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STEREOCHEMISTRY OF THE DESMOTROPOSANTONINS

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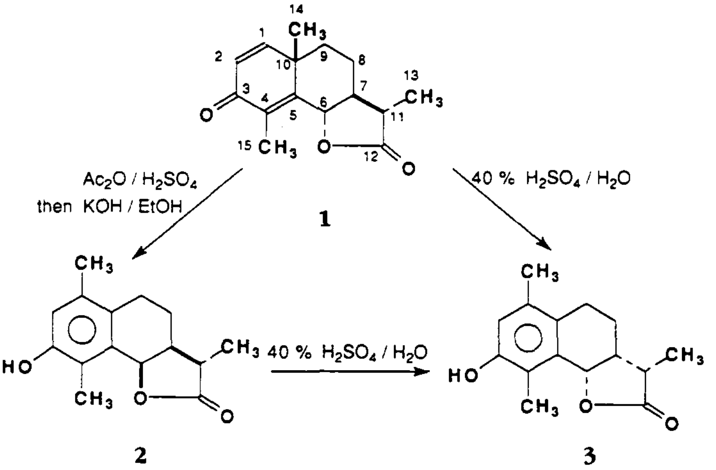
ABSTRACT.—The relative stabilities of the isomers of α-desmotroposantonin [**2**] and β-desmotroposantonin [**3**] have been investigated using molecular mechanics, and the solid state conformation of the acetate of **2** has been determined by X-ray crystallography. On the basis of these data plus ^{1}H- and ^{13}C-nmr spectroscopy, **3** is found to be conformationally homogeneous while **2** is homogeneous as a solid but conformationally inhomogeneous in solution.

The readily available eudesmanolide α-santonin [**1**] has been a well known compound for over a century, and considerable effort was expended in structure elucidation studies and investigations of the rich chemistry of this sesquiterpene (1). These studies resulted in the determination of the gross structure in 1930 (2), and the stereochemistry was confirmed by X-ray crystallography and degradative studies in 1962 (3–5). During the course of these structural studies, it was found that santonin undergoes the dienone-phenol rearrangement under mild conditions to afford (−)-α-desmotroposantonin [**2**], and using more vigorous conditions (+)-β-desmotroposantonin [**3**] is obtained. The abbreviation DTS will be used to denote desmotroposantonin. Reaction of **2** with strong acid also provides **3** (6) (Scheme 1).

On the basis of the formation of **3** from **2** and standard conformational arguments, Woodward and Yates (7) and Corey (8) independently reached the logical (and incorrect) conclusion that (+)-β-DTS was the more stable isomer and that the stereochemistry at C-11 in **1**, **2**, and **3** was opposite to that depicted. A few years ago, work from this laboratory demonstrated that the formation of (+)-β-DTS [**3**] under vigorous acid conditions could be attributed to the extreme insolubility of **3** in most solvents and that the DTS isomers were actually of nearly equal stability (9). First order analysis of the 200 MHz ^{1}H-nmr spectrum of **3** (as the acetate) indicated that the conformation in solution was very similar to that determined by X-ray crystallography of 2-bromo-(−)-β-DTS



SCHEME 1

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(10). Although the nmr data indicated that α-DTS acetate differed conformationally from the β isomer, it was not possible to assign **2** a unique conformation.

We have now carried out an investigation of the relative stabilities of the isomers of DTS using molecular mechanics and have determined the solid state conformation of α-DTS acetate by X-ray crystallography. On the basis of these data, plus a detailed analysis of the ^{1}H- and ^{13}C-nmr spectra of the DTS isomers, we now conclude that while the β isomer is a conformationally homogeneous material, both in solution and the solid state, α-DTS, although homogeneous as a solid, is conformationally inhomogeneous in solution.

RESULTS AND DISCUSSION

The most sensitive probe of solution conformation is nmr spectroscopy, and inasmuch as the original nmr studies of the DTS isomers employed a simple first order analysis of the ^{1}H spectra, a detailed investigation of both the ^{1}H- and ^{13}C-nmr spectra of the acetates of **2** and **3** was carried out. The ^{1}H assignments were verified by employing 2D COSY experiments which confirmed the chemical shifts previously reported (9). For β-DTS [**3**] the coupling constants were also the same as those determined earlier, and in addition the couplings between the quasi-axial proton at C-9 with the equatorial and axial protons at C-8 were found to be 4.5 and 13.0 Hz, respectively. The ^{1}H spectrum of α-DTS [**2**] was much more complex, and a homonuclear decoupling experiment in which the protons at C-13 were irradiated (δ 1.39) gave a value for $J_{7,11}$ of 4.98 Hz rather than 5.69 Hz as previously reported (9).

The ^{13}C spectral assignments for the acetates of **2** and **3** were made using the DEPT spectral editing technique to determine the number of protons bonded to each carbon and 2D HETCOR experiments to correlate the ^{1}H and ^{13}C spectra. The chemical shifts of the carbonyl carbons in both isomers and the quaternary aromatic and aromatic methyl carbons in the β isomer **3** were assigned using the COLOC technique, which reveals long range ^{1}H and ^{13}C coupling. The COLOC spectra for **2** did not permit unambiguous assignments for the quaternary aromatic carbons. The aromatic methyls (C-14 and C-15) were assigned by analogy to **3** and the observation that the di-ortho substituted methyl group will be shielded relative to one with only one ortho substituent (11). These ^{13}C assignments are listed in Table 1.

The ^{13}C spectra of the aromatic portion of both DTS isomers are very similar; however, significant differences are apparent in the chemical shifts of carbons 7, 8, 9, and 13. In particular, in the β isomer, C-8 and C-13 are both shielded by approximately 4 ppm relative to the same carbons in the α isomer. Based on the solid state structure of **3**, the dihedral angle between C-8 and C-13 is 46° (10), which should result in a significant γ-shielding effect. These data, as well as the earlier ^{1}H-nmr spectra (9), are all entirely consistent with the conformation of **3** determined by crystallography in which the alkyl residue at C-7 is equatorial (10).

Although the ^{1}H- and ^{13}C-nmr data indicated that the conformation of (−)-α-DTS [**2**] is clearly different from that of the β isomer, these data could not be interpreted in terms of a unique conformation. In order to ascertain the conformation, at least in the solid state, the structure of the acetate of **2** was determined by X-ray crystallography. As shown in Figure 1, the conformation is essentially identical to that of the β isomer with the C-7 substituent equatorial. However, this conformation is not consistent with the nmr data for the acetate of **2**. In particular, one of the protons at C-8 in the β isomer **3** lies in the shielding cone of lactone carbonyl and appears at quite high field (δ 1.30) (9). Both C-8 protons in the acetate of α-DTS [**2**] appear downfield (δ 1.75 and δ 1.93), indicating that the relationship between C-8 and the lactonic carbonyl must be different in the two DTS isomers. Also, in the experimentally determined structure of **2** (Fig-

TABLE 1. ^{13}C Assignments for the Acetates of (−)-α-DTS [**2**] and (+)-β-DTS [**3**] (75.469 MHz as $CDCl_3$ solutions; reported in ppm relative to Me_4Si).

Carbon	Compound	
	2	**3**
C-1	129.03[a]	128.87
C-2	123.85	124.02
C-3	147.42	147.25
C-4	131.27[a]	134.60[a]
C-5	134.80[a]	130.56
C-6	75.41	75.12
C-7	41.64	39.45
C-8	23.37	19.22
C-9	24.00	25.43
C-10	134.03[a]	134.76[a]
C-11	40.39	40.40
C-12	179.29	178.49
C-13	14.46	9.37
C-14	19.52	19.51
C-15	12.09	11.73
CH_3CO	20.77	20.77
Me*C*O	169.57	169.55

[a] Values are interchangeable within a vertical column.

ure 1), the dihedral angle between H-7 and H-11 is 100°, which would give rise to a very small coupling constant (0–1 Hz), yet the observed coupling constant is 4.98 Hz.

To resolve this dilemma, the conformations of α- and β-DTS were examined by computer modeling using the program PCModel. Minimized structures of α- and β-DTS in which the C-7 alkyl residue was equatorial were essentially superimposable on unminimized structures generated from experimentally determined X-ray coordinates. More significantly, the calculated energies of the two isomers indicated that the α isomer was favored energetically, but only by 0.3 kcal/mol. The alternative conformation for the DTS isomers in which the group at C-7 is axial showed that for β-DTS this conformer was significantly higher in energy (3.5 kcal/mol) than that with the sub-

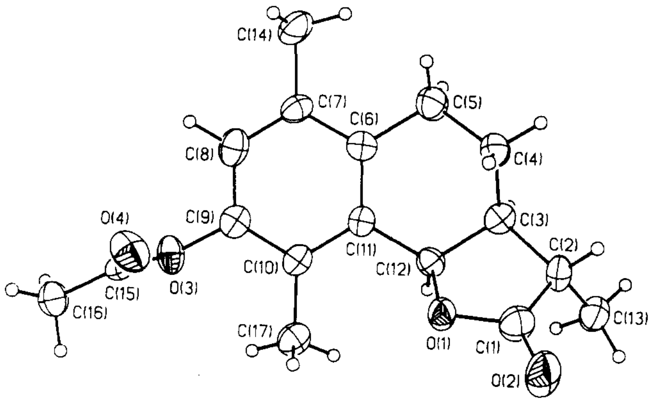

FIGURE 1. Thermal ellipsoid plot (35% probability) of α-DTS acetate.

stituent equatorial. However, for α-DTS [**2**], the axial conformer is only 0.4 kcal/mol higher in energy than the equatorial conformational isomer.

Although this alternative conformation for α-DTS adequately explains the chemical shift data for the protons at C-8, it is incompatible with the observed value of $J_{7,11}$ (4.98 Hz). The calculated dihedral angle of H-7 with H-11 is 161°, which leads to a predicted coupling constant in excess of 10 Hz. All of the data are compatible with a situation in which α-DTS exists in solution as an equilibrium mixture of the two conformers.

Although an attempt to verify this equilibrium using low temperature ^1H nmr was unsuccessful, an indication of changes in the conformational equilibrium was obtained by increasing the temperature. At 27°, $J_{6,7}=6.21$ Hz, which is increased by approximately 1% at 57°, and the complex three-proton multiplet centered about δ 2.5 (H-7, H-9, H-11) showed discernible changes as the temperature was increased. The nature of this equilibrium was substantiated by correlating calculated coupling constants for $J_{6,7}$ and $J_{7,11}$ of a mixture of conformers with the observed values for the acetate of **2**. If it is assumed that the calculated energy difference of the conformers of **2** (0.4 kcal/mol) represents the free energy difference for the conformers, then the equilibrium.mixture at 25° should contain 67% of the equatorial and 33% axial conformer. Coupling constants for each conformer were obtained using the modified Karplus relationship incorporated in the PCModel program (12). For the equatorial conformer this gives $J_{6,7}=5.1$ Hz and $J_{7,11}=0.6$ Hz; and for the axial conformer, 7.4 Hz and 11.5 Hz, respectively. The weighted averages, $J_{6,7}=5.8$ Hz and $J_{7,11}=4.2$ Hz, are in reasonable agreement with the observed values of 6.21 Hz and 4.98 Hz.

Alternatively, if the observed and calculated coupling constants are employed to calculate the energy difference between the two conformers of α-DTS, $J_{6,7}$ indicates that they are of equal stability. Using $J_{7,11}$ the equatorial conformer is more stable by 0.2 kcal/mol. These data are consistent with the calculated energy difference between the two conformers. In order to check the validity of this approach, the modified Karplus equation (12) was used to calculate $J_{6,7}$ for β-DTS. The calculated coupling constant of 4.7 Hz is in excellent agreement with the observed value of 4.59 Hz (9).

These crystallographic and nmr data, which have been interpreted with the assistance of computer modeling, would appear to have finally resolved the remaining questions concerning the relative stabilities and conformations of the desmotroposantonins.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—The conversion of commercial (Polysciences) α-santonin [**1**] to the acetates of α-DTS [**2**] and β-DTS was carried out as described previously (9,13). ^1H- and ^{13}C-nmr spectra were determined as $CDCl_3$ solutions using a Bruker AC300 spectrometer at 300 MHz and 75.469 MHz, respectively. The COSY, HETCOR, and COLOC spectra were all run in absolute value mode using pulse sequences supplied with the spectrometer. The program PCModel is a modified MM2/MMP1 molecular mechanics program which incorporates the MODEL graphical interface marketed by Serena Software, Bloomington, IN.

X-RAY ANALYSIS OF A α-DESMOTROPOSANTONIN ACETATE[2].—A colorless parallelepiped crystal of $C_{17}H_{20}O_4$, having approximate dimensions of 0.12° × 0.27° × 0.38 mm, was mounted on the end of a glass fiber. All measurements were made on a Nicolet R3mV diffractometer with graphite-monochromated MoKα radiation (λ = 0.71073 Å).

Cell parameters and an orientation matrix for data collection, obtained from a least-squares analysis of the setting angles of 18 carefully centered reflections in the range $15.55<2\theta<29.05°$, corresponded to an

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[2] Atomic coordinates for this structure have been deposited with the Cambridge Crystallographic Data Centre and can be obtained on request from Dr. Olga Kennard, University Chemical Laboratory, 12 Union Road, Cambridge CB2 1EZ, UK.

orthorhombic cell with dimensions $a = 7.350$ (4) Å, $b = 9.956$ (6) Å, $c = 21.094$ (18) Å, v = 1543 (2) $Å^3$. For Z = 4 and F.W. = 288.34, the calculated density is 1.24 g/cm^3. Based on the systematic absences of $h00$, $h = 2n + 1$, $0k0$, $k = 2n + 1$; $00l$, $l = 2n + 1$, and the successful solution and refinement of the structure, the space group was determined to be: $P2_12_12_1$ (#19). The data were collected at a temperature of 21 ± 1°, using the ω–2θ scan technique to a maximum 2θ value of 45°. Scans of 0.60° below $K\alpha_1$ to 0.60° above $K\alpha_2$ were made at a speed of 2.09°/min (in omega). Stationary crystal, stationary counter background counts were measured at each end of the scan for one-half of the total scan time. The diameter of the incident beam collimator was 1.0 mm, and the crystal-to-detector distance was 19.5 cm.

A total of 1185 reflections were collected (-8 11 23). The intensities of three representative reflections, measured after every 100 reflections remained constant (±2%) throughout data collection (38.4 hours of X-ray exposure), indicating crystal and electronic stability. The linear absorption coefficient for MoKα radiation is 0.08 mm^{-1}; an absorption correction was not deemed necessary. The data were corrected for Lorentz and polarization effects.

The structure was solved by direct methods. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were located by standard difference Fourier techniques and were included in the structure factor calculation at optimized positions ($d_{C\text{-}H} = 0.96$ Å), and were allowed to ride on the atom to which they were bonded. Methyl groups C-14 and C-17 were found to be disordered; two equivalent sets of half-occupancy hydrogen atoms were included to model this disorder. An isotropic group thermal parameter ($U_{iso} = 0.089$ (6) $Å^2$) was refined for all of the hydrogens. The final cycle of full-matrix least-squares refinement was based on 899 observed reflections [$I > 2\sigma(I)$] and 192 variable parameters and converged (largest parameter shift was 0.01 times its ESD) with final residual values of R = 0.0571, $R_w = 0.0610$ and S = 1.78. The weighting scheme was based on sin θ/λ magnitude of F, and parity class showed no unusual trends. Peaks on the final difference map ranged from −0.22 to 0.31 e^- $Å^3$.

Structure solution, refinement, and the calculation of derived results were performed using the SHELXTL (14) package of computer programs. Neutral atom scattering factors were those of Cromer and Weber (15), and the real and imaginary anomalous dispersion corrections were those of Cromer (16). The atomic coordinates and equivalent thermal parameters are summarized in Table 2.

TABLE 2. Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Thermal Parameters ($Å^2 \times 10^3$) for the Acetate of (−)-α-DTS [**2**].

Atom	x	y	z	U(eq)[a]
O-1	3177 (6)	3718 (4)	7267 (2)	53 (2)
O-2	1905 (9)	3523 (6)	8220 (2)	96 (2)
O-3	7637 (7)	5653 (5)	5494 (2)	55 (2)
O-4	9836 (7)	5502 (5)	6220 (3)	69 (2)
C-1	1997 (11)	3133 (8)	7672 (3)	63 (3)
C-2	894 (9)	2064 (7)	7366 (3)	50 (3)
C-3	1938 (9)	1821 (7)	6741 (3)	47 (2)
C-4	3388 (10	734 (7)	6808 (3)	55 (3)
C-5	4545 (10)	629 (7)	6217 (3)	59 (3)
C-6	5356 (9)	1983 (7)	6037 (3)	42 (2)
C-7	6900 (10)	2025 (7)	5646 (3)	49 (3)
C-8	7647 (11)	3261 (8)	5492 (3)	57 (3)
C-9	6877 (10)	4445 (7)	5717 (3)	48 (3)
C-10	5360 (9)	4446 (7)	6097 (3)	42 (2)
C-11	4594 (9)	3192 (7)	6257 (3)	40 (2)
C-12	2844 (9)	3179 (6)	6627 (3)	44 (2)
C-13	−1096 (10)	2460 (8)	7294 (3)	63 (3)
C-14	7738 (12)	736 (7)	5403 (3)	69 (3)
C-15	9169 (10)	6086 (7)	5781 (4)	48 (3)
C-16	9874 (1)	7324 (7)	5477 (3)	71 (3)
C-17	4590 (10)	5762 (7)	6308 (3)	57 (3)

[a] Equivalent isotropic U defined as one third of the trace of the orthogonalized U_{ij} tensor.

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