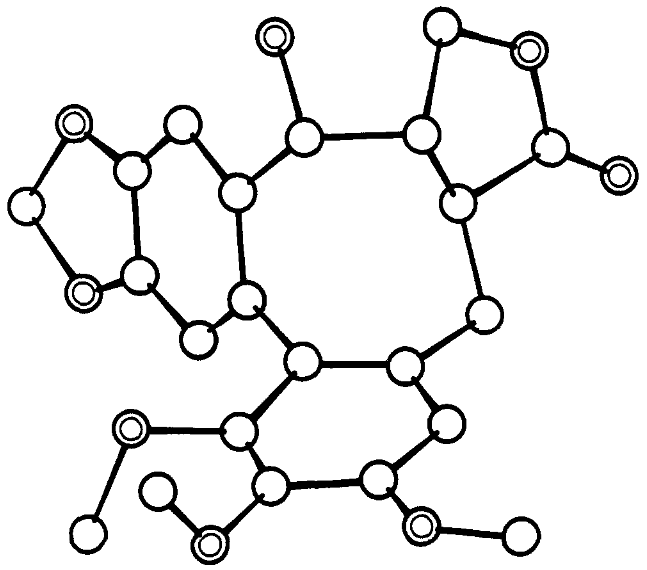

Figure 1. Molecular structure of episteganol (**4**) as found in the crystal. Carbon atoms are indicated by single and oxygen atoms by double circles. The structure is shown in the presumed absolute configuration with respect to a right-handed axial system.

(1) acetylation of steganol (**3**) with acetic anhydride in pyridine gave steganancin (**1**); (2) oxidative osmylation[8] of steganangin (**2**), followed by hydrolysis with dilute base of the intermediate pyruvate, afforded in good yield steganol (**3**); (3) basic hydrolysis of steganangin (**2**) gave angelic acid in quantitative yield; (4) sodium borohydride reduction of steganone (**5**) gave a 1:1 mixture of steganol (**3**) and a crystalline epimer, episteganol (**4**): $C_{22}H_{22}O_8$; $[\alpha]^{23}D$ $-126°$ (c 0.68, pyridine); uv max (EtOH) 288 (ϵ 5400), 254 (ϵ 8170), and 210 nm (end abs); ir (KBr) 2.88, 5.65, 6.28, 8.10, 9.65, and 9.85 μ; mass spectrum m/e 414 (M^+), 396, 330; nmr ($CDCl_3$) τ 6.38, 6.13 (9 H, 2 s, 3 OCH_3), 5.02 (1 H, d, J = 8 Hz, 5-H), 3.97 (2 H, br d, J = 8 Hz, OCH_2O), 3.51, 3.31 (2 H, 2 s, 1-H, 9-H), and 2.92 (1 H, s, 4-H); and finally, (5) manganese dioxide oxidation of **3** and of **4** gave steganone (**5**).

Similarities in spectral properties between the new compounds and the well-characterized podophyllotoxin lignans[9] suggested that **1–5** were probably lignans, but subtle differences, particularly between steganone (**5**) and podophyllotoxone (**6**), indicated the likelihood of a different skeletal type. For example, the nmr spectrum of **6** reveals a one-proton doublet (J = 4 Hz) at τ 5.24 assigned to the dibenzylic methine proton at C-4, and the presence of four aromatic protons, whereas the nmr spectrum of steganone (**5**) shows the presence of only three aromatic protons and no corresponding methine proton. This led us to postulate the bisbenzocyclooctadiene lactone skeleton for the steganin lignans.

Unequivocal proof of the structure and stereochemistry of **1–5** was achieved *via* direct X-ray crystallographic analysis of episteganol (**4**). Crystals of **4** are orthorhombic, space group $P2_12_12_1$, with a = 11.937 (1), b = 14.682 (1), and c = 11.029 (1) Å, and Z = 4. The intensities of 1393 independent reflections measured by counter diffractometry with monochromatic Cu Kα radiation were used in the structure analysis. The phase problem was solved by the multisolution tangent refinement method,[10] and the atomic parameters were refined by block-diagonal least-squares methods to give R = 0.047. Of the 22 hydrogen atoms in the molecule, 12 were identified from a difference electron-density synthesis and included with fixed parameters in the final refinement. Anisotropic thermal parameters were assumed for all the nonhydrogen atoms.

The molecular structure found in the crystal is shown in Figure 1 in the absolute configuration indicated by application of Hamilton's R ratio test.[11] For the two possible enantiomeric structures R was 0.0519 and 0.0524 when the anomalous dispersion terms[12] for oxygen were taken into account, a significant difference at the 99.5% confidence level. The reliability of this test depends on the assumption that there are no systematic errors present in the data which would favor one configuration over the other. A more conservative application of the test to the 18 reflections where the calculated differences in the structure factors are greatest lowers the confidence level to 75%, probably a more realistic assessment of the reliability of the assignment. At this time this conclusion has not been verified by measurement of intensity differences in Bijvoet pairs of reflections. Details of the X-ray structural analysis will be published elsewhere.

Two derivatives of the podophyllotoxin lignan series have been used in the treatment of human malignancies.[13] Studies are in progress to evaluate further the biological potential of the new steganin lignans.

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S. Morris Kupchan,* Ronald W. Britton, Myra F. Ziegler
Christopher J. Gilmore, Roderic J. Restivo, Robert F. Bryan
Department of Chemistry, University of Virginia
Charlottesville, Virginia 22901

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An Intermolecular $^{13}C-\{^1H\}$ Nuclear Overhauser Effect

Sir:

When protons directly bonded to carbon are irradiated at their nmr frequencies, there is a dramatic change in the intensity of the ^{13}C nmr signal. It is recognized that this effect, referred to as the nuclear Overhauser effect (NOE), is caused by a perturbation of the populations of the energy levels of the ^{13}C nuclei upon proton irradiation. In the $^{13}C-\{^1H\}$ case it has been demonstrated[1–3] that the dominant contributing mechanism is $^1H-^{13}C$ dipole–dipole coupling; a ^{13}C enhancement factor upon ^1H irradiation of +2.988 is theoretically possible, and often achieved, at least ap-

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proximately.[1] Changes in a ^{1}H nmr signal intensity upon irradiation of a different ^{1}H resonance have been observed for cases where both protons are in the same molecule[3-5] and where the observed and irradiated protons are in different molecules.[6-8]

We report here the direct observation of an *inter*molecular ^{13}C{^{1}H} NOE in a CS_2–$CHCl_3$ system. The experimental sample consisted of a triple concentric tube arrangement. The innermost region was a sealed 1-mm capillary containing perfluorobenzene which was used as a lock and was centered within a 5-mm (sealed) tube containing perchloroethylene which was used as a standard for integration of peak areas. This arrangement was inserted concentrically into a 10-mm tube that contained a degassed (five freeze–pump–thaw cycles under vacuum) solution of CS_2–$CHCl_3$ in a 1 : 10 mole ratio.

The experiment was performed in the pulse Fourier transform mode on a Bruker HFX-90 spectrometer, interfaced with a Digilab Pulse and FTS/NMR-3 system. The experiment was conducted as follows. First a ^{13}C spectrum was recorded with the proton decoupler (CW) on, and with its frequency centered on the $CHCl_3$ resonance position, as demonstrated by the collapse of the $CHCl_3$ doublet. Second, the spectrum was recorded with the decoupler switched off.[9] The areas of the CS_2 and the $Cl_2C{=}CCl_2$ peaks were determined for both experiments. Then, assuming that the area of the $Cl_2C{=}CCl_2$ signal is independent of ^{1}H decoupling, the $^{13}CS_2$–{$C\mathit{H}Cl_3$} NOE was determined. The results obtained in this manner reveal a *negative* NOE; that is, the CS_2 peak area decreases upon irradiation of the proton in $CHCl_3$. When the time between pulses is 220 sec (approximately $5T_1$ for CS_2), the decrease in intensity is 30%. As a check, a sample of CS_2–$CDCl_3$ was prepared and its spectrum recorded in the same manner; this sample gave essentially no NOE, within the experimental error (about ±5%).

An intermolecular ^{13}C–^{1}H dipole–dipole mechanism cannot account for a negative NOE. This can be seen from the expression for the Z magnetization of nucleus *I*, in the presence of another spin, *S*, which undergoes saturation (eq 1).[10] In the extreme narrowing case

$$\langle I_z \rangle = I_0 + \xi S_0 I(I+1)/S(S+1) \qquad (1)$$

ξ is $+{}^1/_2$ for dipolar coupling.[10] Balaram, Bothner-By, and Dadok[11] have demonstrated a negative ^{1}H–{^{1}H} NOE that may be of dipole–dipole origin for the case of large correlation times for molecular reorientation. However, Kuhlmann, Grant, and Harris[2] have demonstrated that for dipole–dipole coupling even very large correlation times can lead to only a reduced positive NOE, not a negative value, in the ^{13}C–{^{1}H} case. *A priori*, another possible explanation is a dipolar mechanism involving the intermediacy of a third spin.[2,4,11] However, this seems unlikely, as the third spin would be ^{35}Cl, which has a rapid (quadrupolar) relaxation mechanism of its own and, thus, could reduce the magnitude of the NOE but could not make it negative.[2]

An alternative explanation is a time-dependent intermolecular scalar coupling, for which ξ in eq 1 is *minus* one in the extreme narrowing case.[10] This mechanism would arise in what is essentially an exchange modulation of the spin–spin coupling due to electron overlap in the collision complex. This may be reasonable for molecules such as CS_2, in which the pertinent carbon atom is not severely screened away from neighboring molecules by other atoms, *e.g.*, hydrogens.

Although one cannot, on the basis of the results given here, justify a more definite interpretation, these results clearly establish that intermolecular ^{13}C–{^{1}H} NOE's are measurable. Such effects should be useful in studies of intermolecular interactions and molecular reorientation in the liquid state.

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D. P. Miller, B. Ternai,[12] G. E. Maciel*
Department of Chemistry, Colorado State University
Fort Collins, Colorado 80521

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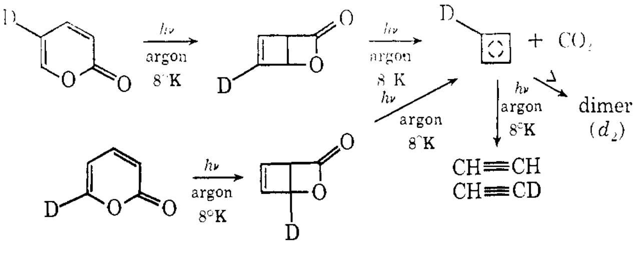
Mono- and Dideuteriocyclobutadienes[1]

Sir:

We wish to report the preparation of monodeuterio-, 1,2-dideuterio-, and 1,3-dideuteriocyclobutadienes. The preparation depends on the synthesis of the appropriate deuterated 2-pyrones,[2] photoisomerization to the β-lactone, and photoelimination of carbon dioxide.

Irradiation of 2-pyrone-*5*-d_1 (84% d_1) and 2-pyrone-*6*-d_1 (92% d_1) matrix isolated in argon at 8°K gives different monodeuterio-β-lactones but the same monodeuteriocyclobutadiene (1223, 780, 654, 583, 576, 535 cm^{-1}). Continued irradiation converts the monodeuteriocyclobutadiene to acetylene (3260, 735 cm^{-1}) and monodeuterioacetylene (3330, 2580, 687 cm^{-1}).



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(1) Photochemical Transformations. XL.

(2) Monodeuterated 2-pyrones were prepared by literature procedures.[3] Dideuterio-2-pyrones were prepared in an analogous manner by halogenation of monodeuterio-2-pyrones followed by reductive incorporation of the second deuterium.

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