GUAYULINS C AND D FROM GUAYULE
(PARTHENIUM ARGENTATUM)

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A recent evaluation of the by-products of processing rubber from the desert shrub guayule (Parthenium argentatum Gray) included quantitative assessments of two unidentified resin constituents termed sesquiterpenes C and D (1). These are identified here as two new natural products, guayulin C, 4β-hydroxy-8α-p-cinnamoyloxy aromadendrene (1), and guayulin D, 4β-hydroxy-8α-p-anisoyloxy aromadendrene (2).

Compounds 1 and 2 were isolated from the resinous by-product of guayule rubber processing and identified by their nmr and ms spectra. The aromadendrene diol (3), obtained by basic hydrolysis of either ester, is the same as that recently reported for an X-ray crystallographic structure (2). A sample of 3 used in the X-ray structure was obtained and its

the guayulins C and D may be artifactual as their concentration in the stored resin increases with time.[1] An hplc analysis of Me_2CO extracts of fresh leaves and stems showed that both are naturally occurring compounds.

The biogenic precursors of guayulins C and D are probably the bicyclogermacrenes guayulin A (4) and guayulin B (5), respectively, both principal constituents of guayule resin (1). Both guayulins C and D were produced in high yield in one step by epoxidation of either guayulin A or B with $mcpba/CH_2Cl_2$. This transformation involves formation of the bicyclogermacrene epoxide which undergoes immediate cyclization in the Markownikoff manner followed by an elimination to the aromadendrene. We recently established that guayulin A

4 R= -COCH=CHC₆H₅
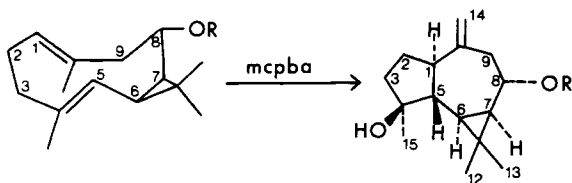
4   R= -COCH=CHC₆H₅
5   R=-p-COC₆H₄OCH₃

1   R=-COCH=CHC₆H₅
2   R=-p-COC₆H₄OCH₃
3   R=-H

identity as the guayulin C and D hydrolysate was determined by the mixed melting point (156.5-157.5°, no mp suppression) and by their 250 MHz [1]H-nmr spectra. The absolute configurations of compounds 1-5 have not been determined. Concern was expressed that

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[1]W.W. Schloman, personal communication.

exists in a conformation with the endocyclic double bonds oriented perpendicular to one another and with protons at H-1 and H-5 parallel in the β direction as indicated for 4 (3). A transannular cyclization from this conformation would lead to an aromadendrane with H-1 and H-5 cis, which is not the structure of guayulins C and D. Examination

of Dreiding models indicates that the 4, 5 epoxide of guayulin A in the crossed conformation is sterically unfavorable, and that rotation of the 1(10) vinyl group must occur before ring closure can lead to **1**.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Guayule resin from rubber processing was obtained from the Goodyear Tire and Rubber Company. Fresh guayule leaf and stem material were obtained from the University of California, Riverside, Guayule Breeding Program. A voucher specimen (no. 22, 992) is on deposit at the Museum of Systematic Biology, University of California, Irvine. Guayulins A-D were isolated from the processed resin by Si gel chromotography with hexane/EtOAc gradient elution and recrystallized from hexane/CHCl$_3$. Migration of guayulins A, B, C, and D on Si gel tlc, hexane-EtOAc (70:30) give respective Rf values of 0.79, 0.70, 0.28, and 0.23. An hplc analysis (C18 RP column, MeOH/H$_2$O gradient elution, detection at 215 nm) of an overnight MeOH extract of freshly harvested plants was made and co-chromatographed with guayulin C and D to confirm their presence in the plant.

Guayulin C (**1**).—Mp 111-112°; $[\alpha]^{26}$D= −7.8° (CHCl$_3$, 2.95%); ^{1}H nmr (250 MHz, CDCl$_3$) δ 7.63 (1H, d, J=16 Hz, H-3'), ca. 7.33 (5H, m, aryl), 6.38 (1H, d, J=16 Hz, H-2'), 4.83 (2H, s, H-14), 4.63 (1H, dt, J=4, 10 Hz, H-8), 2.59 (1H, dd, J=4, 11 Hz, H-9β), 2.47 (1H, dd, J=10, 11 Hz, H-9α), 2.10 (1H, m, H-1), 1.31 (1H, t, J=10 Hz, H-5), 1.30 (3H, s, H-15), 1.15 (3H, s, H-12 or H-13), 1.11 (3H, s), 1.00 (1H, t, J=10 Hz, H-7), .67 (1H, t, J=10 Hz, H-6); ^{13}C nmr (75 MHz, CDCl$_3$) δ 165.8 (s, C1'), 147.5 (s, C10), 144.5 (d, C3'), 134.5 (s, C4'), 130.1 (d, C7'), 128.8 (d, C6',8'), 128.0 (d, C5',9'), 118.6 (d, C2'), 110.2 (t, C14), 80.8 (s, C4), 72.6 (d, C8), 54.6 (d, C5), 52.0 (d, C1), 46.1 (t, C9), 41.6 (t, C3), 31.9 (d, C7), 28.2 (d, C6), 28.1 (q, C12), 26.7 (t, C2), 25.7 (q, C15), 20.8 (s, C11), 16.2 (q, C13); ms (70 eV) *m/z* (rel. int.) 366 (3, M+), 218 (24), 200 (31), 147 (27), 104 (100).

Guayulin D (**2**).—^{1}H nmr 7.95 (2H, d, J=9 Hz), 6.82 (2H, d, J=9 Hz) 3.85 (3H, s), shifts of terpenoid protons were the same as for guayulin C; ms (70 eV) *m/z* (rel. int.) 236 (3.7, M+-C$_8$H$_7$O$_2$), 218 (1.3), 200 (1), 109 (84), 81 (100).

Synthesis of guayulin C from guayulin A.— Solid *m*-chloroperbenzoic acid (43 mg) was added in small portions to a stirred mixture of guayulin A (75 mg) in CH$_2$Cl$_2$ (10 ml) and 0.5 M aqueous NaHCO$_3$ (1.5 ml, pH 8.3). After 5 h at room temperature, the product was isolated in the usual manner. Yield of guayulin C was 70%.

Aromadendrene diol (**3**).—The compound was obtained by alkaline hydrolysis of both guayulins C and D (0.4 M KHCO$_3$ in 80% MeOH, reflux 6 h); mp 156-157.5°; $[\alpha]^{26}$D= +7.1° (CHCl$_3$, 1.71%); ^{1}H nmr (250 MHz, CDCl$_3$) δ 4.77 (2H, s, H-14), 3.44 (1H, dt, J=3,9 Hz, H-8), 2.51 (1H, dd, J=3, 12 Hz, H-9β), 2.38 (1H, dd, J=9, 12 Hz, H-9α), 2.10 (1H, m, H-1) 2.0-1.5 (6H, H-2, 3, OH), 1.26 (3H, s, H-15), 1.18 (1H, t, J=9 Hz, H-5), 1.13 (6H, s, H-12, 13), .77 (1H, t, J=9, H-7), .57 (1H, t, J=9, H-6); ^{13}C nmr (75 MHz, CDCl$_3$) δ 148.7 (s, C10), 109.3 (t, C14), 80.9 (s, C4), 70.1 (d, C8), 54.3 (d, C5), 52.0 (d, C1), 49.0 (t, C9), 41.6 (t, C3), 34.4 (d, C7), 29.0 (d, C6), 28.4 (q, C12), 26.7 (t, C2), 25.9 (q, C15), 20.4 (s, C11), 15.9 (q, C13).

LITERATURE CITED

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