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The Crystal and Molecular Structure of the Unusual Spiro Dihydrofuran Diterpene Nepetaefolin[1]

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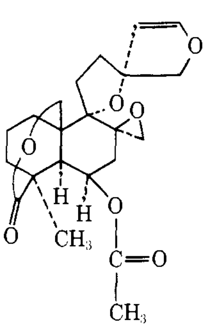
Abstract: The crystal and molecular structure of the spiro dihydrofuran diterpene nepetaefolin (1) has been determined. The structure was solved by direct methods analysis of data from a crystal with space group $P2_12_12_1$ and $a = 11.092 \pm 0.002$ Å, $b = 11.484 \pm 0.002$ Å, $c = 15.379 \pm 0.003$ Å, $Z = 4$ and density $\rho_{calcd} = 1.371$ g/cm^3. An anisotropic large-block least-squares refinement converged to a conventional residual of $R = 0.042$ for 2015 reflections recorded with Cu Kα radiation on an automatic four-circle diffractometer. The effects of the considerable steric interactions in this molecule on the bond lengths are discussed.

Many species of the wide-spread family Labiatae[2] have been employed in primitive medical treatment of cancer.[2,3] In previous attempts to locate discrete antineoplastic agents produced by Labiatae species, a sample of *Leonotis nepetaefolia* (L.) R. Br. collected in India[4] was investigated, and another sample of this plant, collected in Puerto Rico, was also evaluated.[5] In both cases, ethanol (50%) extracts showed activity in the National Cancer Institute's Walker carcinosarcoma 256 (intramuscular, WM) screening system.[6]



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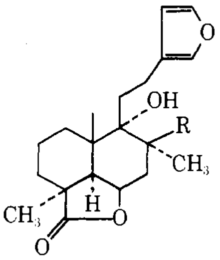
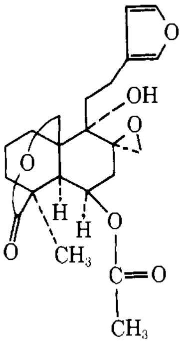


2, R = OH
3, R = H



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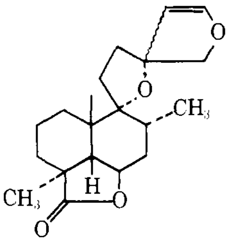

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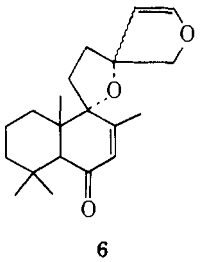

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One component of *Leonotis nepetaefolia* is the spiro dihydrofuran nepetaefolin. After a very thorough chemical study of nepetaefolin (from *Leonotis nepetaefolia* collected in Trinidad), a structure was proposed by two of us.[7] However, this study did not establish the stereochemistry at the spiro dihydrofuran carbon. Although we have not yet been able to obtain enough nepetaefolin to properly assess its antineoplastic activity, we have undertaken a detailed crys-

Table I. Starting Set for Phase Determination

h	k	l	E	Assigned phase	True phase	P+
0	10	0	3.31	0	0	0.99
0	12	0	3.13	0	0	0.98
0	10	2	2.29	0	π	0.89
0	2	18	2.21	π	0	0.29
0	8	10	1.67	π	π	0.23
0	0	8	1.58	π	π	0.20
8	0	12	1.50	0	π	0.69
0	4	14	1.40	0	0	0.74
2	0	16	1.39	0	0	0.76
0	6	4	1.57	π	π	
0	2	10	1.52	π	π	
1	0	4	2.23	0	π	
3	0	1	1.76	$\pi/2$	$-\pi/2$	
8	1	9	2.16	π	-0.94π	
4	8	6	1.85	$\pi/2$	0.37π	

Table II. Atomic Fractional Coordinates[a]

Atom	x	y	z
C1	0.1686 (3)	−0.0811 (3)	0.4853 (2)
C2	0.0728 (3)	−0.0881 (3)	0.5562 (2)
C3	−0.0327 (3)	−0.0083 (3)	0.5361 (2)
C4	−0.0819 (2)	−0.0196 (2)	0.4423 (2)
C5	0.0232 (2)	−0.0034 (2)	0.3774 (2)
C6	−0.0190 (2)	0.0096 (2)	0.2835 (2)
C7	0.0854 (2)	0.0132 (2)	0.2199 (2)
C8	0.1706 (2)	−0.0866 (2)	0.2328 (2)
C9	0.2229 (2)	−0.0948 (2)	0.3249 (2)
C10	0.1177 (2)	−0.1004 (2)	0.3942 (2)
C11	0.3182 (3)	−0.1918 (2)	0.3355 (2)
C12	0.4363 (3)	−0.1285 (3)	0.3155 (2)
C13	0.4157 (2)	−0.0057 (3)	0.3520 (2)
C14	0.4497 (3)	0.0155 (3)	0.4448 (2)
C15	0.5019 (3)	0.1186 (4)	0.4509 (3)
O16	0.5180 (2)	0.1751 (2)	0.3725 (2)
C17	0.4872 (3)	0.0910 (3)	0.3082 (2)
O18	0.2860 (1)	0.0135 (1)	0.3382 (1)
C19	0.0594 (3)	−0.2211 (2)	0.3873 (2)
C4a	−0.1813 (3)	0.0723 (3)	0.4304 (3)
C4b	−0.1361 (3)	−0.1400 (3)	0.4342 (2)
O4c	−0.0621 (2)	−0.2314 (2)	0.4230 (1)
O4d	−0.2423 (2)	−0.1602 (2)	0.4442 (2)
O6a	−0.0950 (2)	−0.0901 (2)	0.2636 (1)
C6b	−0.1852 (3)	−0.0752 (3)	0.2080 (2)
O6c	−0.2057 (3)	0.0152 (2)	0.1731 (2)
C6d	−0.2515 (4)	−0.1869 (3)	0.1935 (3)
O8b	0.1288 (2)	−0.1945 (2)	0.1940 (1)
C8a	0.2322 (3)	−0.1355 (3)	0.1568 (2)

[a] The estimated standard deviations from the last set of least-squares refinements is shown in parentheses.

tal structure analysis to complete the structural assignment (1) for this interesting Labiatae constituent.

Experimental Section

Nepetaefolin ($C_{22}H_{28}O_7$) crystallized as well-formed prisms from acetone-heptane. X-Ray diffraction photographs displayed orthorhombic symmetry with the systematic extinctions $h00$ for $h = 2n + 1$, $0k0$ for $k = 2n + 1$ and $00l$ for $l = 2n + 1$ which uniquely conformed to the noncentrosymmetric space group $P2_12_12_1$. A total of 99 reflections within the angular range $14.0 \leq 2\theta \leq 65.3$ for Cu Kα radiation was automatically centered on a Syntex P$\bar{1}$ autodiffractometer; a least-squares refinement of the angular settings gave the lattice parameters $a = 11.092 \pm 0.002$ Å, $b = 11.484 \pm 0.002$ Å, and $c = 15.379 \pm 0.003$ Å which for $Z = 4$ gives $\rho_{calcd} = 1.371$ g/cm^3 ($\rho_{obsd} = 1.369$ g/cm^3).

The diffraction intensities were measured on a 0.35 × 0.18 × 0.12 mm prismatic crystal using Ni-filtered Cu Kα radiation with the diffractometer operating in the variable speed θ-2θ scan mode. For each reflection, the scan speed, between 1 and 8°/min, was determined from the intensity found in a rapid sampling scan. The scans were taken over the range $2\theta K\alpha_1 - 1.0°$ to $2\theta K\alpha_2 + 1.0°$ with background counts for 0.25 of the scan time taken at each end of the scan. A total of 2112 reflections were investigated within the limits of the diffractometer ($2\theta \leq 140°$) of which 2015 were retained as objectively observed with $|F_0| \geq 0.675\sigma_F$; $\sigma_F = 0.025|F_0| + (C + k^2B)^{1/2}R/(2|F_0|\text{Lp})$, where C is the total count in a scan taken at the rate R, and k is the ratio of scanning time to the time for the total background count B. Periodic monitoring of three reflections showed a maximum 2% random variation in intensity during the time of data collection. Corrections were applied for Lorentz and polarization effects, but absorption and extinction effects proved to be negligible. An average thermal parameter (3.85 Å^2) and a scale factor (3.29) require for the calculation of normalized structure factors, $|E_{hkl}|$, were obtained from a Wilson analysis.[8]

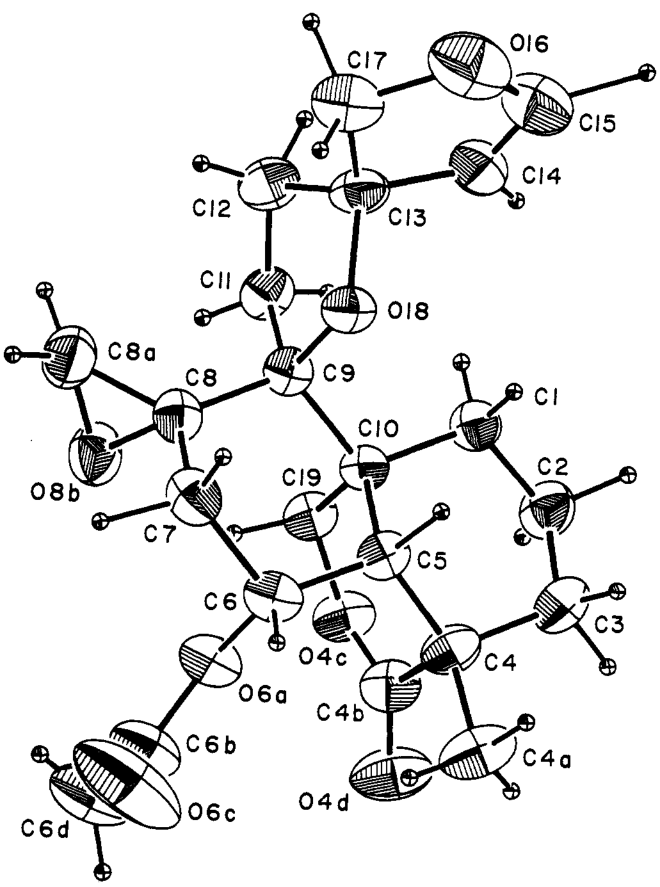

Figure 1. A perspective representation of the structure of nepetaefolin. A hydrogen atom on C6d and C19 is hidden from view.

Structure Determination and Refinement. A starting set (Table 1) of 15 phase angles was developed for the initial phase determination. The first nine were assigned on the basis of Σ_1 interactions[9] in the space group $P2_12_12_1$. The next two were assigned from Σ_2 interactions[10] from within the first nine. The last four reflections specify the origin and the enantiomorph;[11] two of these were assigned phases consistent with values of $2\phi_{hkl}$ (0 or π) obtained from a squared-tangent formalism.[12,13] An additional 78 values of $2\phi_{hkl}$ were used in a generalized tangent[13,14] refinement of 242 reflections. An initial four cycles of refinement with the phases taken from the average of

$$T_{21} = \frac{\langle |E_k|^2 |E_{h-2k}| \sin(2\phi_k + \phi_{h-2k}) \rangle_k}{\langle |E_k|^2 |E_{h-2k}| \cos(2\phi_k + \phi_{h-2k}) \rangle_k} = \tan \phi_k$$

and the more familiar

$$T_{11} = \frac{\langle |E_k||E_{h-k}| \sin(\phi_k + \phi_{h-k}) \rangle_k}{\langle |E_k||E_{h-k}| \cos(\phi_k + \phi_{h-k}) \rangle_k} = \tan \phi_k$$ [9]

gave 168 phases with an average consistency,[13] $C = 0.35$. These phases were applied to three cycles of T_{11} refinement of the 242 reflections followed by an additional three cycles of T_{11} refinement of a larger set of 385 reflections. This gave 283 phases with an average consistency, $C = 0.47$. In a Fourier synthesis utilizing these

Table III. Thermal Parameters[a]

Atom	B_{11}	B_{22}	B_{33}	B_{12}	B_{13}	B_{23}	B_{iso}[b]
C1	3.54 (11)	3.50 (12)	2.76 (10)	0.15 (10)	0.09 (9)	0.41 (9)	3.22
C2	4.52 (14)	4.86 (14)	2.85 (11)	0.11 (13)	0.57 (11)	0.65 (11)	3.90
C3	4.13 (13)	4.63 (14)	3.66 (12)	0.25 (13)	1.38 (11)	0.04 (12)	3.94
C4	3.14 (11)	3.03 (11)	3.99 (12)	0.22 (10)	0.80 (10)	0.63 (10)	3.26
C5	2.73 (9)	2.14 (9)	3.04 (10)	0.05 (8)	0.23 (8)	0.31 (8)	2.59
C6	2.82 (10)	2.37 (10)	3.57 (11)	−0.15 (9)	−0.30 (9)	0.55 (9)	2.83
C7	3.49 (11)	3.12 (11)	2.75 (10)	−0.52 (10)	−0.25 (9)	0.64 (9)	3.02
C8	3.51 (11)	2.66 (10)	2.80 (10)	−0.49 (9)	0.14 (9)	0.11 (9)	2.94
C9	2.86 (10)	2.38 (9)	2.82 (10)	0.24 (9)	0.02 (9)	0.11 (8)	2.67
C10	2.62 (9)	2.62 (10)	2.68 (10)	−0.06 (8)	0.07 (8)	0.38 (8)	2.62
C11	3.86 (12)	2.85 (11)	3.89 (12)	0.84 (10)	0.23 (11)	0.23 (10)	3.41
C12	3.34 (12)	3,73 (12)	4.85 (14)	0.84 (11)	0.29 (11)	0.20 (11)	3,84
C13	2.31 (9)	3.87 (12)	3.69 (11)	0.32 (10)	0.06 (9)	0.35 (10)	3.19
C14	3.52 (12)	5.36 (16)	3.90 (13)	0.05 (13)	−0.66 (11)	−0.08 (12)	4.15
C15	3.82 (14)	6.63 (20)	5.63 (18)	−0.25 (15)	−0.96 (14)	−0.93 (16)	5.10
O16	4.47 (11)	5.06 (12)	6.74 (14)	−1.18 (10)	−0.58 (11)	−0.02 (11)	5.21
C17	3.30 (12)	4.29 (14)	5.06 (15)	−0.31 (12)	−0.00 (12)	0.60 (13)	4.12
O18	2.31 (6)	2.61 (7)	3.44 (7)	−0.12 (6)	0.08 (6)	0.01 (6)	2.74
C19	3.38 (11)	2.54 (10)	3.94 (12)	−0.14 (9)	0.39 (10)	0.62 (9)	3.18
C4a	3.44 (13)	4.18 (14)	6.38 (18)	0.89 (12)	1.40 (13)	0.87 (14)	4.27
C4b	3.73 (12)	3.71 (12)	4.19 (14)	−0.64 (11)	0.61 (11)	1.16 (11)	3.65
O4c	3.61 (8)	2.81 (8)	5.04 (10)	−0.50 (7)	0.76 (8)	1.09 (8)	3.61
O4d	3.66 (10)	4.91 (11)	8.44 (16)	−0.88 (9)	1.42 (11)	1.46 (12)	4.98
O6a	3.30 (8)	2.69 (7)	4.15 (9)	−0.40 (7)	−0.86 (7)	0.75 (7)	3.20
C6b	3.73 (13)	3.85 (13)	5.44 (16)	0.01 (12)	−1.74 (12)	0.44 (12)	4.04
O6c	9.02 (19)	4.41 (12)	11.87 (22)	−1.05 (13)	−7.31 (19)	2.14 (14)	6.00
C6d	4.72 (17)	4.74 (17)	9.09 (28)	−1.07 (14)	−2.91 (18)	0.62 (18)	5.37
O8b	5.11 (10)	3.78 (9)	3.77 (9)	−0.92 (9)	0.27 (9)	−0.79 (8)	4.05
C8a	4.70 (14)	4.90 (15)	3.29 (12)	−0.01 (13)	0.45 (12)	−0.42 (12)	4.20

[a] The estimated standard deviations from the last set of least-squares refinements is shown in parentheses. The relation between B_{ij} in Å^2 and the dimensionless β_{ij} used during refinement is $B_{ij} = 4\beta_{ij}/a_i^*a_j^*$. [b] Isotropic thermal parameter calculated from $B_{iso} = 4[V^2 \det(\beta_{ij})]^{1/3}$.

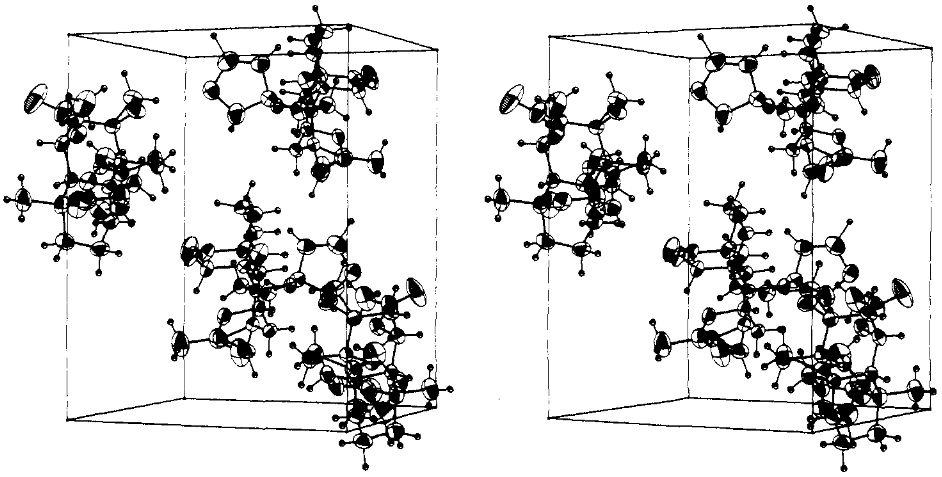

Figure 2. A stereodiagram of the unit cell and four molecules of nepetaefolin.

phases, 16 maxima were identified as a fragment of a plausible molecule. The 385 reflections were phased with these positions and subjected to four cycles of T_{11} refinement.[15] The Fourier synthesis on the 319 phases thus obtained revealed 28 maxima for a nearly complete molecule. The complete structure of 29 atoms was obtained from a Fourier synthesis of $|F_O|$ phased with these results, and a subsequent least-squares refinement (initial R = 0.41) of atom occupancy allowed unambiguous atom identification.

The model was refined with isotropic thermal parameters by full-matrix least-squares[16] analysis with each reflection assigned a weight, $w = 1/\sigma_F^2$, and with atomic scattering factors for C° and O° calculated by Cromer and Mann.[17] At convergence, the standard residual was R = 0.124 and the weighted residual, $R_w = (\Sigma w(|F_O| - |F_c|)^2/\Sigma w|F_O|^2)^{1/2}$, was 0.153. Guided by a difference Fourier synthesis based on these results, all the hydrogen atoms were placed in idealized positions 1.00 Å from their respective heavy atoms and assigned a temperature factor of B = 3.0 Å^2. The model with isotropic thermal motion and including the hydrogen positional parameters was refined by full-matrix least-squares to give the residuals R = 0.101 and R_w = 0.126. The model with anisotropic thermal motion of the nonhydrogen atoms was then refined by large-block least-squares. The blocks, in order of refinement, consisted of hydrogen positions (84 parameters), nonhydrogen positions, and the diagonal temperature factors β_{ii} (175 parameters), and all the nonhydrogen temperature factors β_{ij} (175 parameters). A scale factor was included in each block. The residuals at convergence were R = 0.042 and R_w = 0.053. The estimated error in a reflection of unit weight was 1.163.[18]

Results

Final atomic coordinates and thermal parameters for nepetaefolin (1) are presented in Tables II, III, and IV along with the estimated standard deviations derived from the least-squares analysis. The perspective view shown in Figure 1 displays the essential configurational and conformational features of the molecule. In addition, a stereodiagram of the unit cell is shown in Figure 2. Each nonhydrogen atom is represented by an ellipsoid consistent with the anisotropic thermal parameters in Table III. Since the ab-

Table IV. Hydrogen Atomic Parameters[a]

Atom bound to	x	y	z	Bond, A
C1	0.238	-0.131	0.487	0.96
C1	0.206	-0.007	0.488	0.95
C2	0.108	-0.067	0.620	1.08
C2	0.040	-0.175	0.567	1.07
C3	-0.016	0.078	0.545	1.02
C3	-0.094	-0.008	0.578	0.94
C5	0.069	0.075	0.389	1.04
C6	-0.057	0.075	0.280	0.86
C7	0.123	0.083	0.224	0.90
C7	0.054	0.022	0.157	1.03
C11	0.301	-0.256	0.301	0.93
C11	0.316	-0.222	0.401	1.07
C12	0.450	-0.126	0.252	0.99
C12	0.512	-0.164	0.342	1.03
C14	0.425	-0.041	0.490	0.99
C15	0.538	0.160	0.519	1.22
C17	0.564	0.057	0.290	0.99
C17	0.438	0.129	0.270	0.92
C19	0.107	-0.269	0.424	0.94
C19	0.047	-0.256	0.327	1.02
C4a	-0.143	0.155	0.428	1.04
C4a	-0.213	0.064	0.374	0.94
C4a	-0.237	0.050	0.477	0.98
C6d	-0.265	-0.219	0.251	0.98
C6d	-0.327	-0.166	0.181	0.88
C6d	-0.202	-0.232	0.154	0.97
C8a	0.230	-0.102	0.090	1.09
C8a	0.309	-0.188	0.161	1.04

[a] Reasonable estimates of the error in the fractional coordinates and the bond lengths are ~0.003 and ~0.06 A, respectively.

solute configuration of the decalin ring system in nepetaefolin was found[7] to be the same as for leonotin (**2**)[19] and marrubiin (**3**),[20] nepetaefolin is shown in the correct enantiomorphic form. The configuration of the seven chiral centers are (*S*)-C4, (*S*)-C5, (*R*)-C6, (*S*)-C8, (*S*)-C9, (*S*)-C10, and (*R*)-C13. Bond lengths and angles within the molecule are systematically recorded in Table V.

Discussion

The structure of nepetaefolin (**1**) as proposed by White and Manchand[7] is in complete accord with the results of this crystal structure analysis and, in addition, the stereochemistry at the spiro carbon C13 is now established. This also provides further confirmation of the structures of leonotin and marrubiin which had been correlated[7,19,20] with nepetaefolin via nepetaefuran (**4**).

As expected, the two six-membered rings of the *trans*-decalin system are both in normal chair conformations. All of the bonds in the system are C-C single bonds, and the bond angles are approximately normal tetrahedral angles. However, the very long C9-C10 bond, 1.582 Å, clearly shows the effects of severe crowding between these two tertiary carbon atoms. Similarly the bond C8-C9, 1.534 Å, is affected by crowding between the epoxide at C8 and the large group at C9. In the absence of steric effects, this bond would be as short as the bond C7-C8, 1.498 Å, due to the electronegativity of the epoxide group. Despite the crowding, the epoxide is normal and is an almost perfect equilateral triangle. Its attachment at C8 is assymmetric with C8a closer, 0.52 Å, to the plane C7-C8-C9 than O8b, 0.91 Å.

The very unusual[7] spiro dihydrofuran group attached via the spiro carbon C9 also shows the effects of severe steric crowding. In particular, the bond C13-O18, which is easily broken in acid conditions, is very long, 1.471 Å, for an ether linkage. The neighboring ether bond C9-O18, 1.441 Å, is quite normal. The source of the crowding is the two very close van der Waals contacts at C12-C8a, 3.330(4) Å, on one side and at C14-C1, 3.368(4) Å, on the other. For comparison, the normal van der Waals radius of a methyl group is 2.0 Å.[21] The closest intrahydrogen contacts are 2.32 Å for C14-C1 and 2.22 Å for C12-C8a which are at the low end of the scale for the van der Waals radius of hydrogen, 1.1-1.3 Å.[21] Clearly the easy acid cleavage for the other two compounds having a spiro dihydrofuran group, premarrubiin (**5**)[22] and presolidagenone (**6**),[23] is a consequence of similar steric crowding. Because of this reactivity, the configuration of the spiro carbon C13 in these two compounds has not been correlated with that of nepetaefolin and hence cannot be assigned on the basis of this structure analysis.

Table V. Bond Distances and Angles[a,b]

Bond	Distance, A	Angle, deg	
C1-C2	1.524 (4)	C2-C1-C10	113.0 (2)
C1-C10	1.527 (4)		
C2-C3	1.518 (5)	C1-C2-C3	111.1 (2)
C3-C4	1.548 (4)	C2-C3-C4	114.3 (2)
C4-C5	1.547 (4)	C3-C4-C5	109.0 (2)
C4-C4a	1.537 (4)	C3-C4-C4a	107.8 (2)
C4-C4b	1.512 (4)	C3-C4-C4b	107.1 (2)
		C5-C4-C4a	112.4 (2)
		C5-C4-C4b	110.9 (2)
		C4a-C4-C4b	109.4 (2)
C5-C6	1.525 (4)	C4-C5-C6	113.0 (2)
C5-C10	1.551 (3)	C4-C5-C10	108.4 (2)
		C6-C5-C10	115.9 (2)
C6-C7	1.517 (4)	C5-C6-C7	112.3 (2)
C6-O6a	1.455 (3)	C5-C6-O6a	107.5 (2)
		C7-C6-O6a	109.1 (2)
C7-C8	1.498 (4)	C6-C7-C8	112.0 (2)
C8-C9	1.534 (4)	C7-C8-C9	114.1 (2)
C8-C8a	1.466 (4)	C7-C8-C8a	118.8 (2)
C8-O8b	1.451 (3)	C7-C8-O8b	113.3 (2)
C8a-O8b	1.450 (4)	C9-C8-C8a	122.4 (2)
		C9-C8-O8b	116.6 (2)
		C8a-C8-O8b	59.6 (2)
		C8-C8a-O8b	59.7 (2)
		C8a-O8b-C8	60.7 (2)
C9-C10	1.582 (4)	C8-C9-C10	110.2 (2)
C9-C11	1.544 (4)	C8-C9-C11	113.6 (2)
C9-O18	1.441 (3)	C8-C9-O18	105.2 (2)
		C10-C9-C11	113.9 (2)
		C10-C9-O18	107.3 (2)
		C11-C9-O18	105.9 (2)
C10-C19	1.533 (4)	C1-C10-C5	107.4 (2)
		C1-C10-C9	109.9 (2)
		C1-C10-C19	110.5 (2)
		C5-C10-C9	110.9 (2)
		C5-C10-C19	110.6 (2)
		C9-C10-C19	107.5 (2)
C11-C12	1.528 (4)	C9-C11-C12	102.9 (2)
C12-C13	1.535 (4)	C11-C12-C13	103.6 (2)
C13-C14	1.496 (4)	C12-C13-C14	117.4 (3)
C13-C17	1.521 (4)	C12-C13-C17	115.6 (2)
C13-O18	1 471 (3)	C12-C13-O18	103.3 (2)
		C14-C13-C17	99.9 (2)
		C14-C13-O18	111.1 (2)
		C17-C13-O18	109.7 (2)
C14-C15	1.321 (5)	C13-C14-C15	108.9 (3)
C15-O16	1.381 (5)	C14-C15-O16	114.5 (3)
O16-C17	1.423 (4)	C15-O16-C17	104.9 (3)
		O16-C17-C13	108.2 (3)
		C13-O18-C9	111.5 (2)
C4b-O4c	1.343 (4)	C4-C4b-O4c	118.8 (3)
C4b-O4d	1.211 (4)	C4-C4b-O4d	123.4 (3)
		O4c-C4b-O4d	117.5 (3)
O4c-C19	1.460 (4)	C4b-O4c-C19	123.3 (2)
		O4c-C19-C10	115.9 (2)
O6a-C6b	1.328 (4)	C6-O6a-C6b	118.1 (2)
C6b-O6c	1.190 (4)	O6a-C6b-O6c	123.2 (3)
C6b-C6d	1.495 (5)	O6a-C6b-C6d	110.9 (3)
		O6c-C6b-C6d	125.9 (3)

[a] Estimated standard deviations are shown in parentheses.
[b] Uncorrected for thermal motion effects.

Both rings of the spiro dihydrofuran group are in the envelope conformation. The atom C12 is 0.54 Å out of the plane C11-C9-O18-C13 (average deviation 0.013 Å) and C17 is 0.28 Å out of the plane C13-C14-C15-O16 (average deviation 0.014 Å). Except for C13-O18, all the bonds are normal. In particular the bond C14-C15, 1.321 Å, is a normal double bond, the bond C15-O16, 1.381 Å, is typical for a C-O next to a double bond, and all other bonds are normal single bonds.

The apparent bond lengths in the acetate at C6 are seriously affected by the considerable thermal motion of that group. After application of riding corrections to these bonds and C4b-O4d, both the group of C6 and the δ-lactone, which bridges C4 and C19, display bonding geometries typical of acetate esters. In particular, the corrected bond lengths for O6a-C6b, 1.342(4) Å, and C6b-C6d, 1.518(5) Å, are identical with their counterparts in the δ-lactone group, O4c-C4b and C4-C4b, respectively. The corrected carbonyl bond C4b-O4d, 1.240(4) Å, is typical but the large riding correction obtained for the C6b-O6c bond, 1.255(4) Å, is probably not valid because of the extreme thermal motion of atom O6c.

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Supplementary Material Available. A table of observed and calculated structure amplitudes from the final refinement will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Business Office, Books and Journals Division, American Chemical Society, 1155 16th St., N.W., Washington, D.C. 20036. Remit check or money order for \$4.50 for photocopy or \$2.50 for microfiche, referring to code number JACS-75-6236.

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Uracil and Its Interaction with Silver Ion in Aqueous Alkaline Media[1]

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Abstract: Carbon-13 nuclear magnetic resonance (^{13}C NMR) and uv spectrophotometric data show that uracil is a weak dibasic acid (H_2L) in aqueous alkaline medium: $pK_{a_1} = 9.7$; $pK_{a_2} = 14.2$. ^{13}C NMR data of uracil in neutral media show that the compound exists in the lactam form and ionizes first at the N^3 position and then at N^1. The lactam structure is retained in the monoanion (HL^-). Potentiometric and solubility measurements have shown that four complexes having the formulas AgHL, $Ag(HL)_2^-$, AgL^-, and AgL_2^{3-} can exist depending upon the pH and ratio of silver ion to uracil in the system. Stability constants for these ions were found to be $\beta_{11} = 10^6$, $\beta_{12} = 6 \times 10^8$, $\beta_{21} = 1.5 \times 10^8$, and $\beta_{22} = 1.8 \times 10^{11}$. ^{13}C NMR data show that the site of binding of silver for uracil in species AgL^- and AgL_2^{3-} is N^1-C^2-O.

The interaction of silver (Ag^+) and cyclic imides such as uracil to give alkali-soluble Ag^+ complexes has been known in photographic chemistry and in the patent literature for years.[2] The exact nature of this solubilization process remains largely unexplored in terms of structure and bonding.[3]

In addition, for uracil, a major constituent of ribonucleic acid, the study of model nucleic acid metal compounds assists in the understanding of the complex behavior of nucleic acids.[4]

Recent carbon-13 NMR (^{13}C NMR) studies of nitrogen heterocycles have demonstrated the value of this technique