(379 mg): mp 147–148°; $[\alpha]^{23}D$ +48° (c 0.95); ir λ_{max} 5.88, 6.85, 6.94, 7.24, 7.29, 7.91, 8.30, 8.38, 8.67, 9.40, and 10.80 μ; nmr (100 MHz) τ 6.36 (1 H, m, C-20 H), 7.50 (4 H, q, J = 7 Hz, NCH_2CH_3), 7.90 [6 H, s, $N(CH_3)_2$], 9.01 (6 H, t, J = 7 Hz, NCH_2CH_3), 9.03 (3 H, s, C-19 CH_3), 9.20 (3 H, d, J = 7 Hz, C-21 CH_3), and 9.40 (3 H, s, C-18 CH_3); mass spectrum m/e 416 (M^+), 402, 401, 139, 138, 113, 112, 99, 84, 73, 72, 71, 58, and 56.

Anal. Calcd for $C_{27}H_{48}N_2O$: C, 77.83; H, 11.61; N, 6.72. Found: C, 77.62; H, 11.58; N, 6.70.

Fractions 8 and 9 gave colorless gums (22 and 2 mg, respectively) which did not crystallize.

Lithium Aluminum Hydride Reduction of Diamine 45.—A solution of **45** (180 mg) in dioxane (20 ml) was added to a suspension of $LiAlH_4$ (275 mg) in dioxane (15 ml). The mixture was heated under reflux for 48 hr, cooled, and treated with ether saturated with water. The suspension was filtered, and the inorganic precipitate was washed with boiling dichloromethane (2 × 30 ml). The combined filtrates were dried and concentrated to leave a colorless, crystalline solid (164 mg). Partition chromatography separated this residue into three bands.

Band 1 (highest R_f) gave a colorless solid (44 mg), mp 130–133°, which was shown by nmr to be a mixture of two compounds. Repeated partition chromatography of this material gave two red bands. Removal of solvent from the first band gave a colorless oil (24 mg) which crystallized from methanol to give 11α-hydroxydiamine **48** as colorless plates: mp 165–167°; $[\alpha]^{24}D$ +21° (c 0.50); ir λ_{max} 2.93, 6.88, 6.94, 7.29, 7.36, 8.39, 8.66, 9.15, 9.31 9.51, and 10.80 μ; nmr (100 MHz) τ 5.83 (1 H, m, C-11 H), 6.46 (1 H, m, C-20 H), 7.50 (4 H, q, J = 7 Hz, NCH_2CH_3), 7.94 [6 H, s, $N(CH_3)_2$], 9.00 (6 H, t, J = 7 Hz, NCH_2CH_3, and 3 H, s, C-19 CH_3), 9.13 (3 H, s, C-18 CH_3), and 9.28 (3 H, d, J = 6 Hz, C-21 CH_3); mass spectrum m/e 418 (M^+), 417, 403, 347, 138, 113, 112, 99, 98, 86, 84, 81, 73, 72, 71, 69, 57, 56, 55, 43, and 41.

Anal. Calcd for $C_{27}H_{50}N_2O$: C, 77.45; H, 12.04; N, 6.69. Found: C, 77.32; H, 11.88; N, 6.59.

The second band gave **47** as a colorless solid (11 mg), identical with the product obtained from band 2 of the first chromatography.

Band 2 gave 3β-diethylamino-20α-dimethylamino-5α-pregnan-11β-ol (**47**) as a colorless solid (94 mg) which crystallized from methanol as colorless plates: mp 178–179°; $[\alpha]^{24}D$ +30° (c 0.69); ir λ_{max} 2.94, 6.92, 7.36, 8.38, 8.68, 9.43, 9.53, and 10.85 μ; nmr (100 MHz) τ 5.80 (1 H, m, C-11 H), 6.38 (1 H, m, C-20 H), 7.49 (4 H, q, J = 7 Hz, NCH_2CH_3), 7.89 [6 H, s, $N(CH_3)_2$], 9.00 (6 H, t, J = 7 Hz, NCH_2CH_3, and 3 H, s, C-19 CH_3), 9.15 (3 H, s, C-18 CH_3), and 9.16 (3 H, d, J = 6 Hz, C-21 CH_3); mass spectrum m/e 418 (M^+), 417, 403, 348, 347, 138, 113, 112, 84, 73, 72, 57, 56, 55, and 41.

Anal. Calcd for $C_{27}H_{50}N_2O$: C, 77.45; H, 12.04; N, 6.69. Found: C, 77.25; H, 12.04; N, 6.66.

Band 3 gave a colorless oil (24 mg) which was shown to be a mixture of at least two compounds (tlc). It showed bands at 5.77, 6.88, 7.26, and 7.94 μ in the ir spectrum.

Registry No.—**10**, 34599-35-4; **11**, 34564-99-3; **12**, 34565-00-9; **13**, 34608-93-0; **15**, 34565-01-0; **17**, 34599-36-5; **19**, 34565-02-1; **21**, 34565-03-2; **22**, 34599-37-6; **27**, 34599-38-7; **28**, 34565-04-3; **29**, 34565-05-4; **30**, 34565-06-5; **31**, 34565-07-6; **32**, 34565-08-7; **33**, 34565-09-8; **35**, 34565-10-1; **36**, 34565-11-2; **37**, 34565-12-3; **39**, 34599-39-8; **40**, 34565-13-4; **41**, 34565-14-5; **42**, 34565-15-6; **43**, 34565-16-7; **44**, 34565-17-8; **45**, 34565-18-9; **46**, 34599-40-1; **47**, 34565-19-0; **48**, 34565-20-3.

Berlandin and Subacaulin, Two New Guaianolides from *Berlandiera Subacaulis*[1]

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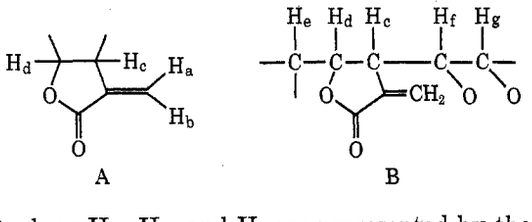
Two new guaianolides, berlandin and subacaulin, have been isolated from *Berlandiera subacaulis* (Nutt.) Nutt. Structure **2a** has been deduced for subacaulin. Berlandin is either **1a** or differs from acetylsubacaulin (**2b**) in configuration of the epoxide ring.

In the course of our investigations of subtribe Melampodiinae, tribe Heliantheae, family Compositae,[2] we are studying constituents of the North American genus *Berlandiera*.[3] The isolation and structure determination from *Berlandiera subacaulis* (Nutt.) Nutt. of two new guaianolides, which we have named berlandin and subacaulin, is reported herewith.

Berlandin (**1**), $C_{22}H_{26}O_7$ (high-resolution mass spectrum), mp 183–185°, $[\alpha]D$ +110.9°, was a conjugated γ lactone (ir bands at 1780 and 1670 cm^{-1}, very strong uv end absorption). The nmr spectrum (Table I) exhibited the characteristic doublets of H_a and H_b in partial structure A at 6.13 and 5.43 ppm. These signals were replaced by a new methyl doublet in the nmr spectrum of the tetrahydro derivative **3**. Irradiation at the frequencies of H_a and H_b established the location of H_c at 3.33 ppm in the usual fashion,[4] but the location of H_d, one of three protons in the region 3.6–5.8 ppm, could not be established unambiguously at this stage. Irradiation at the frequency of H_c did not affect a broad doublet at 5.59 ppm, but collapsed a triplet at 5.21 ppm to a doublet. The appearance of the broad doublet and the triplet suggested that the protons responsible for them were coupled to each other. Since the chemical shift of the signal at 5.21 ppm was too low for a proton under a lactone ether oxygen and since the nmr spectrum contained a doublet of doublets at 3.71 ppm,[5] it appeared very likely that A should be expanded



to B where H_d, H_f, and H_g are represented by the signals at 3.71, 5.21, and 5.59 ppm, respectively.

The ir spectrum of berlandin showed the presence of two additional carbonyl groups (bands at 1744 and 1722 cm^{-1}) which were attributed to ester functions,

(1) Supported in part by grants from the U. S. Public Health Service (GM-05814-13 and CA-13121-14) and Hoffmann-La Roche, Inc.

(2) The original impetus for these studies is given by W. Herz, S. V. Bhat, and A. L. Hall, *J. Org. Chem.*, **35**, 1110 (1970).

(3) D. J. Pinkava, *Brittonia*, **19**, 285 (1967).

(4) W. Herz, S. Rajappa, M. V. Lakshmikantham, and J. J. Schmid, *Tetrahedron*, **22**, 693 (1966).

(5) This partially overlapped the H_c resonance and could therefore not be decoupled satisfactorily.

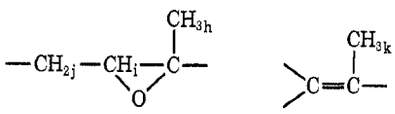
TABLE I

NMR SPECTRA OF BERLANDIN, SUBACAULIN, AND DERIVATIVES[a]

Compd	H-2	H-3	H-5	H-6	H-7	H-8	H-9	H-13	H-14[b]	H-15[b]	Ac[b]	H-3′	2-Me[b]	3′-Me[b]
1	2.89 d br[c] (18) 2.41 d br[c] (18)	3.42 br	3.32 d br[d] (10.7)	3.71 dd (10.7, 10)	3.33 m[d]	5.21 t[c] (10)	5.59 d br[c] (10)	6.13 d (3.1) 5.43 d (2.8)	1.64 br	1.68	1.99	6.25 dq	2.02 dq	1.87 m
2a	2.76 d br[c] (18) 2.45 d br[c] (18)	3.39 br	3.17 d br[d] (10)	3.64 t[c] (10)	3.03 m[d]	3.75 td[e,g] (9.8, 4.8)	5.42 d (9.8)	6.18 d[f,h]	1.59 br	1.65		6.10 m[f]	~2.0 m	1.95 m
2b	2.80 d br[c] (17) 2.49 d br[c] (17)	3.42 br	3.22 d br[d] (10)	3.69 t (10)	3.27 m[d]	5.14 t[c] (10)	5.62 d br[c] (10)	6.14 d[f] (3.0) 5.42 d (2.8)	1.63 br	1.68	2.04	6.19 m[f]	2.01 dq	1.87 m
3	2.77 d br[c] (18) 2.47 d br[c] (18)	3.40 br	3.07 d br (10.5)	3.65 dd (10.5, 9.5)	*i*	4.95 t[c] (10)	5.44 d br[c] (10)	1.19[b,i] (7)	1.60 br	1.69	2.06	*i*	1.30 d (7)[j]	0.93 t (7)
4a	*i*	3.40 br	3.04 t (10)	3.66 t[d] (10)	*i*	3.54 t[d] (10)	5.27 d br (10)	1.18 d[b,i] (7)	1.59 br	1.64		*i*	1.42 d[i] (7)	0.94 t (7)
4b	2.77 d br[c] (18) 2.47 d br[c] (18)	3.40 br	3.10 d br (10.5)	3.66 dd (10.9, 9.5)	*i*	4.95 t (10)	5.50 d br (10)	1.19 d[b,i] (7)	1.64 br	1.69	2.06	*i*	1.31 d[i] (7)	0.95 t (7)
5	2.47 d br[d] (16) *i*	3.46 br	2.50 d[d] (11)	3.88 dd (11, 10.6)	3.22 m	5.41 t[c] (10.6)	4.82 d (10.6)	6.20 d[f] (3.2) 5.53 d[e] (3.0)	1.36	1.72	2.01	6.3 m[f]	2.04 m	1.87 m
6	*i*	4.30 t[d] (10)	*i*	4.20 t[d] (10)	3.15 m	5.35 t[c] (8.5)	5.55 d br[c] (8.5)	6.27 d[e] (3.4) 5.66 d (3.0)	1.65 br	1.39	2.02[f]	6.27 m[e]	2.0 m[f]	1.88 m
7	*i*	4.18 d br (4.5)	3.07 d br[d] (10)	4.55 t (10)	3.24 m[d]	5.37 t[c] (8.5)	5.50 d br[c]	6.24 d[e] (3.4) 5.60 d (3.0)	1.73 br	1.89[f]	2.02[f]	6.3 m[e]	2.02 m[f]	1.89[f]

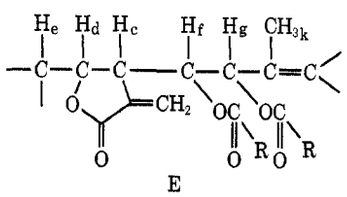
[a] Run at 90 MHz on a Bruker nmr spectrometer in $CDCl_3$ using TMS as internal standard. Chemical shifts are in parts per million. Signals are denoted in the usual way: d, doublet; t, triplet; q, quartet; m, multiplet; br, broadened singlet. Unmarked signals are singlets. Figures in parentheses are line separations or coupling constants in hertz. [b] Three-proton signal. [c] AB part of more complex system. [d–f] Overlapping signals. [g] Collapses to triplet on D_2O exchange. [h] Two-proton signal. [i] Obscured. [j] Arbitrary assignment.

one conjugated, the other unconjugated, since the CD curve lacked the n,π^* transition of a ketone. Confirmation was provided by the nmr spectrum, which displayed the typical signals of an angeloyl group (one-proton multiplet at 6.25, vinyl methyl multiplets at 2.02 and 1.87 ppm).[6] These disappeared on reduction to **3** and were replaced by a new methyl doublet and a methyl triplet (Table I). The unconjuated ester was an acetate (molecular formula and nmr singlet at 1.99 ppm). The presence of the angeloyl and acetyl function was further shown by the high-resolution mass spectrum, which had peaks corresponding to M − C_2H_2O, M − $C_2H_4O_2$, M − C_5H_7O, and M − $C_5H_8O_2$ and a base peak at 83 corresponding to C_5H_7O. The seventh and last oxygen atom was ascribed to the presence of partial formula C (three-proton singlet of



C

D



E

H_h at 1.68 ppm). Although H_i of C was a broad singlet at 3.42 ppm, its environment was clarified by treatment of berlandin with HCl–dioxane. This resulted in opening of the epoxide ring and formation of two isomeric chlorohydrins, **6** and **7**. In the nmr spectra of these compounds, H_i appeared as a sharp triplet or a broadened doublet, thus establishing the presence of a neighboring $-CH_2-$ group (H_j).[7]

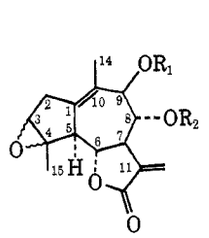
The presence of partial structure D was indicated by a somewhat broadened three-proton signal (H_k) at 1.64 ppm which sharpened and moved upfield on epoxidation of berlandin to **5**. Since the number of low-field protons remained unaffected by this transformation, the double bond of D was tetrasubstituted. The only other significant alteration in the nmr spectrum of **5** was a sharpening and pronounced diamagnetic shift to 4.82 of the broad H_g doublet formerly at 5.59 ppm. It was reasonable to associate this change with the effect produced on an allylic proton by epoxidation of D; consequently, and in view of the presence of two ester functions, B and D were combined to give E.

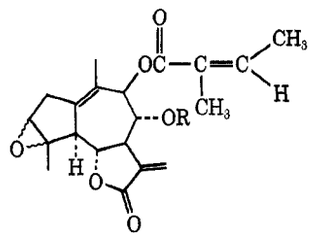
Irradiation of **5** at the frequency of H_e established the correctness of E by collapsing a triplet at 5.41, now logically assigned to H_f, and a doublet of doublets at 3.88 ppm, now logically assigned to H_d,[8] to doublets. Irradiation at 5.41 collapsed the doublet at 4.82 (H_g) and irradiation at 3.88 collapsed a doublet at 2.50 ppm (H_e). Combination of C and E then leads to the carbon skeleton of **1** because of the multiplicity of the

(6) W. Herz and M. V. Lakshmikantham, *Tetrahedron*, **21**, 1711 (1965).

(7) In the nmr spectrum of **1**, H_i, H_{j_1}, and H_{j_2} appeared as an ABX system with H_i as a broad singlet at 3.42, and H_{j_1} and H_{j_2} as broadened doublets ($|J|$ = 18 Hz) at 2.89 and 2.41 ppm. The assignment was confirmed by spin decoupling.

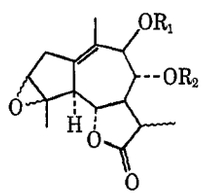
(8) Nmr spectra of a large number of sesquiterpene lactones containing ester functions at C-6 or C-8 and at C-9 are now on record. Invariably, the resonance of the ester protons is found at lower field than the signal of the lactone proton.



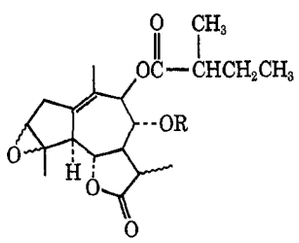


1a, R^1 = Angeloyl; R_2 = Ac
b, R^1 = Ac; R^2 = Angeloyl

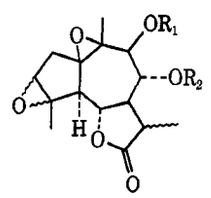
2a, R = H
b, R = Ac



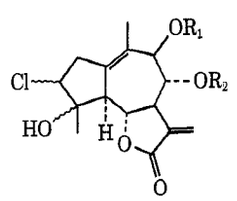
3a, R_1 = 2-methylbutyryl; R_2 = Ac
b, R_1 = Ac, R_2 = 2-methylbutyryl



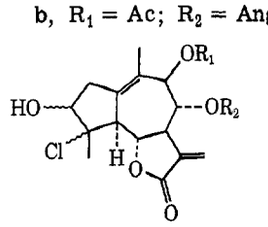
4a, R = H
b, R = Ac



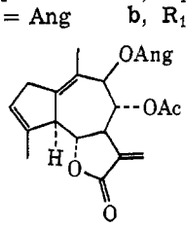
5a, R_1 = Ang; R_2 = Ac
b, R_1 = Ac; R_2 = Ang



6a, R_1 = Ang; R_2 = Ac
b, R_1 = Ac, R_2 = Ang



7a, R_1 = Ang, R_2 = Ac
b, R_1 = Ac; R_2 = Ang



8

H_e and H_j signals. Moreover, the upfield shift of these protons on conversion of **1** to **5** indicates that they, like H_g, are allylic as required by the formula.

This was confirmed by examining the nmr spectrum of **3**. In this spectrum the signal at 5.44 (H_g = H-9) and not the signals at 4.95 (H_f = H-8) and 3.65 ppm (H_d = H-6) was shown by double irradiation to be partially responsible for broadening of the C-10 methyl singlet. The existence of long-range coupling between H-14 (H_k) and H-5 (H_e), between H-14, H-2a, and H-2b and between H-9 and H-2b was also demonstrated and was consonant with the derived structure.

We defer consideration of the remaining problem of how to distribute the acetoxy and angeloxy residues over C-8 and C-9 until we have dealt with the structure of subacaulin (**2a**). This substance, $C_{20}H_{24}O_6$ (high-resolution mass spectrum), mp 160–162° dec, $[\alpha]_D$ +129.9°, polymerized at room temperature and dif-

fered from berlandin in having a free secondary hydroxyl group instead of an acetate function. This was evidenced by the empirical formula and the mass spectrum, which had peaks at M − C_5H_7O and M − $C_5H_8O_2$ and the base peak at 83. The nmr spectrum was similar to that of berlandin but lacked the sharp acetate singlet and had a triplet (after D_2O exchange) characteristic of HCOH at 3.75 instead of at 5.21 ppm (Table I). Double irradiation showed that this triplet was coupled to H-7 and H-9. Hence the free hydroxyl group was located at H-8[9] and subacaulin possesses formula **2a**.

Acetylation of subacaulin furnished a monoacetate **2b**, mp 154–156°, whose tlc behavior, rotation, and ir spectrum were practically identical with those of berlandin but whose nmr spectrum differed reproducibly in minor, but significant detail from that of **1** (Table I). Again, the optical and spectral properties of acetyltetrahydrosubacaulin (**4b**) and tetrahydroberlandin (**3**) were exceedingly similar, but the compounds were not identical. On this basis the conclusion lay near that berlandin probably differed from **2b** in having the acetoxyl and angeloxyl groups interchanged as in **1b**.

Attempts to settle this question by partial hydrolysis of berlandin were generally frustrated, although one run employing sodium carbonate–methanol treatment of berlandin resulted in isolation of a fraction containing an inseparable mixture of desacetyl derivatives (ir and nmr spectrum). In the nmr spectrum of the mixture, the signal apparently corresponding to H-8 had moved upfield to *ca.* 3.7 ppm while, more significantly, the signals of H-13a and H-13b had coalesced. This definitely suggested[11] that the free hydroxyl group of the hydrolysate was at C-8 and that the acetate function of berlandin had originally been attached to C-8 as in **1a**. On this basis berlandin and acetylsubacaulin would have to be epimers. On the other hand the possibility of an acyl migration from C-8 to C-9 or a relactonization from C-6 to C-8[13] during the K_2CO_3 treatment of berlandin, which would also account for the nmr spectrum of the hydrolysate, could not be excluded.

In the following we briefly consider the stereochemistry of **1** and **2a**. If the assumption be made that the C-7 side chain of berlandin is equatorial and β as in all guaianolides of established absolute configuration, the lactone ring fusion is trans and H-6 is β because of the magnitude of $J_{6,7}$ (10 Hz). The magnitude of $J_{7,8}$ (10 Hz) requires that H-7 and H-8 be cis if the seven-membered ring is a boat, and trans if the seven-membered ring is a chair. Dreiding models indicate that H-6 and H-9 interact strongly in the former and H-6 and H-8 in the latter case. Experimentally the existence of a strong (18%) nuclear Overhauser effect between H-6 and H-8 shows[15] that H-8 is β.

The values of $J_{5,6}$ (10.7 Hz) and $J_{8,9}$ (10.0 Hz) require a trans relationship of H-5 and H-6 on the one hand and H-8 and H-9 on the other; hence H-5 and H-9 are both α. Inspection of the model indicates that this forces H-5, H-7, and H-9 into close proximity and indeed an appreciable NOE between H-5 and H-9 (18%) was found.[16] The epoxide ring is constrained to be cis, by virtue of its attachment to a five-membered ring. However, the absolute stereochemistry at C-3 and C-4 remains in doubt because the observed coupling constants between H-2 and H-3 (Table I) are satisfied in both the α and β orientation of the epoxide ring (model).

Since the nmr spectra of berlandin and acetylsubacaulin exhibit almost identical coupling constants and chemical shifts, we conclude that the configurations of these compounds at C-5, C-6, C-7, C-8, and C-9 are identical. If berlandin possesses formula **1a**, the difference between berlandin and acetylsubacaulin must lie in the configuration at C-3 and C-4. Although this should not affect the coupling constants appreciably, one might expect somewhat greater differences in the chemical shifts of certain signals than are actually observed (model). In that case deoxygenation of berlandin and acetylsubacaulin should produce the same guaianolide **8**; however, an attempt to carry out this transformation by treatment with zinc–copper couple[17] failed.[18] If berlandin possesses formula **1b**, the close coincidence in the nmr spectra suggests that configurations of **1b** and **2b** at C-3 and C-4 are the same. A solution to the dilemma will be sought when more berlandin becomes available.

Experimental Section[19]

Isolation of Berlandin and Subacaulin.—Above ground parts of *Berlandiera subacaulis* (Nutt.) Nutt., wt 15.2 kg, collected by Mr. Robert Lazor on July 19, 1969, 6 miles west of Steinhatchee, Taylor County, Florida (Lazor voucher #3736 on deposit in herbarium of Florida State University), was extracted with chloroform and worked up in the usual manner.[20]

The crude gum, wt 45 g, was chromatographed over 1 kg of silicic acid (Mallinckrodt 100 mesh), 1-l. fractions being collected in the following order: 1–15 (benzene), 16–30 (benzene–chloroform, 3:1), 31–45 (benzene–chloroform, 1:1), 46–60 (benzene–chloroform, 1:3), 61–80 (chloroform), 81–95 (chloroform–methanol, 97:3), 96–110 (chloroform–methanol, 19:1), 111–125 (chloroform–methanol, 9:1). Fractions 32–41, which showed a major spot on tlc, were combined and recrystallized from ethyl acetate–hexane to give 1.4 g of pure berlandin. Fractions 47–55 on recrystallization from ethyl acetate–hexane gave 4.3 g of subacaulin. All other fractions were gums showing several spots.

Pure berlandin (1) had mp 183–185°; $[\alpha]^{20}D$ +110.9° (*c* 2.8); ir bands at 1780, 1748, 1722, 1670, and 1742 cm^{-1}; uv end ab-

(9) Table I contains an additional item which provides conspicuous evidence for the location of the hydroxyl group at C-8 and for its α orientation (*vide infra*). Comparison of the spectra of **2a** and **2b** reveals that acetylation is accompanied by a large diamagnetic shift of H-13a Such a shift is characteristic of an 8α-oriented hydroxyl group in eudesmanolides and guaianolides[10,11] and, to a somewhat lesser degree, in pseudoguaianolides.[11,12]

(10) See, for example, M. A. Irwin and T. A. Geissman, *Phytochemistry*, **10**, 637 (1971); **8**, 305 (1969).

(11) H. Yoshioka, T. J. Mabry, M. A. Irwin, T. A. Geissman, and Z. Samek, *Tetrahedron*, **27**, 3317 (1971).

(12) N. F. Fischer and T. J. Mabry, *ibid.*, **23**, 2529 (1967).

(13) Germacranolides containing α-oriented lactonizable groups at C-6 and C-8 preferentially lactonize toward C-8.[14] Lactone ring orientation in the guaianolide series under basic conditions is well-known but the factors determining the preferential direction of ring closure are not defined.

(14) H. Yoshioka, W. Renold, and T. J. Mabry, *Chem. Commun.*, 148 (1970).

(15) Tetrahydroberlandin was used for the NOE experiments because the signals of H-5, H-6, H-8, and H-9 were well separated and since inspection of the models showed that the relative orientation of these protons and of H-7 did not differ significantly in berlandin and tetrahydroberlandin.

(16) Since the H-7 resonance was obscured in **1** and superimposed on the signal of H-5 in **5**, the NOE'S involving H-7 could not be investigated experimentally.

(17) S. M. Kupchan and M. Maruyama, *J. Org. Chem.*, **36**, 1187 (1971).

(18) Prolonged exposure (1 week) to the reagent in ethanol solution resulted not in deoxygenation but in partial opening of the epoxide ring.

(19) Experimental conditions specified by W. Herz, S. V. Bhat, and A. L. Hall, *J. Org. Chem.*, **35**, 110 (1970), apply. High-resolution mass spectra were run at 70 meV on a MS-902 high resolution mass spectrometer.

(20) W. Herz and G. Högenauer, *J. Org. Chem.*, **27**, 905 (1962).

sorption at 207 nm (ε 25,800); CD curve λ_{max} 246 nm (θ +1377, c 1.02). The high resolution mass spectrum exhibited a very weak M^+ peak.

Anal. Calcd for $C_{22}H_{26}O_7$: C, 65.66; H, 6.51; O, 27.83; mol wt, 402.1678. Found: C, 65.80; H, 6.58; O, 27.79; mol wt, 402.1682.

Subacaulin (**2a**) had mp 160–162°; $[\alpha]^{26}D$ +129.9° (c 2.1); ir bands at 3582, 3520, 1770, 1720, 1670, and 1644 cm^{-1}; CD curve λ_{max} 249 nm (θ +2226, c 0.56); it polymerized on standing. The high resolution mass spectrum exhibited a weak M^+ peak (0.4%).

Anal. Calcd for $C_{20}H_{24}O_6$: C, 66.65; H, 6.71; O, 26.64; mol wt, 360.1571. Found: C, 67.04; H, 6.85; O, 26.16; mol wt, 360.1558.

Acetylsubacaulin (**2b**).—Acetylation of 0.2 g of **2a** with 1 ml of acetic anhydride and 2 ml of pyridine overnight at room temperature followed by the usual work-up gave a gum which showed one major and two minor spots on tlc. Repeated preparative tlc resulted in homogeneous, crystalline material which had mp 154–156°; ir bands (KBr) at 1775, 1748, 1715 (split), 1662, and 1630 cm^{-1}; $[\alpha]^{26}D$ +110.6° (c 1.85).

Anal. Calcd for $C_{22}H_{26}O_7$: C, 65.66; H, 6.51; O, 27.83; mol wt, 402.1679. Found: C, 65.25; H, 6.62; O, 27.61; mol wt, 402.1686.

Tetrahydroberlandin (**3**).—A solution of 78 mg of berlandin in 20 ml of ethyl acetate was reduced catalytically with 58 mg of 5% Pd–C in an atmosphere of hydrogen for 5 hr. The filtered solution was evaporated *in vacuo*, and the residue was purified by preparative tlc and recrystallized from ethyl acetate–hexane: yield 48 mg; mp 130–132°; ir bands at 1778, 1745, 1735, and 1645 cm^{-1}.

Anal. Calcd for $C_{22}H_{30}O_7$: C, 65.01; H, 7.44; O, 27.55; mol wt, 406.1991. Found: C, 65.33; H, 7.40; O, 27.21; mol wt, 406.1991.

Tetrahydroacetylsubacaulin (**4b**).—Hydrogenation of 60 mg of **2b** in the manner described for berlandin and purification by preparative tlc gave 58 mg of a gum, ir bands at 1778, 1740, 1735, and 1650 cm^{-1}. The gum did not give a satisfactory elemental analysis, but its mass spectrum exhibited a relatively weak (1.2%) molecular ion of the correct composition. Other significant peaks in the high-mass region corresponded to the loss of C_2H_4 (1.4%), C_2H_2O (1%), C_2H_3O (1.5%), C_2H_4O (1.4%), and $C_2H_4O_2$ (14.0%); base peak $C_5H_9O^+$.

Anal. Calcd for $C_{22}H_{30}O_7$: mol wt, 406.1990. Found: mol wt, 406.1979.

Tetrahydrosubacaulin (**4a**).—Hydrogenation of 102 mg of **2a**, purification by preparative tlc, and recrystallization from ethyl acetate–hexane afforded 80 mg of **4b**, mp 165–168°, ir bands at 3500, 1770, 1735, and 1640 cm^{-1}. The mass spectrum exhibited a weak molecular ion (0.7%); the next three peaks were also weak and corresponded to M − H_2O (0.2%), M − C_5H_8O (0.6%), and M − C_5H_9O (1.0%).

Anal. Calcd for $C_{20}H_{28}O_6$: C, 65.92; H, 7.74; O, 26.34; mol wt, 364.1884. Found: C, 65.54; H, 7.72; O, 26.23; mol wt, 364.1886.

Berlandin Epoxide (**5**).—A solution of 0.1 g of **1** and 75 mg of *m*-chloroperbenzoic acid in 3 ml of chloroform was left overnight and worked up in the usual manner. Purification of the product by preparative tlc and recrystallization of the major fraction from ethyl acetate–hexane afforded 46 mg of **5**, mp 228–232° dec, ir bands at 1775, 1750, 1720, 1665, and 1640 cm^{-1}.

Anal. Calcd for $C_{22}H_{28}O_8$: C, 63.15; H, 6.28; O, 30.59. Found: C, 63.46; H, 6.28; O, 29.90.

Reaction of Berlandin with HCl.—A mixture of 102 mg of **1**, 5 ml of dioxane, and 0.2 ml of concentrated HCl was stirred at room temperature for 2 days and concentrated at reduced pressure. The residue was purified by preparative tlc. The less polar fraction (**6**) was recrystallized from ethyl acetate–hexane: yield 80 mg; mp 144–145°; ir bands at 3662, 3580, 1775, 1740, 1720, 1662, and 1642 cm^{-1}. Since the material was recovered unchanged after attempted acetylation with acetic anhydride–pyridine at room temperature, the hydroxyl group was assumed to be tertiary.

Anal. Calcd for $C_{22}H_{27}O_7Cl$: C, 60.10; H, 6.10; Cl, 8.20. Found: C, 60.58; H, 6.27; Cl, 7.96.

The more polar fraction (**7**) was recrystallized from ethyl acetate–hexane: yield 10 mg; mp 200–202°; ir bands at 3670, 3590, 3450, 1770, 1745, 1720, 1662, and 1645 cm^{-1}.

Anal. Calcd for $C_{22}H_{27}O_7Cl$: C, 60.10; H, 6.10; Cl, 8.20. Found: C, 59.97; H, 6.24; Cl, 7.93.

Registry No.—**1**, 34829-00-0; **2a**, 34837-46-2; **2b**, 34837-47-3; **3**, 34829-01-1; **4a**, 34837-48-4; **4b**, 34837-49-5; **5**, 34829-02-2; **6**, 34829-03-3; **7**, 34829-04-4.

Neighboring Group Participation in Carbohydrate Chemistry. III.[1] Neighboring Group Participation of the 6-Hydroxyl Group in a Nucleophilic Displacement of a 5-*p*-Toluenesulfonate[2a]

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The neighboring group participation of a 6-hydroxyl group in the nucleophilic displacement of a 5-*p*-tolylsulfonyl group by acetate in a model compound, 1,2-*O*-isopropylidene-3,5-di-*O*-*p*-tolylsulfonyl-α-D-glucofuranose (**3**), was investigated. The conversion of **3** into 6-*O*-acetyl-1,2-*O*-isopropylidene-3-*O*-*p*-tolylsulfonyl-β-L-idofuranose (**5**) by refluxing a solution of **3** in *N*,*N*-dimethylformamide containing anhydrous potassium acetate was assumed to proceed *via* a transition state or an intermediate involving the protonated 5,6-anhydro derivative **12**. The solvent dependence of the reaction was studied. Solvolysis of **3** in *N*,*N*-dimethylformamide, in the presence and absence of $CaCO_3$, yielded 6-*O*-formyl-1,2-*O*-isopropylidene-3-*O*-*p*-tolylsulfonyl-β-L-idofuranose (**13**). A mechanism for this reaction, which probably involves the neighboring group participation of the hydroxyl group, is proposed.

The hydroxyl group in its un-ionized form has generally been considered to have a low driving force for neighboring group participation,[3,4] and there are only a few examples reported in the carbohydrate literature where such participation could be assumed.[5,6] However, the alkoxide anion is known[7] as a good par-

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(7) S. Winstein and H. J. Lucas, *ibid.*, **61**, 1576 (1939); A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," 2nd ed, Wiley, New York, N. Y., 1961, p 291.