THE MOLECULAR STRUCTURE OF 9α-ACETOXYZEXBREVIN

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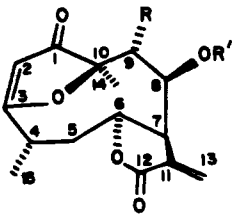
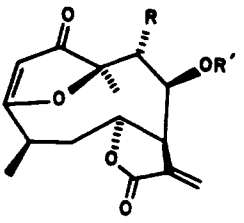
ABSTRACT.—The molecular structure of 9α-acetoxyzexbrevin was determined by single crystal X-ray diffraction. The crystallographic data require revision from the stereostructure **1c** of 9α-acetoxyzexbrevin to **2c** and strongly suggest a change of the stereochemistry at C4 from **1a** to **2a** for zexbrevin as well as its analogs **1b** and **1d** to the respective structures **2b** and **2d**.

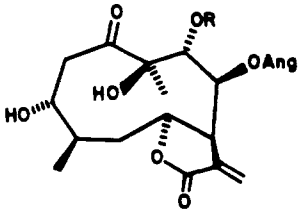
We have recently reported (1) the structure of a new furan-type germacranolide, 9α-acetoxyzexbrevin, which on the basis of extreme similarities with the ^{1}H nmr parameters of zexbrevin was assigned structure **1c**. The structure of zexbrevin had been first reported by Romo de Vivar and coworkers (2). Herz and collaborators (3) later revised the stereochemistry at C8 of zexbrevin. Based on chemical correlation with tirotundin (4), which had been confirmed by X-ray analysis (4), the authors assigned structure **1a** to zexbrevin.



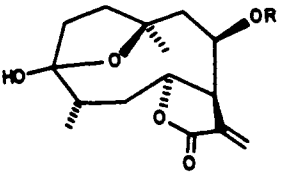
	R	R'
1a,	H	Mac[1]
1b,	H	Tig[1]
1c,	OAc	Mac
1d,	OAc	Ang



	R	R'
2a,	H	Mac
2b,	H	Tig[1]
2c,	OAc	Mac
2d,	OAc	Ang



3a, R=Ac
3b, R=Mebu



4, R=i-Bu

In our recent investigations of the constituents of *Calea ternifolia* var. *calyculata* (5), we had isolated two new sesquiterpene lactones (**3a** and **3b**). Chromate oxidation of **3a** provided a furan-type germacranolide which exhibited ^{1}H nmr parameters for the medium-ring portion that were nearly identical with those of 9α-acetoxyzexbrevin. The change of the C–4 stereochemistry in the transformation of **3a** to **1d** could have occured during the acid-mediated oxidation of **3a**. Alternatively, the configuration at C–4 in 9α-acetoxyzexbrevin (**1c**) and by analogy

[1]Mac=α-methylacrylate; Tig=tiglate; Ang=angelate; Mebu=2-methylbutanoate; i-Bu=isobutyrate.

of zexbrevin (**1a**) required revision. Because of this ambiguity, single crystal X-ray crystallography was performed on 9α-acetoxyzexbrevin, and the stereochemistry at C4 has thus been established to be that depicted in **2c**.

TABLE 1. Coordinates for nonhydrogen atoms in 9α-acetoxyzexbrevin.

Atom	x	y	z
O1	0.7075(3)	0.7064(2)	0.8178(2)
O2	0.6447(3)	0.6784(2)	0.9594(2)
O3	1.0593(2)	0.8389(1)	0.6539(2)
O4	0.9801(3)	1.0712(2)	0.6286(2)
O5	0.8267(2)	0.9600(1)	0.7902(2)
O6	0.8547(3)	1.0728(2)	0.8912(2)
O7	1.2087(3)	0.8913(1)	0.8165(2)
O8	1.2734(4)	1.0117(2)	0.8991(2)
C1	0.9821(4)	0.9882(2)	0.6264(2)
C2	0.8889(4)	0.9242(3)	0.5821(2)
C3	0.9341(4)	0.8419(2)	0.6050(2)
C4	0.8679(4)	0.7486(2)	0.5973(3)
C5	0.8688(4)	0.7063(2)	0.6923(2)
C6	0.8043(4)	0.7666(2)	0.7657(2)
C7	0.9062(3)	0.8103(2)	0.8375(2)
C8	0.9496(4)	0.9121(2)	0.8280(2)
C9	1.0890(4)	0.9413(2)	0.7771(2)
C10	1.0978(4)	0.9316(2)	0.6756(3)
C11	0.8190(4)	0.7966(2)	0.9228(2)
C12	0.7160(4)	0.7220(3)	0.9070(3)
C13	0.8167(5)	0.8414(3)	0.9995(3)
C14	1.2479(4)	0.9528(3)	0.6385(3)
C15	0.7168(5)	0.7519(3)	0.5564(3)
C16	0.7916(4)	1.0413(2)	0.8271(2)
C17	0.6703(4)	1.0868(2)	0.7798(3)
C18	0.6345(6)	1.1781(3)	0.8101(4)
C19	0.5995(5)	1.0467(3)	0.7128(3)
C20	1.2981(4)	0.9365(2)	0.8742(2)
C21	1.4244(5)	0.8810(3)	0.8989(3)

RESULTS AND DISCUSSION

The molecular structure of 9α-acetoxyzexbrevin is illustrated in figure 1. The relative configurations of all chiral centers are established; particularly, methyl group C15 has a β-orientation. Selected torsion angles are listed in table 2. No unusual geometrical features are noted.

The α-methylene-γ-lactone ring is *trans*-fused to the main ring at C6–C7 and exists in an envelope conformation. C7 forms the flap of the envelope and tends in the α-direction 0.36Å out of the plane of the other four atoms of the ring. C13 lies 0.37Å to the opposite (β) side of this plane. The 5-membered lactone ring is distinctly nonplanar, having the sum of five endocyclic torsion angle magnitudes ($\Sigma|\omega|$) of 71.0°. The furanone ring is much more nearly planar, having $\Sigma|\omega| = 20.2°$.

The overall conformation of the molecule is quite similar to that of the related molecule 9-α-hydroxy-11,13-dihydro-11α, 13-epoxyatripliciolide-8β-O-[2-methylacrylate] (1). In comparable portions of the molecules, bond distances and angles are indistinguishable, with a few exceptions, as noted below. Endocyclic torsion angles (table 2) agree well except in the region of C4–C5, which is saturated in the present structure and unsaturated in the epoxide structure. Although both molecules have an 8β-O-[2-methylacrylate] substituent at C8, the orientation of this substituent with respect to the main ring differs. The C7–C8–O5–C16 torsion angle is 136.3° in the present structure and 73.7° in the epoxide structure. This difference appears to be a result of differences in intermolecular interactions. The observed orientation of the methylacrylate group in 9α-acetoxyzexbrevin allows a packing in which there are no unusually close intermolecular contacts.

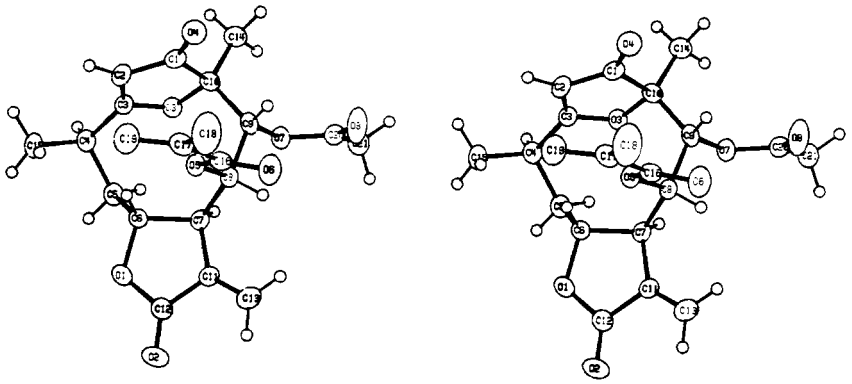


FIGURE 1. Molecular Structure of 9α-acetoxyzexbrevin.

All H · · · H distances are greater than 2.4Å, and all intermolecular contacts between heavy atoms are longer than 3.5Å.

One further difference in the methylacrylate substituents of the two molecules exists. In the epoxide structure, the two terminal groups on C17 are equidistant from C17, with C–C bond length 1.396(4)Å. This indicates disorder involving equally probable methyl and methylene groups at both C18 and C19. In the 9α-acetoxyzexbrevin structure, the two C–C distances are quite different, indicating an ordered structure. The C17–C19 distance, 1.325(5)Å, is identical with that of the C2–C3 double bond, and the C17–C18 distance, 1.455(5)Å, compares well with the C–C single bond length of the acetoxy group, C20–C21 1.464(5)Å.

TABLE 2. Selected Torsion Angles for 9α-acetoxyzexbrevin.

Atom 1	Atom 2	Atom 3	Atom 4	Angle (Deg.)
C1	C2	C3	C4	165.6
C2	C3	C4	C5	−125.3
C3	C4	C5	C6	50.5
C4	C5	C6	C7	−109.0
C5	C6	C7	C8	101.7
C6	C7	C8	C9	−91.6
C7	C8	C9	C10	70.1
C8	C9	C10	C1	61.4
C9	C10	C1	C2	−115.4
C10	C1	C2	C3	3.4
C1	C2	C3	O3	−6.3
C2	C3	O3	C10	6.5
C3	O3	C10	C1	−3.7
O3	C10	C1	C2	0.3
O1	C6	C7	C11	−20.3
C6	C7	C11	C12	21.6
C7	C11	C12	O1	−15.2
C11	C12	O1	C6	1.1
C12	O1	C6	C7	12.8
C7	C8	O5	C16	136.3

The similarities of the ^{1}H nmr parameters of 9α-acetoxyzexbrevin (**2c**) zexbrevin (**1a**) (2,3) and the analogs **1b** (6) and **1d** (5) suggest that the configuration at the C4 methyl group in the latter three compounds is β as in **2c**. Therefore, the stereochemistry at C4 in compounds **1a**,**1b** and **1d** should be changed to **2a**,**2b** and **2d**, respectively.

EXPERIMENTAL

Crystals of **2c** were grown by evaporation of an ethyl acetate solution as large, colorless prisms. A crystal of dimensions 0.24x0.40x0.60mm was used for data collection, performed with MoKα radiation on an Enraf-Nonius CAD4 diffractometer equipped with a graphite

monochromator. *Crystal Data*: $C_{21}H_{24}O_8$, MW=404.4, orthorhombic space group $P2_12_12_1$ a=9.175(3), b=14.716(4), c=14.841(5)Å, Z=4, d_c=1.340 g cm^{-3}, λ=0.71073Å, μ (MoKα)=0.964 cm^{-1}.

Intensity data were measured by use of ω–2θ scans of variable speed designed to yield I~50σ(I) for all significant reflections. Background measurements were made at the beginning and end of each scan, and intensities were corrected accordingly. Of the 2363 reflections in one octant having $2°<2\theta<53°$, 1242 had $F>3\sigma(F)$, and were used in the refinement.

The structure was solved by use of direct methods program MULTAN (7) and refined by full matrix least squares; nonhydrogen atoms were treated anisotropically. Hydrogen atoms were located in difference maps and included as fixed contributions but were not refined. Final R=0.032 (0.087 for all data). Coordinates for nonhydrogen atoms are given in table 1; hydrogen atom coordinates can be obtained from one of the authors (N.H.F.).

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