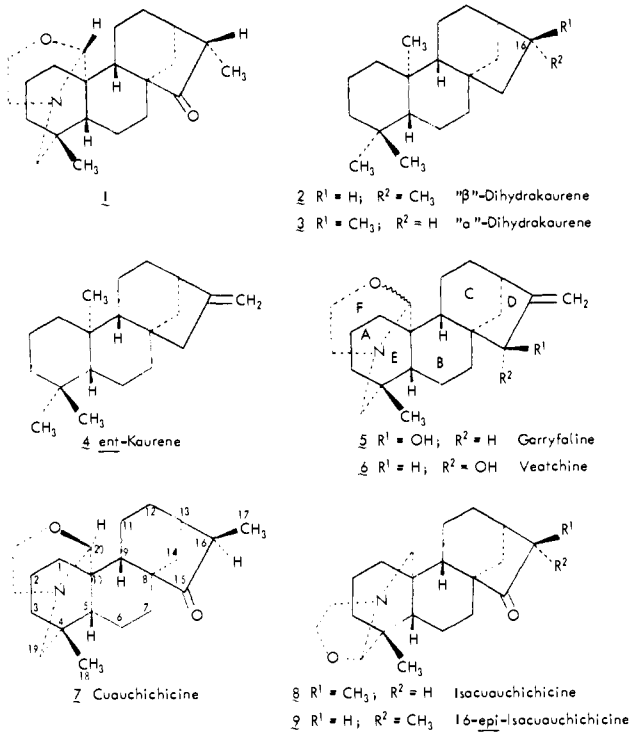
Communications to the Editor

Structure of Cuauchichicine. Its Chemical Correlation with (−)-"β"-Dihydrokaurene

Sir:

During a recent investigation of the constituents of the bark and leaves of *Garrya ovata* var. *lindheimeri*, we isolated cuauchichicine and garryfoline, as well as two new alkaloids.[1] In earlier work, the stereochemistry of the C(16) methyl group in cuauchichicine was assigned the α configuration (**1**) on the basis of chemical correlation of cuauchichicine azomethine with (−)-"β"-dihydrokaurene (**2**).[2,3] The structure of the latter, a minor hydrogenation product of *ent*-kaurene (**4**),[4,5] was assigned on the basis of the behavior of *ent*-kaurene during hydrogenation.[2,5] Our recent observation[6,7] that the normal-type oxazolidine-ring-containing alkaloids, e.g., garryfoline[1] (**5**) and veatchine (**6**), exist as a mixture of epimers at C(20) prompted us to reinvestigate the structure of cuauchichicine. We now have revised the structure of cuauchichicine to **7** on the basis of a ^{13}C NMR spectral analysis and single-crystal X-ray crystallography (Figure 1).



The incorrect structure (**1**) originally assigned[2] to cuauchichicine requires that either the structure of the final degradation product, (−)-"β"-dihydrokaurene (**2**), is incorrect, or that epimerization of the C(16) CH_3 group occurred somewhere in the correlation sequence. Because the structural assignments of almost 100 natural products depend on (−)-"β"-dihydrokaurene, we have reinvestigated the structure of this key diterpene. Catalytic hydrogenation of a small sample of *ent*-kaurene,[4] mp 49–50 °C, $[\alpha]^{26}_D$ −71.4° (*c* 1.0, $CHCl_3$), gave a mixture of *ent*-kauranes consisting mainly of a compound, mp 84.5–85.0 °C, $[\alpha]^{25}_D$ −34.6° (*c* 0.479, $CHCl_3$), identified as (−)-"α"-dihydrokaurene (stevane A[8]), lit.[5] mp 83–84 °C, $[\alpha]^{21}_D$ −32°. The "β" epimer was produced in too small a yield to permit isolation in a pure state. A single-crystal

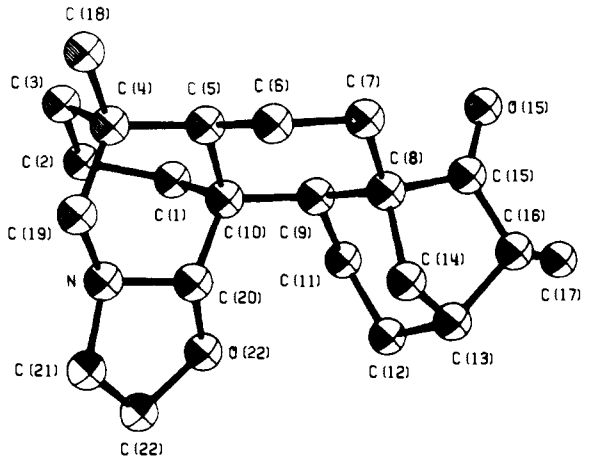


Figure 1. ORTEP drawing of cuauchichicine.

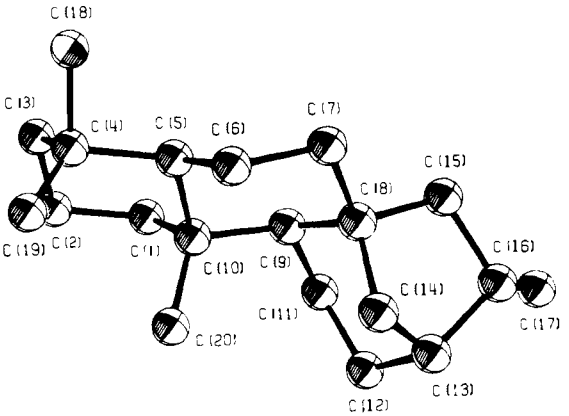


Figure 2. ORTEP drawing of (−)-"α"-dihydrokaurene.

X-ray structure analysis of (−)-"α"-dihydrokaurene demonstrates the structure to be **3** (Figure 2), and therefore the structure of the epimeric (−)-"β"-dihydrokaurene must be as originally assigned,[2,5] i.e., structure **2**.

A large, clear, plate-like crystal of (−)-"α"-dihydrokaurene was chosen for data collection. The crystal belonged to the acentric monoclinic space group $P2_1$ with a = 11.489 (1) Å, b = 6.296 (1) Å, c = 11.995 (7) Å, and β = 100.58 (2)°. Intensities for all unique reflections with $\theta \leq 60.0°$ were measured with ω–2θ scans and Cu Kα radiation on an Enraf-Nonius CAD-4 diffractometer, and 65% of these were judged observed on the basis of counting statistics. The structure was solved by direct methods and has refined to a standard R factor of 5.4%.[9,10]

The above results indicate that epimerization at C(16) must have occurred during degradation of cuauchichicine azomethine to (−)-"β"-dihydrokaurene. This unanticipated epimerization most likely occurred during Wolff-Kishner reduction of the intermediate ketone and accounts for the error in the assignment of configuration of the C(16) methyl in cuauchichicine azomethine[2] and therefore in cuauchichicine.[2b]

Cuauchichicine, $C_{22}H_{33}NO_2$, mp 152–154°C (cor), $[\alpha]^{18}_D$ −69° (*c* 1.0, $CHCl_3$), isolated from the leaves of *G. ovata* var. *lindheimeri*, was identified by comparison with an authentic

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specimen prepared by the acid-catalyzed rearrangement of garryfoline.[11] The 100-MHz ^{1}H NMR spectrum shows a sharp singlet at δ 0.81 for the C(4) methyl group, a doublet centered at δ 1.11 for the C(16) methyl group, a broad singlet at δ 2.65 for the C(19) methylene group, and a broad singlet at δ 4.29 for the C(20) proton. Comparison of the ^{13}C NMR spectrum of cuauchichicine in $CDCl_3$ with that of veatchine and garryfoline revealed the presence of *a single set of signals* for the oxazolidine ring F, the piperidine ring E, and the methyl groups at C(4) and C(16). This result indicates that cuauchichicine exists as a single C(20) epimer with the C(20) proton in the α configuration. Early work on the configuration of garryfoline assumed, without evidence, a β configuration for the C(20) proton.[12] Since cuauchichicine had been chemically correlated with garryfoline,[11] the β configuration was presumed for the C(20) proton in cuauchichicine.[2b]

To establish the stereochemistry of the C(16) methyl group in cuauchichicine by ^{13}C NMR spectral analysis, isocuauchichicine (**8**) and its C(16) methyl epimer (**9**) were prepared from cuauchichicine by boiling them in a solution of 2% sodium hydroxide in methanol. These epimers were separated by careful column chromatography over alumina using hexane and benzene as eluants. Comparing molecular models of compound **8** and its epimer **9** reveals that the methyl group at C(16) is spatially crowded in the β position in contrast to the α position. The chemical shift of the β-methyl group should appear at higher field than that of the α-methyl group because of steric compression. Accordingly, we have assigned the chemical shifts at 10.15 and 15.95 ppm to the β- and α-methyl groups in **8** and **9**, respectively. These results provide evidence for the presence of the β-methyl group at C(16) (10.15 ppm) in cuauchichicine, and therefore structure **7** may be assigned to cuauchichicine. This assignment was confirmed subsequently by a single-crystal X-ray analysis of cuauchichicine.

Cuauchichicine formed large, clear crystals with orthorhombic symmetry, space group $P2_12_12_1$, $Z = 4$, $a = 7.373$ (3) Å, $b = 10.370$ (4) Å, $c = 24.877$ (8) Å, and $d_{calcd} = 1.19$ g/cm^3. All unique reflections with $\theta \leq 60°$ were measured with an ω-2θ scan technique on an Enraf-Nonius CAD-4 diffractometer using Cu Kα radiation ($\lambda = 1.5418$ Å). There was no indication of crystal decomposition during data collection. Data were corrected for Lorentz and polarization effects before conversion to structure factor amplitudes. Out of 1672 measured reflections, 1180 (70.6%) were observed at the 3σ level of significance. The structure (Figure 1) was solved with a multiple-solution tangent formula program[9] and refined using the programs of the X-RAY system.[10] Anisotropic refinements of the nonhydrogen atoms and isotropic refinements of the hydrogens converged at $R = 0.071$ and $Rw = 0.083$ for the observed reflections. At the conclusion of refinement a difference electron density map showed no peaks >0.27 e Å^{-3}.

Cuauchichicine (**7**) has the veatchine skeleton with a C(16) β-methyl group and a carbonyl functionality at C(15). In contrast to veatchine, it exists as only one C(20) epimer in the solid state.[7] Comparison of the dihedral angles of cuauchichicine with those of veatchine shows that the major conformational differences between the two structures are in rings D and F. Ring D approximates an envelope conformation in veatchine with C(14) as flap, while in cuauchichicine it is in the twist conformation. The oxazolidine ring F is disordered in veatchine and exists both in the twist conformation and in the envelope conformation with C(20) as flap. In cuauchichicine this ring assumes an N-flap envelope conformation. One of the C(14) hydrogens is much closer to the α side of C(20) in cuauchichicine than in veatchine (2.65 compared to 2.96 Å), and it may be this close contact which prevents formation of the second cuauchichicine epimer during isolation via the ternary imminium salt. Both atisine[13] and cuauchichicine[2] have been correlated with veatchine. Cuauchichicine, therefore, has the absolute configuration determined for atisine by X-ray diffraction.

It is interesting to note that cuauchichicine is the first normal-type oxazolidine-ring-containing alkaloid which does not exist in the epimeric form at C(20) either in solution or in the solid state. This result is compatible with our earlier conclusion[6,14] that the C(20) epimers of normal-type oxazolidine-ring-containing alkaloids, in nonionic solvents, are not interconvertible via a zwitterion. Because the stereochemistry of the C(16) methyl group in cuauchichicine is reassigned, *certain previously assigned[2] structures for the degradation products of cuauchichicine, garryfoline, and veatchine must be revised.* By analogy, the acid-catalyzed rearrangement of napelline to isonapelline[15,16] would result in a C(16) β-methyl group in isonapelline.

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Supplementary Material Available: Fractional coordinates, bond distances, bond angles, and structure factors for cuauchichicine and (−)-"α"-dihydrokaurene (24 pages). Ordering information is given on any current masthead page.

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Asymmetric Synthesis of *allo*-Heteroyohimbine Alkaloids

Sir:

The synthesis of pharmacologically interesting heteroyohimbine alkaloids has been extensively investigated in the past

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