proton decoupling, $^{13}$C–$^{1}$H splitting patterns, and consideration of the effects manifest in the proton magnetic resonance spectrum of **8**.[2]

The $^{13}$C magnetic resonance spectrum of $^{13}$C-labeled nybomycin butyrate showed four enormously enriched peaks of roughly equal intensity for C-4, C-6, C-8, and C-10 and no observable enrichment at any other carbons. Thus, the proposition arrived at from the $^{14}$C data—of incorporation of four acetate units into the exterior carbons of the pyridone rings—is substantiated. More importantly, the present results establish that the carbon atoms of the central ring *do not* come from acetate *via* a phloroglucinol-type pathway.[10] The origin of those carbon atoms will be described in future reports.

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[10] J. D. Bu'Lock, "The Biosynthesis of Natural Products," McGraw-Hill, London, 1965, p 88.

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## Structures of Stemodin and Stemodinone

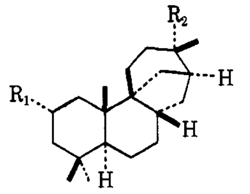
*Sir:*

Examination of leaf constituents of the rare littoral plant *Stemodia maritima* L. (Scrophulariaceae),[1] obtained from the Palisadoes peninsula of Jamaica, has brought to light two new diterpenes containing an unusual tetracyclic skeleton. Structural elucidation of these substances is reported herein.

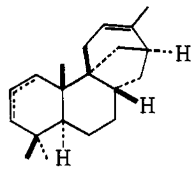
Stemodin (**1**), $C_{20}H_{34}O_2$,[2] mp 196–197°, $[\alpha]_D$ $-2.6°$ (*c* 1.07, pyridine), shows hydroxyl (3340, 3220 cm$^{-1}$) but no carbonyl absorption in its infrared spectrum. The presence of two OH groups is deduced from 1 H singlets in the nmr spectrum (DMSO-$d_6$) of **1** at $\delta$ 3.23 and 3.79; in addition the spectrum (in $CDCl_3$) revealed four methyl groups at $\delta$ 0.90, 0.93, 0.97, and 1.08 and a proton ($\delta$ 3.71, t of t, $J$ = 11, 3.5 Hz) attached to carbon bearing a hydroxyl group and flanked by two methylene groups.[3] From the coupling constants this proton is axial, and hence the hydroxyl group must be equatorial.

Acetylation of stemodin (acetic anhydride in pyridine at 50° for 6 hr) yielded a monoacetate **2**, mp 141–142°, $[\alpha]_D$ $-30.0°$ (*c* 1.19, $CHCl_3$), $\nu$ 3620, 3460, and 1730 cm$^{-1}$, $\delta$ 2.02 (3 H, s), 4.87 (1 H, t of t, $J$ = 11, 3.5 Hz), confirming the presence of secondary and tertiary OH groups in **1**.

Dehydration of stemodin (phosphorus oxychloride in pyridine at 65° for 1.5 hr) afforded an oily hydrocarbon **3**, $C_{20}H_{30}$, which contained a vinylic methyl group ($\delta$ 1.60, d, $J$ = 2 Hz) and three olefinic protons ($\delta$ 5.22, 2 H, m, and $\delta$ 5.00 1 H, broad). Hydrogenation of this substance over 5% Pd/C at atmospheric pressure resulted in the uptake of 2 equiv of hydrogen with the formation of a saturated derivative **4**, $C_{20}H_{34}$, $[\alpha]_D$ $+10.1°$ (*c* 1.13, $CHCl_3$).[4]



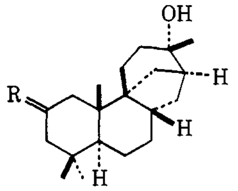
**1**, $R_1 = R_2 = OH$
**2**, $R_1 = OCOCH_3$; $R_2 = OH$
**4**, $R_1 = R_2 = H$



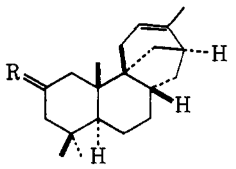
**3**

Stemodinone (**5**), $C_{20}H_{32}O_2$, mp 215–216°, $[\alpha]_D$ $+14.3°$ (*c* 1.00, $CHCl_3$), was isolated from a less polar fraction of *S. Maritima* and showed carbonyl (1700 cm$^{-1}$) as well as hydroxyl (3600, 3460 cm$^{-1}$) absorption in its infrared spectrum. Its relationship with stemodin was established by oxidation of the latter with Jones reagent, which gave **5** in good yield. The Raman spectrum of **5** showed no lines due to C=C functionality; this, in conjunction with the failure to observe hydrogen uptake, provided evidence for the tetracyclic nature of the stemodin skeleton. Treatment of stemodinone with $POCl_3$ in pyridine (65°, 1.5 hr) afforded the dehydro compound **6**, mp 93–95°, which showed carbonyl (1700 cm$^{-1}$) but no hydroxyl absorption. The ultraviolet spectrum of this compound ruled out an $\alpha,\beta$-unsaturated ketone, and the nmr spectrum revealed a single olefinic proton ($\delta$ 5.00) which was coupled to vicinal methylene hydrogens. This latter feature, taken with the foregoing evidence, rendered a structural compromise between the stemodins and the familiar tetracyclic diterpene skeletons[5] unlikely.

Reduction of stemodinone (**5**) under Huang–Minlon conditions[6] furnished desoxy derivative **7**, $C_{20}H_{34}O$, mp 143–144°, $[\alpha]_D$ $+6.2°$ (*c* 1.02, $CHCl_3$), containing a tertiary methyl carbinol ($\delta$ 1.13, 3 H, s, and ir absorption at 3590 and 3430 cm$^{-1}$). Dehydration of **7** (phosphorus oxychloride in pyridine) gave a crystalline olefin **8**, $C_{20}H_{32}$, mp 52–53°, $[\alpha]_D$ $+36.6°$ (*c* 1.00, $CHCl_3$), which displayed the anticipated broad olefinic proton ($\delta$ 5.00) and vinylic $CH_3$ ($\delta$ 1.60, d, $J$ = 2 Hz) in the nmr spectrum.



**5**, R = O
**7**, R = $H_2$



**6**, R = O
**8**, R = $H_2$

Structural elucidation of the novel stemodin ring

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[1] C. D. Adams, "Flowering Plants of Jamaica," University of the West Indies Press, Mona, Jamaica, 1972, p 662.

[2] Elemental analyses and mass spectra were obtained in agreement with all compositions shown.

[3] C. M. Chen and T. Murakami, *Tetrahedron Lett.*, 1121 (1971).

[4] Addition of hydrogen is presumed to occur from the less hindered side of the bicyclo[3.2.1]octane system, resulting in the stereochemistry shown.

[5] R. McCrindle and K. H. Overton, *Advan. Org. Chem.*, **5**, 47 (1965).

[6] H. O. House, "Modern Synthetic Reactions," 2nd ed, W. A. Benjamin, Menlo Park, Calif., 1972, p 228.

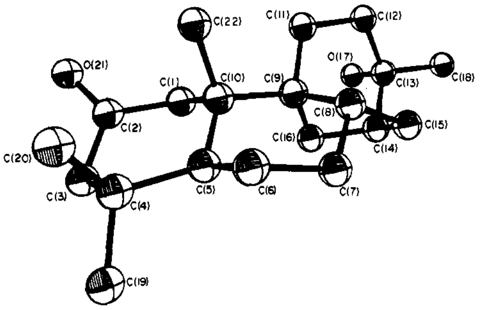

Figure 1. A computer generated perspective view of stemodinone (**5**).

system was effected through a single-crystal X-ray analysis of stemodinone (**5**). Crystals of stemodinone were grown from a solvent system of chloroform and ethyl acetate. The crystals belong to the orthorhombic crystal class with $a = 12.96$ (1), $b = 6.78$ (2) and $c = 20.16$ (1) Å. Systematic extinctions uniquely indicated space group $P2_12_12_1$, and a calculated density of 1.15 g/cm$^3$ for $Z = 4$ implied one molecule of stemodin per asymmetric unit. A total of 1675 unique reflections with $\theta \leq 55°$ were measured on a fully automated Hilger-Watts four-circle diffractometer with Ni-filtered Cu K$\alpha$ (1.5418 Å) radiation. After correction for background, Lorentz, and polarization effects, a total of 1189 reflections were judged observed ($I \geq 3\sigma(I)$). Phases were assigned to 183 $E$'s with magnitudes greater than 1.50 with a multiple solution, weighted tangent formula approach.[7] Three solutions with essentially identical phasing were strongly indicated. Inspection of the phased, three-dimensional E synthesis showed all 22 nonhydrogen atoms of the diterpene. Full-matrix least-squares refinement, with all atoms anisotropic and no hydrogens included, has lowered the crystallographic discrepancy index to 0.104.[8] Figure 1 is a computer generated drawing of the X-ray model indicating the structure and conformation of stemodinone.[9] All bond distances and angles agree well within estimated experimental error (0.02 Å and 2°) with generally accepted values.[10] There were no abnormally short intermolecular contacts. As can be seen from Figure 1 each of the six-membered rings is in the chair conformation and the five-membered ring in the envelope conformation with C(16) serving as the flap.

The structure of stemodinone (**5**), and thus stemodin (**1**), bears a close resemblance to that of the antibiotic aphidicolin, recently isolated from *Cephalosporium aphidicola*.[11] However, the stemodin stereochemistry differs from that reported for aphidicolin at C-9, 13, and 14 (stemodane numbering). The ORD of stemodinone exhibits a positive Cotton effect ($[\alpha]_{308} = 2460$), in agreement with an absolute configuration containing 5$\alpha$-H and 10$\beta$-CH$_3$.[12] These results therefore add a further variant to the family of tetracyclic diterpene skeletons found in higher plants.

**Acknowledgments.** We are indebted to Professor C. D. Adams, University of the West Indies, for botanical identification of *S. maritima*. Financial support was provided by the National Science Foundation (J. D. W.).

[7] G. Germain, P. Main, and M. M. Woolfson, *Acta Crystallogr., Sect. A*, 27, 368 (1971); J. Karle, *Acta Crystallogr.*, **9**, 635 (1968).

[8] W. R. Busing, K. O. Martin, and H. F. Levy, "A Fortran Crystallographic Least-Squares Program," USAEC Report ORNL-TM-305, Oak Ridge National Laboratory, Oak Ridge, Tenn., 1964.

[9] C. K. Johnson, "ORTEP, A Thermal-Ellipsoid Plot Program for Crystal Structure Illustrations," USAEC Report ORNL-3794, Oak Ridge National Laboratory, Oak Ridge, Tenn., 1965.

[10] O. Kennard and D. G. Watson, "Molecular Structure and Dimensions," Crystallographic Data Centre, Cambridge, 1970.

[11] K. M. Brundret, W. Dalziel, B. Hesp, J. A. J. Jarvis, and S. Neidle, *J. Chem. Soc., Chem. Commun.*, 1027 (1972).

[12] W. Moffitt, R. B. Woodward, A. Moscowitz, W. Klyne, and C. Djerassi, *J. Amer. Chem. Soc.*, **83**, 4013 (1961).

[13] Camille and Henry Dreyfus Foundation Awardee, 1972–1977.

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## Effect of Solvation on the Intrinsic Relative Acidity of Methanol and Ethanol

*Sir:*

It has been well known for many years that in solution *tert*-butoxide is a stronger base than ethoxide, and ethoxide in turn is a stronger base than methoxide. These observations lead to the conclusion that the relative order of acidity is $CH_3OH > C_2H_5OH > t\text{-}C_4H_9OH$.[1] Recently, however, Brauman and Blair reported that in the *gas phase* the relative order of acidities is reversed from that in solution.[2] This dramatic reversal in acid strengths indicates that the solvent assumes a major role in determining relative acidities.

Using the pulsed ion cyclotron resonance technique,[3] we have been able to determine quantitatively the relative gas-phase acidity of $CH_3OH$ and $C_2H_5OH$. Methoxide ions, generated by electron impact on $CH_3ONO$,[4] react rapidly in the gas phase with $C_2H_5OH$ to produce ethoxide ions. If a gaseous $CH_3OH$–$C_2H_5OH$ mixture of known relative concentration is added to the spectrometer, a chemical equilibrium is established with respect to the reaction in eq 1.[5] This result confirms

$$CH_3O^- + C_2H_5OH = C_2H_5O^- + CH_3OH \quad K_1 = 23 \pm 2 \quad (1)$$

that $C_2H_5OH$ is a stronger acid than $CH_3OH$ in the gas phase and is in agreement with the qualitative order reported by Brauman and Blair. By using the relation $\Delta G° = -RT \ln K$, the free energy change for reaction 1 at 298°K can be calculated as $-1.9 \pm 0.2$ kcal/mol.

[1] (a) J. Hine and M. Hine, *J. Amer. Chem. Soc.*, **74**, 5266 (1952); (b) W. K. McEwen, *ibid.*, **58**, 1124 (1936).

[2] (a) J. I. Brauman and L. K. Blair, *ibid.*, **92**, 5986 (1970); (b) J. I. Brauman and L. K. Blair, *ibid.*, **90**, 6561 (1968).

[3] (a) R. T. McIver, Jr., and J. R. Eyler, *ibid.*, **93**, 6334 (1971); (b) R. T. McIver, Jr., and R. C. Dunbar, *Int. J. Mass Spectrom. Ion Phys.*, 7, 471 (1971); (c) R. T. McIver, Jr., *Rev. Sci. Instrum.*, **41**, 555 (1970).

[4] K. Jager and A. Henglein, *Z. Naturforsch. A*, **22**, 700 (1967).

[5] Reaction 1 has previously been studied by D. K. Bohme, E. Lee-Ruff, and L. B. Young, *J. Amer. Chem. Soc.*, **93**, 4608 (1971). A value of $K_1 = 3$ was obtained using the flowing afterglow technique to measure the rate constants for both the forward and reverse direction of proton transfer.