contributions. Hydrogen atoms H6 and H7 were refined isotropically. A secondary extinction coefficient refined to a value of $1.0(1) \times 10^{-6}$. Final agreement indices were $R = 0.049$, $R_w = 0.059$, error of fit $= 1.85$ for 2221 data and 244 variables; the maximum residual electron density was 0.18eÅ^{-3}. Refinement in $P4_12_12$ in an attempt to directly determine the absolute configuration was inconclusive.

Fractional coordinates for guayulin A are given in Table 1,[1] and the molecular structure is illustrated in Figure 1. The relative configurations of the three chiral centers are determined: the cyclopropane ring is cis-fused to the main ring and β-oriented, while the cinnamate group is α-oriented. The conformation of the ten-membered ring is specified by the torsion angles in Table 2. The endocyclic double bonds are trans-trans and are oriented in crossed fashion which is required for favorable Cope reaction transition states (12). Both double bonds are twisted from planarity, probably due to steric crowding of the syn-oriented vinyl methyls [C14 . . . C15

TABLE 1. Coordinates for Guayulin A

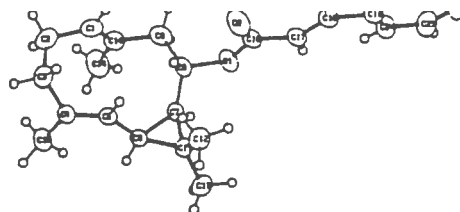| Atom	x	y	z	Atom	x	y	z
O1	−0.0669(2)	0.3341(2)	−0.02838(3)	C12	−0.1955(2)	0.1453(2)	0.03619(5)
O2	0.0359(2)	0.1531(2)	−0.04054(4)	C13	−0.3491(2)	0.3314(3)	0.04504(6)
C1	0.2420(3)	0.3843(3)	0.05219(6)	C14	0.1217(4)	0.5910(3)	0.05404(6)
C2	0.2886(3)	0.3828(3)	0.08908(7)	C15	0.0257(3)	0.4425(3)	0.13328(6)
C3	0.2032(3)	0.2925(3)	0.11140(6)	C16	−0.0361(2)	0.2359(2)	−0.04851(5)
C4	0.0651(2)	0.3374(2)	0.10947(5)	C17	−0.1047(2)	0.2474(3)	−0.08195(5)
C5	−0.0050(2)	0.2948(2)	0.08293(5)	C18	−0.0949(2)	0.1633(3)	−0.10674(6)
C6	−0.1199(2)	0.3546(2)	0.06806(5)	C19	−0.159(X2)	0.1674(3)	−0.14020(5)
C7	−0.1174(2)	0.3834(2)	0.02892(5)	C20	−0.1492(3)	0.0631(3)	−0.16247(6)
C8	−0.0086(2)	0.3437(2)	0.00622(5)	C21	−0.2102(4)	0.0638(4)	−0.19401(6)
C9	0.1013(3)	0.4398(2)	0.00330(6)	C22	−0.2799(3)	0.1691(4)	−0.20421(6)
C10	0.1647(2)	0.4680(2)	0.03767(5)	C23	−0.2891(3)	0.2760(4)	−0.18313(6)
C11	−0.2119(2)	0.2876(2)	0.04363(5)	C24	−0.2276(3)	0.2739(3)	−0.15131(6)

FIGURE 1. Perspective drawing of guayulin A.

TABLE 2. Endocyclic Torsion Angles on Guayulin A

Atom 1	Atom 2	Atom 3	Atom 4	Angle
C1	C2	C3	C4	−57.9
C2	C3	C4	C5	85.7
C3	C4	C5	C6	−156.6
C4	C5	C6	C7	124.9
C5	C6	C7	C8	4.8
C6	C7	C8	C9	−88.6
C7	C8	C9	C10	60.6
C8	C9	C10	C1	163.0
C9	C10	C1	C2	
C10	C1	C2	C3	95.9

stance, 3.582(3)Å], and probably increasing the reactivity of the vinyl groups. Guayulin A is unstable in acidic conditions, leading to transannular cyclization products. A very similar ring conformation has been reported for a cyclogermacrene isolated from *Citrus* nos by Nishimura and co-workers and identified using nOe measurements (17,18).

Bond distances and angles are normal with standard deviations 0.002-0.004Å and 0.1-0.2°.

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