Two \((E,E)\)- and \((Z,E)\)-thiazol-5-ylpenta-2,4-dienones

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Two \((E,E)\) - and \((Z,E)\)-thiazol-5-yl-penta-2,4-dienones

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In order to characterize the structural elements that might play a role in non-covalent DNA binding by the antitumor antibiotic leinamycin, we have solved the crystal structures of the two leinamycin analogs, methyl \((R)-5\{2-[1-\text{tert-butoxycarbonylamino}]\text{ethyl}\}\text{thiazol-4-yl}\) penta-\((E,E)\)-2,4-dienoate, \(\text{C}_{14}\text{H}_{22}\text{N}_{2}\text{O}_{4}\text{S}\), (II), and 2-methyl-8-oxa-16-thia-3,17-diaza-bicyclo[12.2.1]heptadeca-\((Z,E)-1(17),10,12,14\)-tetraene-4,9-dione, \(\text{C}_{15}\text{H}_{16}\text{N}_{2}\text{O}_{3}\text{S}\), (III). Our results provide the first detailed structural information regarding leinamycin analogs containing the thiazol-5-ylpenta-2,4-dienone moiety.

Comment

Leinamycin, (I), is a natural product with promising antitumor activity (Hara et al., 1989, 1990). This activity is believed to result from the ability of the compound to damage cellular DNA (Hara et al., 1990; Asai et al., 1996; Mitra et al., 1997; Breydo et al., 2001). Leinamycin has a unique structure, containing an unusual 1,2-dithiolan-3-one 1-oxide moiety connected by a spiro linkage to an 18-membered macrocycle. This antibiotic is capable of both DNA alkylation and oxidative DNA damage (Gates, 2000).

Recent studies showing that leinamycin does not efficiently alkylate single-stranded DNA suggest that non-covalent association of leinamycin with the double helix facilitates DNA alkylation by the antibiotic (Asai et al., 1996; Breydo et al., 2002). It seems likely that the macrocycle of leinamycin plays a major role in non-covalent binding of the compound to DNA. Thus, in order to understand better the nature of the interaction between leinamycin and DNA, it is important to characterize the three-dimensional structure of the thiazol-5-ylpenta-2,4-dienone fragment of the antibiotic. Although the crystal structures of leinamycin and several of its derivatives have been solved previously (Hirayama & Matsuzawa, 1993; Kanda et al., 1999), the coordinates for these structures have not been published.

As part of an investigation of non-covalent DNA binding by leinamycin, we prepared several \((E,E)\)- and \((Z,E)\)-thiazol-5-ylpenta-2,4-dienones. Here, we present the crystal structures of methyl \((R)-5\{2-[1-\text{tert-butoxycarbonylamino}]\text{ethyl}\}\text{thiazol-4-yl}\) penta-\((E,E)\)-2,4-dienoate, (II), and 2-methyl-8-oxa-16-thia-3,17-diaza-bicyclo[12.2.1]heptadeca-\((Z,E)-1(17),10,12,14\)-tetraene-4,9-dione, (III). Our results provide the first detailed structural information regarding leinamycin analogs containing the thiazol-5-ylpenta-2,4-dienone moiety.

The structures of (II) and (III) reveal that the penta-2,4-dienone fragment is nearly planar (to within 0.02 Å for (II) and 0.05 Å for (III)), similar to the known structures of compounds containing an \(\alpha,\beta,\gamma,\delta\)-conjugated carbonyl group (Cox, 1994; Rabinovich & Schmidt, 1967). The bond lengths in the penta-2,4-dienone system indicate conjugation (Ladd & Palmer, 1993; Wiberg et al., 1991) between the double bonds and with the thiazole ring. In both compounds, the thiazole ring is twisted out of plane relative to the penta-2,4-dienone moiety, by 12.9 (2)° in (II) and by 21.4 (4)° in (III).

Figure 1

A view of the molecule of (II), shown with 50% probability displacement ellipsoids. H atoms are drawn as small spheres of arbitrary radii.
indicate that the antibiotic also adopts a conformation with a nearly planar penta-2,4-dienone moiety and with the thiazole ring twisted slightly out of plane. The 18-membered macrocycle of leinamycin clearly presents a large hydrophobic surface that may drive association of the natural product with the hydrophobic major groove of duplex DNA (Jadhav et al., 1999). In addition, it is possible that the conjugated thiazol-5-ylpenta-2,4-dienone moiety found in leinamycin may represent a novel type of DNA intercalator, where individual double bonds are part of the intercalating system. Several examples of such small intercalators are known and include esperamycin A1 (Yu et al., 1994), C-1027 (Yu et al., 1995), and amiloride (Bailly et al., 1993). The results reported here may provide important structural information that will ultimately help in the understanding of the detailed nature of the noncovalent interactions between leinamycin and DNA.

**Experimental**

Compounds (II) and (III) were prepared from (R)-N-tetra-butoxy-carbonylalanine and their syntheses will be described separately. Racemization of compound (III) occurred in the course of the synthesis. Crystals of both compounds suitable for X-ray diffraction analysis were obtained by slow evaporation of dichloromethane solutions.

### Compound (II)

**Crystal data**

- **C<sub>16</sub>H<sub>22</sub>N<sub>2</sub>O<sub>4</sub>S**
- **M<sub>r</sub> = 338.42**
- **Triclinic, P<sub>1</sub>**
- **a = 5.207 (2) Å**
- **b = 5.876 (3) Å**
- **c = 15.339 (7) Å**
- **α = 82.21 (1)**
- **β = 81.43 (1)**
- **γ = 72.17 (1)**
- **V = 439.8 (3) Å<sup>3</sup>**
- **Z = 1**
- **D<sub>c</sub> = 1.278 Mg m<sup>−3</sup>**
- **Mo Kα radiation**
- **Cell parameters from 2894 reflections**
- **θ = 2.7–27.1°**
- **µ = 0.20 mm<sup>−1</sup>**
- **T = 173 (2) K**

**Data collection**

- **Bruker SMART CCD area-detector diffractometer**
- **2820 independent reflections**
- **2702 reflections with l > 2σ(l)**
- **θ<sub>min</sub> = 27.1°**
- **θ<sub>max</sub> = 27.1°**
- **h = −6 → 6**
- **k = −7 → 7**
- **l = −19 → 16**
- **4384 measured reflections**

**Refinement**

- **Re-refinement on F<sup>2</sup>**
- **R<sup>2</sup> = 0.035**
- **wR<sup>2</sup> = 0.100**
- **S = 1.12**
- **2820 reflections**
- **213 parameters**
- **H-atom parameters constrained**

**Selected geometric parameters (Å, °) for (II).**

<table>
<thead>
<tr>
<th>Bond/ Angle</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>C2–C3</td>
<td>1.363 (3)</td>
</tr>
<tr>
<td>C2–C11</td>
<td>1.460 (3)</td>
</tr>
<tr>
<td>O4–C15</td>
<td>1.475 (4)</td>
</tr>
<tr>
<td>C11–C12</td>
<td>1.340 (3)</td>
</tr>
<tr>
<td>C3–C2–N1</td>
<td>114.5 (2)</td>
</tr>
<tr>
<td>C3–C2–C11</td>
<td>125.5 (2)</td>
</tr>
<tr>
<td>C12–C11–C2</td>
<td>123.9 (2)</td>
</tr>
<tr>
<td>N1–O4–C15</td>
<td>120.5 (3)</td>
</tr>
<tr>
<td>N1–O4–C15–C14</td>
<td>170</td>
</tr>
</tbody>
</table>

**Table 1**

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</tr>
<tr>
<td>N1–O4–C15–C14</td>
<td>170</td>
</tr>
</tbody>
</table>

### Compound (III)

**Crystal data**

- **C<sub>16</sub>H<sub>22</sub>N<sub>2</sub>O<sub>4</sub>S**
- **M<sub>r</sub> = 292.55**
- **Monoclinic, P<sub>2</sub>1**
- **a = 10.078 (1) Å**
- **b = 8.882 (1) Å**
- **c = 8.512 (1) Å**
- **β = 109.89 (1)**
- **V = 716.5 (1) Å<sup>3</sup>**
- **Z = 2**
- **D<sub>c</sub> = 1.355 Mg m<sup>−3</sup>**
- **Mo Kα radiation**
- **Cell parameters from 2334 reflections**
- **θ = 2.3–27.0°**
- **µ = 0.23 mm<sup>−1</sup>**
- **T = 173 (2) K**

**Data collection**

- **Bruker SMART CCD area-detector diffractometer**
- **2391 independent reflections**
- **2177 reflections with l > 2σ(l)**
- **θ<sub>min</sub> = 0.023**
- **θ<sub>max</sub> = 27.1°**
- **h = −12 → 12**
- **k = −10 → 11**
- **l = −10 → 8**
- **3484 measured reflections**
Refinement

Reefinement on $F^2$

$R[F^2 > 2\sigma(F^2)] = 0.030$

$wR(F^2) = 0.070$

$S = 1.00$

2391 reflections

182 parameters

H-atom parameters constrained

$w = 1/[\sigma^2(F^2) + (0.0425P)^2]$

where $P = (F^2 + 2F_O^2)/3$

$\Delta\rho_{\text{max}} = 0.24$ e Å$^{-3}$

$\Delta\rho_{\text{min}} = -0.17$ e Å$^{-3}$

Table 3

Selected geometric parameters (Å, °) for (III).

<p>| | | |</p>
<table>
<thead>
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<th></th>
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</tr>
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<tbody>
<tr>
<td>O3—C9</td>
<td>1.205 (3)</td>
<td>C9—C10</td>
</tr>
<tr>
<td>N1—C1</td>
<td>1.292 (3)</td>
<td>C10—C11</td>
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<tr>
<td>C1—C4</td>
<td>1.522 (3)</td>
<td>C11—C12</td>
</tr>
<tr>
<td>C2—C3</td>
<td>1.359 (3)</td>
<td>C12—C13</td>
</tr>
<tr>
<td>C1—N1—C3</td>
<td>111.45 (17)</td>
<td>O3—C9—C10</td>
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<tr>
<td>C4—C1—C3</td>
<td>120.68 (14)</td>
<td>C11—C10—C12</td>
</tr>
<tr>
<td>C1—C2—C3</td>
<td>110.85 (15)</td>
<td>C10—C11—C12</td>
</tr>
<tr>
<td>C2—N3—C13</td>
<td>124.04 (18)</td>
<td>C11—C12—C13</td>
</tr>
<tr>
<td>N1—C3—C13</td>
<td>121.84 (18)</td>
<td>C12—C13—C13</td>
</tr>
</tbody>
</table>

Table 4

Hydrogen-bonding geometry (Å, °) for (III).

<table>
<thead>
<tr>
<th>D—H···A</th>
<th>D—H</th>
<th>H···A</th>
<th>D···A</th>
<th>D—H···A</th>
</tr>
</thead>
<tbody>
<tr>
<td>N2—H2—O1’</td>
<td>0.88</td>
<td>2.00</td>
<td>2.869 (2)</td>
<td>168</td>
</tr>
</tbody>
</table>

Symmetry code: (i) x, 2−y, z−1

H atoms were placed at calculated positions and were updated with each cycle of refinement, but not refined. The C—H distances were fixed in the range 0.95–1.00 Å and N—H distances were fixed at 0.88 Å. The displacement parameters were fixed at 1.2 times the equivalent isotropic displacement parameter of the parent atom. The analysis of (II) [with a Flack (1983) parameter of 0.07 (7)] establishes the $R$ absolute configuration. For racemic (III) in space group $Pc$, the Flack parameter [0.05 (7)] shows that the correct polarity has been chosen.

For both compounds, data collection: SMART (Bruker, 1998); cell refinement: SAINT (Bruker, 1998); data reduction: SAINT; program(s) used to solve structure: SHELX97 (Sheldrick, 1997); program(s) used to refine structure: SHELXL97 (Sheldrick, 1997); molecular graphics: ORTEPIII (Burnett & Johnson, 1996); software used to prepare material for publication: CIFTAB in SHELXL97.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: FR1371). Services for accessing these data are described at the back of the journal.

References


