2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranoside (from intermediates from reactions I and III; see Table I) and methyl 2,3,4-tri-*O*-benzyl-6-*O*-*p*-methoxybenzoyl-α-D-glucopyranoside (from reaction IV, Table I). The order of reactivity of these three reagents seems to follow sulfonium > ammonium > phosphonium. The sulfonium salt (reaction II, Table I) seems to be the most unstable and the most loose of the ion pairs for it gives lower steric purity in the methanolysis reaction. The phosphonium salt, on the other hand, required elevated temperature (Table I) in order to obtain complete conversion to the methyl glucopyranoside within the same reaction time. However, higher reaction temperature did not influence the stereoselective control of the product isolated from this intermediate.

At present further studies are being conducted in this laboratory to apply these and related nucleophilic reagents to the synthesis of a number of more complex glycosides.

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Steganacin and Steganangin, Novel Antileukemic Lignan Lactones from *Steganotaenia araliacea*[1-3]

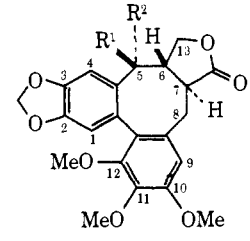
Sir:

An alcoholic extract of *Steganotaenia araliacea* Hochst.[4] was found to show significant activity *in vivo* against the P-388 leukemia in mice and *in vitro* against cells derived from human carcinoma of the nasopharynx (KB).[5] We report herein the isolation and structural elucidation of steganacin (**1**) and steganangin (**2**), two novel antileukemic[6] lignan lactones. These compounds and the companion lignans steganone (**5**) and steganol (**3**) appear to be the first reported bisbenzocyclooctadiene lactones.[7]

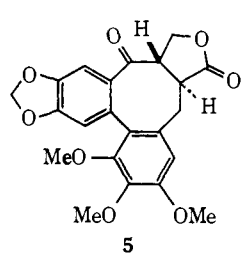
Fractionation of an ethanol extract, guided by assay against KB and P-388, revealed that the inhibitory activity was concentrated in the chloroform layer of a chloroform–water partition. The chloroform layer was partitioned between 10% aqueous methanol and Skellysolve B, and the 10% aqueous methanol layer was further partitioned between 20% aqueous methanol and carbon tetrachloride, which concentrated all of the activity in the final CCl_4 layer. Chromatography of this material on silica gel yielded a KB cytotoxic fraction (A) upon elution with 5% ether in benzene, an *in vivo* active fraction (B) on elution with 10% ether in benzene, and a further cytotoxic fraction (C) on elution with 100% ether. Preparative tlc of fraction A on Chromar 7GF plates with 10% ether in benzene gave two crystalline compounds. The first, steganangin (**2**, 0.1%), $C_{27}H_{28}O_9$, showed: mp 142.5–143°; $[\alpha]^{23}D$ −113° (*c* 0.72, $CHCl_3$); uv max (EtOH) 285 (ε 5180), 256 (ε 10,600), and 210 nm (end abs); ir (KBr) 5.66, 5.83, 5.88 (sh), 6.29, 8.20, 8.70, 8.78, and 9.65 μ; mass spectrum *m/e* 496 (M^+), 396, and 366; nmr (C_6D_6) τ 8.43 (3 H, m, angelate α methyl), 8.25 (3 H, br d, J = 7.6 Hz, angelate β methyl), 6.48, 6.42, 6.26 (9 H, 3 s, 3 OCH_3), 4.49, 4.48 (2 H, 2 d, AB quartet, J = 9 Hz, OCH_2O), 4.33 (1 H, m, angelate vinyl *H*), 4.27 (1 H, d, J = 10 Hz, 5-*H*), 3.68, 3.55 (2 H, 2 s, 1-*H*, 9-*H*), and 3.13 (1 H, s, 4-*H*). The second, steganone (**5**, 0.1%), $C_{22}H_{20}O_8$, showed: mp 155–156°; $[\alpha]^{23}D$ −202° (*c* 0.76, $CHCl_3$); uv max (EtOH) 317 (ε 5710), 276 (ε 9200), 238 (ε 27,600), and 210 nm (end abs); ir (KBr) 5.67, 6.00, 6.21, 6.30, 6.39, and 8.10 μ; mass spectrum *m/e* 412 (M^+), 398, 397, 328; nmr ($CDCl_3$) τ 6.46 (3 H, s, OCH_3), 6.17 (6 H, s, 2 OCH_3), 5.71 (1 H, q, B of ABX, 13-*H*), 5.58 (1 H, q, A of ABX, 13-*H*), 3.98 (2 H, br s, OCH_2O), 3.54, 3.44 (2 H, 2 s, 1-*H*, 9-*H*), and 2.55 (1 H, s, 4-*H*).

Preparative tlc of fraction B on Chromar 7GF using 10% ether in benzene gave steganacin (**1**, 0.4%): $C_{24}H_{24}O_9$; $[\alpha]^{23}D$ −114° (*c* 0.74, $CHCl_3$); uv max (EtOH) 285 (ε 5450), 255 (ε 10,700), and 210 nm (end abs); ir (KBr) 5.65, 5.78, 6.29, 8.10, 9.63, and 9.84 μ; mass spectrum *m/e* 456 (M^+), 396, 366; nmr ($CDCl_3$) τ 8.08 (3 H, s, $OCOCH_3$), 6.28, 6.14, 6.10 (9 H, 3 s, 3 OCH_3), 4.19 (1 H, br d, $J_{5,6}$ = 8 Hz, 5-*H*), 4.00 (2H, s, OCH_2O), 3.57, 3.42 (2 H, 2 s, 1-*H*, 9-*H*), and 3.11 (1 H, s, 4-*H*).

Preparative tlc of fraction C on silica gel plates with 1:1 ether–benzene gave steganol (**3**, 0.001%): $C_{22}H_{22}O_8$; $[\alpha]^{23}D$ −163° (*c* 0.87, $CHCl_3$); uv max (EtOH) 287 (ε 5600), 255 (ε 11,200), and 210 nm (end abs); ir (KBr) 2.90, 5.65, 6.28, 8.15, 9.62, and 9.85 μ; mass spectrum *m/e* 414 (M^+), 396, 330; nmr ($CDCl_3$) τ 6.27, 6.13, 6.09, (9 H, 3 s, 3 OCH_3), 3.98 (2 H, s, OCH_2O), 3.55, 3.43 (2 H, 2 s, 1-*H*, 9-*H*), and 3.22 (1 H, s, 4-*H*).



1, R^1 = OAc; R^2 = H



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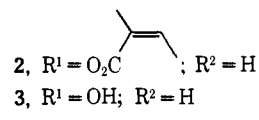
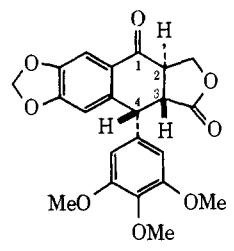


2, R^1 = O_2C ; R^2 = H
3, R^1 = OH; R^2 = H
4, R^1 = H; R^2 = OH



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From the spectral data it appeared that all four compounds were related and indeed it was shown that:

(1) Tumor Inhibitors. LXXX. Part LXXIX is ref 2.

(2) S. M. Kupchan, A. J. Liepa, R. L. Baxter, and H. P. J. Hintz, *J. Org. Chem.*, in press.

(3) Supported by grants from the National Cancer Institute (CA-11718 and CA-11760) and American Cancer Society (T-275 and T-541), and a contract with the National Cancer Institute (NIH-NCI-C-71-2099).

(4) Wood of stems and stem bark were collected in Ethiopia in March 1971. We thank Dr. Robert E. Perdue, Jr., U. S. Department of Agriculture, Beltsville, Md., for supplying the plant material.

(5) Cytotoxicity and *in vivo* activity were assayed as in *Cancer Chemother. Rep.*, 25, 1 (1962).

(6) Steganacin and steganangin showed significant antileukemic activity against P-388 leukemia in the mouse, and cytotoxicity against a KB cell culture at 10^{-1}–10^{-3} μg/ml.

(7) N. K. Kochetkov, A. Khorlin, O. S. Chizov, and V. I. Sheichenko [*e.g.*, *Tetrahedron Lett.*, 730 (1961)] have described the only other representatives of the unusual bisbenzocyclooctadiene lignans.

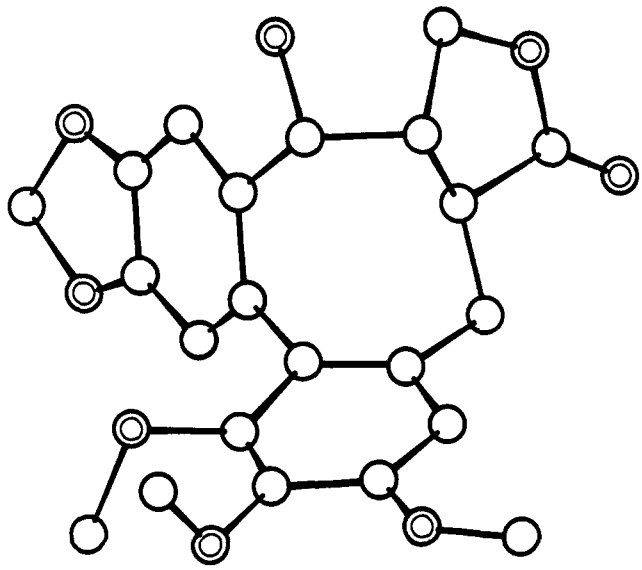

Figure 1. Molecular structure of episteganol (**4**) as found in the crystal. Carbon atoms are indicated by single and oxygen atoms by double circles. The structure is shown in the presumed absolute configuration with respect to a right-handed axial system.

(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 OC*H*$_3$), 5.02 (1 H, d, *J* = 8 Hz, 5-*H*), 3.97 (2 H, br d, *J* = 8 Hz, OC*H*$_2$O), 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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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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