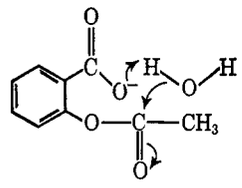
concentration of carboxylate in the hydrolysis of aspirin.



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A difference in the relative orientation of the catalytic residue and the carbonyl carbon atom in **6** and **7** is probably responsible for the difference in the efficiencies of the two catalysts. Also, if a significant fraction of **1** exists, in the unreactive tetrahedral form **5**, the estimate of the effective concentration of the imidazole residue in **6** would be too low.

Registry No.—**1**, 5959-80-8; **2**, 20452-82-8; **3**, 20452-83-9; **4**, 550-44-7.

Stereochemistry of Flexuosin A and Related Compounds[1,2]

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2-Acetylflexuosin A and autumnolide, two new sesquiterpene lactones, were isolated from an Alabama collection of *Helenium autumnale* L. Correlation of the former with linifolin A led to the elucidation of the complete stereochemistry of flexuosin A and its congeners.

Helenium autumnale L. collections of unspecified provenance are reported[3] to serve as sources of the pseudoguaianolide helenalin (**1**), but more recent extractions of plant material from North Carolina[4] and Pennsylvania[5] yielded other sesquiterpene lactones and no helenalin.[6] In an effort to shed light on these variations we have examined several southeastern collections of *H. autumnale*. Material from northwestern Florida and southern Georgia gave respectable yields of helenalin, as claimed in the early[3] literature. On the other hand material from Greene County, Ala., gave instead of helenalin two previously unreported sesquiterpene lactones. The study of these compounds allowed us to clarify the structure of flexuosin A[10] and is described in this paper.

The substance obtained in larger yield (0.3%), $C_{19}H_{26}O_7$, mp 124–126°, exhibited ir bands (see Experimental Section) which indicated the presence of one hydroxyl group, two esters, and an α,β-unsaturated γ-lactone. That the ester bands were derived from two secondary acetates as suggested by the empirical formula was verified by the nmr spectrum, which had two singlets at 1.98 and 2.00, a doublet at 5.36, and a triplet of doublets at 4.52 ppm. The nmr spectrum also had the signals characteristic of the usual α,β-unsaturated γ-lactone function associated with pseudoguaianolides of the helenalin series (two narrowly split doublets at 6.18 and 5.97 and a complex triplet at 4.9 ppm), one secondary hydroxyl group (broadened doublet at 3.8 ppm), a methyl singlet, and a methyl doublet.

Acetylation of the new lactone afforded diacetylflexuosin A (**2d** devoid of stereochemistry) of known structure and uncertain configuration.[10] Comparison of the nmr spectra of the new lactone, flexuosin A (gross structure **2a**),[10,11] alternilin (gross structure **2b**),[11] and **2d** gave clear evidence for its formulation as 2-acetylflexuosin A (gross structure **2c**). The broadened doublet associated with H-4 exhibited the same chemical shift in the nmr spectra of **2a**, **2b**, and the new lactone, but moved downfield on acetylation to **2d**. On the other hand, **2d** and the new lactone displayed identical chemical shifts for the triplet of doublets associated with H-2 and the doublet associated with H-6.[12]

Oxidation of the new sesquiterpene lactone gave the cyclopentanone derivative **3** (new carbonyl band at 1750 cm^{-1}) whose nmr spectrum (absence of 3.8-ppm signal) confirmed the assignments of the previous paragraph. Pyrolysis of **3** in a nitrogen atmosphere afforded a crystalline substance identical in all respects with linifolin A, whose absolute configuration has been shown[11] to be **4**. This result defined the previously unknown asymmetric centers C-1, C-5, C-6, C-7, and C-8 of flexuosin A, alternilin, and their congeners.

There remained the problem of determining the configuration at C-2 and C-4. Unlike pulchellin,[13] flexuosin A could not be induced to form a carbonate or a sulfite. Hence, the hydroxyl groups were *trans*. The nature of the five-membered ring is such that this information, even with knowledge of the absolute configuration at C-1 and C-5 and of the coupling constants $J_{H\text{-}1,H\text{-}2}$, $J_{H\text{-}2,H\text{-}3a}$, $J_{H\text{-}2,H\text{-}3b}$, $J_{H\text{-}3a,H\text{-}4}$, and $J_{H\text{-}3b,H\text{-}4}$, does not permit an unambiguous assignment of stereochemistry to C-2 and C-4. However, the configura-

(1) Constituents of *Helenium* Species. XXIII. Previous paper, L. Tsai, R. J. Highet, and W. Herz, *J. Org. Chem.*, **34**, 945 (1969).

(2) Supported in part by grants from the National Science Foundation (GP-6362) and the National Institutes of Health (GM-05814).

(3) For leading references see W. Herz, A. Romo de Vivar, J. Romo, and N. Viswanathan, *J. Amer. Chem. Soc.*, **85**, 19 (1963); W. Herz and P. S. Santhanam, *J. Org. Chem.*, **32**, 507 (1967).

(4) R. A. Lucas, R. G. Smith, and L. Dorfman, *ibid.* **29**, 2101 (1964).

(5) W. Herz and P. S. Subramaniam, unpublished results.

(6) The existence of subspecies or varieties may be responsible for these differences. A collection labeled *H. autumnale* var. *canaliculatum* (Lam.) T. and G. (equivalent to *H. latifolium* Mill. according to Rydberg,[7] but not according to Gleason and Cronquist[8] where *H. latifolium* is absorbed in *H. autumnale* var. *autumnale*) furnished[9] tenulin and no helenalin.

(7) P. A. Rydberg, *North American Flora*, **34**, part 2, 119(1915).

(8) H. A. Gleason and A. Cronquist, "Manual of Vascular Plants of the Northeastern United States and Adjacent Canada," D. Van Nostrand Company, Princeton, N. J., 1963.

(9) Unpublished work by B. F. Aycock and A. E. Senear, cited by R. Adams and W. Herz, *J. Amer. Chem. Soc.*, **71**, 2546 (1949).

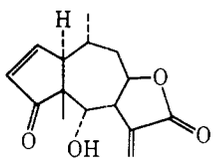
(10) W. Herz, Y. Kishida, and M. V. Lakshmikantham, *Tetrahedron*, **20**, 979 (1964).

(11) W. Herz, C. M. Gast, and P. S. Subramaniam, *J. Org. Chem.*, **33**, 2780 (1968).

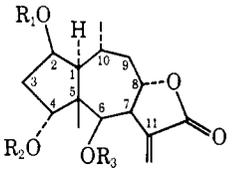
(12) The isolation of authentic **2c** requires that the monoacetylflexuosin A, mp 158–160°, obtained previously[10] in low yield by treatment of flexuosin A with isopropenyl acetate–toluenesulfonic acid be formulated as **2e** (4-acetylflexuosin A).

(13) W. Herz, K. Ueda, and S. Inayama, *Tetrahedron*, **19**, 483 (1963).

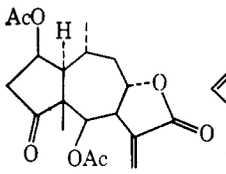
tion at C-4 of dehydroflexuosin A (**5**)[10] has already been deduced as R by application of the Horeau method.[14] Hence the configuration at C-2 of flexuosin A and its derivative must be R also, and the complete formulas of the naturally occurring compounds flexuosin A, 2-acetylflexuosin A, and alternilin are **2a**, **2c**, and **2b**. A



1



2a, R_1, R_2 = H; R_3 = Ac
b, R_2, R_3 = H; R_1 = Ac
c, R_2 = H; R_1, R_3 = Ac
d, R_1, R_2, R_3 = Ac
e, R_1 = H; R_2, R_3 = Ac



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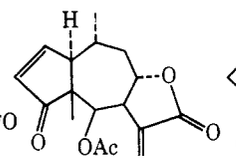

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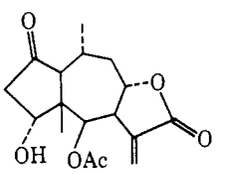

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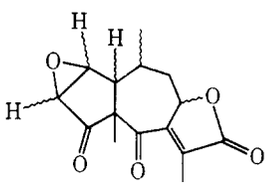
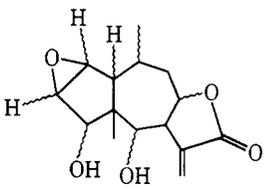


6



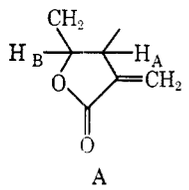
7

comparison of the molecular rotations of **2a**, **2c**, **2d**, and **2e** (Table I) independently indicates that the stereochemistry at C-2 and C-4 is identical (both atoms R).

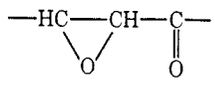
TABLE I
$[M]^{CHCl_3}$ OF FLEXUOSIN A DERIVATIVES

Flexuosin A (**2a**)	40°		
2-Acetylflexuosin A (**2c**)	1°	Δ[M]	−39°
4-Acetylflexuosin A (**2e**)	−0.2°	Δ[M]	−40°
Diacetylflexuosin A (**2d**)	−46°	Δ[M]	−86°

The minor constituent of *H. autumnale* from Alabama, $C_{15}H_{20}O_5$, mp 188–190°, $[\alpha]^{25}D$ 20.6°, has been named autumnolide. The nmr spectrum of this substance (DMSO-d_6) exhibited two doublets associated with the hydroxylic protons of two secondary hydroxyl groups, signals characteristic of partial structure A



A



B

(narrowly split doublets at 6.02 and 5.81, multiplet of H_B at 4.8 ppm), a five-proton multiplet in the range 3.3–3.8 ppm, a methyl doublet, and a methyl singlet. Hence, four of the five oxygen atoms were accounted for.

(14) W. Herz and H. B. Kagan, *J. Org. Chem.*, **32**, 216 (1967).

On conversion of autumnolide into a diacetate, two of the five protons in the 3.3–3.8-ppm cluster experienced a downfield shift and now appeared as doublets at 4.70 and 4.63 ppm, thus establishing the presence of two hydroxyl groups of the type $R_2CH-CH(OH)R_3$. The remaining three low-field protons were assigned to H_A of partial structure A, generally found in the range of 2.9–3.4 ppm, and, because of the presence of a fifth oxygen atom, to two protons on carbon carrying an ethereal oxygen.

Oxidation of autumnolide furnished in very low yield a crystalline diketone which gave a positive KI test for the presence of partial structure B. The nmr spectrum was consonant with formula **6** (disappearance of H_A signal and downfield shift of H_B signal of A, disappearance of all other low-field signals with the exception of a two-proton multiplet near 3.75 ppm, presence of a vinyl methyl resonance) arising from migration of the exocyclic double bond into conjugation with one of the carbonyl groups. This would lead to structure **7** for autumnolide, but the amount of material on hand was not sufficient to establish this unambiguously.

Experimental Section[15]

Extraction of *Helenium autumnale* L.—(A) Powdered *H. autumnale* L., (1.55 kg), collected by Dr. S. McDaniel on Sept 30, 1967, 1 mile north of Pleasant Ridge, Greene County, Ala. (McDaniel voucher 9867 on deposit in herbarium of Mississippi State University), was extracted with chloroform and worked up in the usual manner.[16] The crude gum (26.0 g) was dissolved in the minimum amount of benzene (no tenulin crystallized out on being left overnight) and was chromatographed over 420 g of silicic acid (Mallinckrodt 100 mesh), 400-ml fractions being collected. Fractions 1–6 (benzene), 7–16 (benzene–chloroform 4:1), 17–25 (benzene–chloroform 3:2), and 26–28 (benzene–chloroform 1:1) eluted practically nothing. Fractions 29–31 (benzene–chloroform 1:1) eluted a small amount of gum which showed several spots on tlc and was discarded. Fractions 32–33 (benzene–chloroform 1:1) also eluted a small amount of gum which showed two major spots, one of which corresponded to 2-acetylflexuosin A. Fractions 34–37 (benzene–chloroform 1:1) and 38–49 (benzene–chloroform 2:3) eluted gums showing essentially one spot. Combination and purification by preparative tlc (developer chloroform–methanol 24:1) gave 3.6 g of 2-acetylflexuosin A. The colorless stout needles melted at 124–126° after recrystallization from ether–petroleum ether: ir 3525 (OH), 1765, 1668 (α,β-unsaturated lactone), and 1730 cm^{-1} (double strength, two acetates); nmr 6.18 and 5.97 (d, 3.5, $=CH_2$), 5.36 (d, 3, H-6), 4.9 (td, 7.5, 2, H-8), 4.52 (td, 9, 2.5, H-2), 3.8 (br, sharpens to doublet, J = 4.5 Hz, on addition of D_2O, H-4) 3.15 (m, H-7), 2.0 and 1.98 (acetates), 1.03 (d, 6, C-10 methyl), and 0.79 ppm (C-5 methyl).

Anal. Calcd for $C_{19}H_{26}O_7$: C, 62.28; H, 7.15; O, 30.57. Found: C, 62.27; H, 7.16; O, 30.57.

Fractions 50–53 (benzene–chloroform 1:3) eluted 1.0 g of gum containing 2-acetylflexuosin and impurities which required double preparative tlc before 0.24 g of pure **2c** could be isolated. Fractions 63–69 (benzene–chloroform 1:3) and 57–62 (benzene–chloroform 1:4) eluted complex mixtures. Fractions 63–69 (chloroform) eluted solid material. Two recrystallizations from ethyl acetate–hexane afforded 0.48 g of autumnolide which had mp 188–190°; $[\alpha]^{25}D$ 20.6° *c* 1.84, ($CHCl_3$); ir (Nujol) 3520, 3400 (OH), 1760, and 1660 cm^{-1} (conjugated lactone); nmr DMSO-d_6) 6.02 (d, 2) and 5.61 (d, 1.5, $=CH_2$), 5.15 (d), and

(15) Melting points are uncorrected. Rotations were run in chloroform, ultraviolet spectra in 95% ethanol, infrared spectra in chloroform. Nmr spectra were determined in deuteriochloroform unless specified otherwise on a Varian A-60 spectrometer using tetramethylsilane as internal standard. Chemical shifts are quoted in parts per million, line separations in hertz. Signals are denoted in the usual manner: d, doublet; t, triplet; c, complex signal whose center is given; m, multiplet; br, somewhat broadened singlet. Singlets are unmarked. Analyses were by Dr. F. Pascher, Bonn, Germany.

(16) W. Herz and G. Högenauer, *Ibid.*, **27**, 905 (1962).

4.8 (d, 4, two OH, disappears on exchange with D_2O), the latter superimposed on a one-proton multiplet near 4.75 (H-8), 3.3–3.8 (five-proton multiplet), 1.08 (d, 5, C-10 methyl), and 0.74 ppm (C-5 methyl).

Anal. Calcd for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19; O, 28.54. Found: C, 64.43; H, 7.23; O, 28.88.

(B) Powdered *H. autumnale* L. (5.4 kg), collected by Mr. Robert R. Lazor at the east end of the bridge on Florida Route 20 over the Apalachicola River near Bristol, Liberty County, Fla., in Sept 1968 (Lazor voucher no. 1306 on deposit in the herbarium at Florida State University), was extracted with chloroform and worked up in the usual way. Chromatography of the crude gum (79 g) over 800 g of silicic acid gave in the benzene eluates a small amount of a triterpene mixture. Benzene–chloroform (2:1 and 1:1) gave mixtures. Elution with chloroform gave 20 g of helenalin. Elution with chloroform–ether (9:1 and 8:2) gave mixtures which were not separated satisfactorily on rechromatography.

Extraction of *H. autumnale* L., collected by Mr. R. Lazor and Dr. R. K. Godfrey on Sept 9, 1968, 13 miles south of Moultrie, Ga. (Lazor–Godfrey voucher no. 1185 on deposit in the herbarium of Florida State University), gave results which did not differ significantly from the ones described in the preceding paragraph.

Linifolin A.—Dehydro-2-acetylflexuosin A (**3**) (100 mg) was heated at 180° under nitrogen for 1 hr. The straw-colored solid which formed on cooling was dissolved in benzene and recrystallized to give 95 mg of linifolin A, mp 202–203° (lit. mp 202–204°), mixture melting point with authentic material, undepressed, and nmr and ir spectra superimposable.

Reaction of Flexuosin A with Thionyl Chloride.—A solution of 0.15 g of flexuosin A in 3 ml of dry pyridine was mixed with 10 drops of thionyl chloride at 0°, left at room temperature for 4 hr, and then poured on ice. The product was extracted with ether. The ether extract was washed, dried, and evaporated. The amorphous residue which could not be recrystallized satisfactorily exhibited ir bands at 1770 (γ-lactone), 1745, and 1200 cm^{-1} (acetate), but had no bands characteristic of hydroxyl or sulfite functions. The product gave a positive test for chlorine.

Reactions of 2-Acetylflexuosin.—Acetylation of 120 mg of 2-acetylflexuosin A with acetic anhydride–pyridine in the usual manner afforded, after recrystallization from ether–petroleum ether, 102 mg of material, mp 130–131°, which was identical in all respects (tlc, mixture melting point, and ir and nmr spectrum) with authentic diacetylflexuosin A.

To a solution of 150 mg at 2-acetylflexuosin A in 6 ml of acetone was added dropwise 0.5 ml of Jones reagent[17] with stirring at 0°. After 20 min at room temperature, excess oxidant was destroyed by adding a few drops of methanol. The solution was diluted with water and extracted with ether. Removal of ether followed by recrystallization from acetone–isopropyl ether afforded 114 mg of dehydro-2-acetylflexuosin A (**3**), which had mp 168–170°; ir 1765 and 1670 (unsaturated lactone), 1750 (cyclopentanone), 1740 (esters), and 1410 cm^{-1} (CH_2CO); nmr 6.18 (d, 3.5) and 5.61 (d, 3, $=CH_2$), 5.95 (d, 3.5, H-6), 5.12 (dq, 12, 7, 3, H-2), 4.51 (td 10, 3, H-8), 3.2 (m, three protons, H-3 and H-7), 2.03 and 1.97 (acetates), 1.09 (C-10 methyl), and 1.06 ppm (C-5 methyl); ORD (*c* 0.083, methanol) $[\Phi]_{600}$ 397°, $[\Phi]_{589}$ 442°, $[\Phi]_{310}$ 4575°, $[\Phi]_{276}$ −485°, $[\Phi]_{230}$ 3170°.

Anal. Calcd for $C_{19}H_{24}O_7$: C, 62.63; H, 6.60; O, 30.28. Found: C, 62.70; H, 6.67; O, 30.35.

Diacetylautumnolide.—A mixture of 100 mg of autumnolide, 1 ml of pyridine, and 1 ml of acetic anhydride was heated at 80° for 2 hr. After the usual work-up the crude product was chromatographed over 2 g of silicic acid. Chloroform eluted a product (single spot on tlc) which was recrystallized from ether: yield 52 mg; mp 101–103°; $[\alpha]^{26}D$ −14.6° (*c* 0.835, $CHCl_3$); nmr 6.24 (d) and 5.71 (d, 2, $=CH_2$), 4.70 (d, 6, H-6), and 4.63 (H-4) superimposed on 4.65 (m, H-8), 3.3 (two protons, H-2 and H-3) superimposed on 3.3 (m, H-7), 2.04 and 2.02 (acetates), 1.18 (d, 6, C-10 methyl), and 1.09 ppm C-5 methyl).

Anal. Calcd for $C_{19}H_{24}O_7$: C, 62.63; H, 6.64; O, 30.73. Found: C, 62.48; H, 6.75; O, 30.88.

Attempts to prepose a monoacetyl derivative by acetylation at room temperature resulted in the formation of a glass which appeared to polymerize on standing.

Oxidation of Autumnolide.—Oxidation of 50 mg of autumnolide in 3 ml of acetone with 0.2 ml of Jones reagent in the usual manner afforded a colorless solid mixture (tlc). Preparative tlc over silica gel (developer 6% methanolic chloroform) and recrystallization from acetone–ether permitted isolation of 8 mg of the compound responsible for the major spot. It gave a positive 2-epoxy ketone test with potassium iodide and negative ferric chloride and Zimmermann tests. The poorly resolved nmr spectrum exhibited signals at 5.5 (m, H-8), 3.75 (m, two protons, H-2 and H-3), 1.83 (br, C-11 methyl), and 1.30 (d, 6, C-10 methyl).

Registry No.—**2c**, 20483-26-5; **3**, 20505-31-1; **7**, 20505-32-2; diacetyl **7**, 20483-27-6.

(17) L. Fieser and M. Fieser, "Reagents for Organic Synthesis," John Wiley & Sons, Inc., New York, N. Y., 1967, p 142.

Cleavage of α-Nitro Ketones

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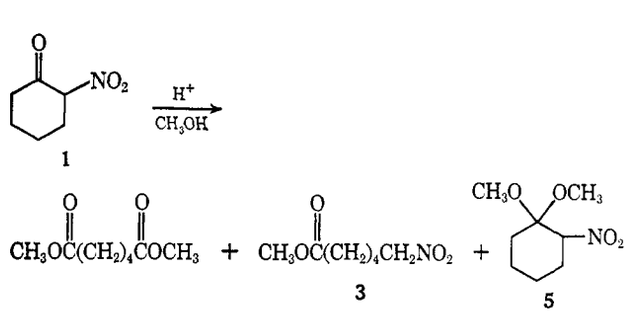
Received January 17, 1969

The cleavage of α-nitro ketones has been recently the subject of several investigations.[2-7] In a previous publication we noted that in refluxing methanolic acetic acid 2-nitrocyclohexanone (**1**) and 2-nitro-3,5,5-trimethylcyclopentanone (**2**) were converted into methyl 6-nitrohexanoate (**3**) and methyl 2,2,4-trimethyl-5-nitropentanoate, respectively, while under similar conditions 2-nitrocycloheptanone (**4**) and 2-nitrocyclooctanone failed to react.

In continuation of our work we have found that cleavage in methanol containing a catalytic amount of concentrated sulfuric acid at room temperature led to different products. As shown in Table I, **1** was converted into dimethyl adipate, 2,2-dimethoxynitrocyclohexane (**5**), and **3** (eq 1). Nitro ketone **4** behaved similarly.



(1)

The respective α-nitro ketals were prepared directly from **1** and **4** in high yield by an acid-catalyzed reaction

(1) Dow Chemical Corp. Fellow, 1963–1964.
(2) H. Feuer and P. M. Pivawer, *J. Org. Chem.*, **31**, 3152 (1966).
(3) A. S. Matlack and D. S. Breslow, *ibid.*, **32**, 1995 (1967).
(4) R. G. Pearson, D. H. Anderson, and L. L. Alt, *J. Amer. Chem. Soc.*, **77**, 527 (1955).
(5) H. O. Larson and E. K. Wat, *ibid.*, **85**, 827 (1963).
(6) A. Hassner and J. Larkin, *ibid.*, **85**, 2181 (1963).
(7) T. Simmons and K. L. Kreuz, *J. Org. Chem.*, **33**, 836 (1968).