Nucleic Acid Binding Drugs. XVI. Structure of (7R)-*trans*-7,11-Di-O-acetyl-4-demethoxydaunomycinone, an Analogue of the Antitumour Compound Daunomycin

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Abstract. (7R)-*trans*-7,9,11-Tri-O-acetyl-7,8,9,10-tetrahydro-6,9-dihydroxy-5,12-naphthacenedione, $C_{24}H_{20}O_9$, $M_r = 452.42$, monoclinic, $P2_1/c$, $a = 8.521$ (2), $b = 10.737$ (2), $c = 22.874$ (2) Å, $\beta = 91.47$ (1)°, $V = 2091.9$ Å^3, $Z = 4$, $D_x = 1.436$, $D_m = 1.423$ Mg m^{-3} (by flotation), λ(Cu $K\alpha$) $= 1.54184$ Å, $\mu = 9.485$ mm^{-1}, $F(000) = 944$, $T = 298$ K, final $R = 0.062$ for 2272 observed reflections. The aromatic rings of the chromophore have overall planarity. Small deviations from this are attributable to asymmetry in intramolecular hydrogen bonding. The cyclohexene-like ring A has a pseudo-chair pucker with C(9) deviating from the least-squares plane.

Introduction. Daunomycin and adriamycin are clinically useful anticancer agents (Arcamone, 1981). Their mechanism of action is believed to involve intercalation of their planar chromophores into double-stranded DNA (reviewed in Neidle & Sanderson, 1983). There has been a continuing search for analogues that have reduced toxicity yet improved therapeutic index. One such compound is 4-demethoxydaunomycin (I) (Broadhurst, Hassall & Thomas, 1982a). The title compound (II) was produced during synthetic approaches to the aglycone of this 4-demethoxy compound (Broadhurst, Hassall & Thomas, 1982b). The present X-ray study confirms the structure assignment of NMR methods and provides further information on the conformation of ring A which has been the subject of several studies crystallographically *e.g.* in daunomycin itself (Neidle & Taylor, 1977; Angiuli *et al.*, 1971), and by theoretical methods (Brown, Kollman & Weiner, 1982). The flexibility and puckering preferences of this ring are important in the definition of theoretical models for the interactions of anthracyclines with DNA sequences (Chen, Gresh & Pullman, 1985).

Experimental. Yellow prismatic, air-stable crystals, CAD-4 diffractometer, cell dimensions from measurements on 25 reflections, $\omega/2\theta$ scan with Ni-filtered Cu $K\alpha$ radiation ($1.5 \le \theta \le 60°$). Range of *hkl*: $0 \le h \le 9$, $0 \le k \le 12$, $-25 \le l \le 25$. Maximum scan time per reflection 75 s. Three standards measured during data collection; no significant decomposition. 3491 unique reflections, 2272 with significant intensity $[I < 1.5\sigma(I)]$ used in analysis, measured on a crystal of dimensions $0.30 \times 0.10 \times 0.10$ mm, structure solved by *MULTAN82* (Main, Fiske, Hull, Lessinger, Germain, Declercq & Woolfson, 1982), full-matrix least-squares refinement on F. Some H atoms located in difference Fourier map and refined; others placed in positions calculated geometrically and not refined. Final $R = 0.062$, $wR = 0.071$ with weights $w = 1/[\sigma^2(F) + (0.05I)^2]$ with σ from counting statistics, number of variables 334, max. $\Delta/\sigma = 0.02$, highest peak in final ΔF map was 0.15 e Å^{-3}. No corrections for absorption or secondary extinction. Atomic scattering factors from *International Tables for X-ray Crystallography* (1974), calculations performed with the *SDP* program package (Frenz, 1980), and molecular plots obtained with *ORTEP* II (Johnson, 1976). Table 1 gives the nonhydrogen-atom positional parameters.†

Discussion. The molecular structure of the aglycone is shown in Figs. 1 and 2 and geometric parameters are detailed in Table 2. The three aromatic rings of the daunomycinone ring system have an overall planarity, although detailed examination shows deviations from this picture. Ring A is the most closely coplanar, with a χ^2 of 9 for the six atoms in the ring. Ring B has a χ^2 of 339; this relatively high non-planarity results in the substituent carbonyl oxygen atom O(12) being 0.191 (3) Å out of the least-squares plane. Ring C has a χ^2 of 165 for its six ring atoms. As shown in Fig. 2, these three rings are not coplanar, with rings A and B being inclined at an angle of 7.2 (4)°. It is not anticipated that this non-planarity would be sufficient to interfere with the intercalative binding to nucleic acids of appropriate derivatives of this aglycone.

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† Lists of H-atom parameters, anisotropic thermal parameters and structure factors have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 43518 (13 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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Table 1. Nonhydrogen-atom positional parameters, with e.s.d.'s in parentheses

$$B_{eq} = \tfrac{1}{3}(B_{11} + B_{22} + B_{33}).$$

	x	y	z	B_{eq}(Å^2)
O(5)	0.8070 (4)	0.5331 (3)	1.0201 (1)	5.65 (8)
O(6)	0.9267 (4)	0.7023 (3)	0.9598 (1)	4.57 (7)
O(7)	0.9041 (3)	0.9187 (2)	0.8869 (1)	3.98 (6)
O(9)	1.1036 (3)	0.6591 (2)	0.7665 (1)	3.96 (6)
O(11)	0.6337 (3)	0.5048 (3)	0.7648 (1)	3.68 (6)
O(12)	0.4626 (3)	0.3678 (3)	0.8365 (1)	5.58 (8)
O(13)	1.1657 (4)	0.7669 (3)	0.6680 (1)	5.05 (7)
O(15)	1.1339 (4)	1.0156 (3)	0.9004 (2)	7.07 (9)
O(17)	0.4283 (4)	0.6349 (3)	0.7678 (1)	6.76 (9)
C(1)	0.4512 (5)	0.2316 (4)	0.9396 (2)	5.5 (1)
C(2)	0.4445 (6)	0.1737 (5)	0.9936 (2)	7.0 (1)
C(3)	0.5304 (7)	0.2155 (5)	1.0405 (2)	7.2 (1)
C(4)	0.6256 (6)	0.3200 (5)	1.0355 (2)	5.9 (1)
C(4A)	0.6347 (5)	0.3787 (4)	0.9818 (2)	4.3 (1)
C(5)	0.7336 (5)	0.4928 (4)	0.9763 (2)	3.95 (9)
C(5A)	0.7462 (4)	0.5525 (4)	0.9192 (2)	3.17 (8)
C(6)	0.8470 (5)	0.6560 (4)	0.9133 (2)	3.31 (8)
C(6A)	0.8701 (4)	0.7095 (4)	0.8585 (2)	3.05 (8)
C(7)	0.9805 (5)	0.8188 (4)	0.8544 (2)	3.30 (9)
C(8)	1.0133 (5)	0.8633 (4)	0.7927 (2)	3.79 (9)
C(9)	1.0007 (5)	0.7563 (4)	0.7488 (2)	3.12 (8)
C(10)	0.8345 (4)	0.7026 (3)	0.7491 (2)	2.96 (8)
C(10A)	0.7982 (4)	0.6579 (3)	0.8096 (2)	2.77 (8)
C(11)	0.6945 (4)	0.5579 (3)	0.8159 (2)	2.85 (8)
C(11A)	0.6640 (4)	0.5052 (4)	0.8701 (2)	3.03 (8)
C(12)	0.5517 (5)	0.3997 (4)	0.8759 (2)	3.81 (9)
C(12A)	0.5471 (5)	0.3369 (4)	0.9339 (2)	4.2 (1)
C(13)	1.0432 (5)	0.8018 (4)	0.6879 (2)	3.47 (9)
C(14)	0.9338 (5)	0.8878 (4)	0.6554 (2)	4.4 (1)
C(15)	0.9956 (6)	1.0101 (4)	0.9092 (2)	4.6 (1)
C(16)	0.9023 (7)	1.0979 (4)	0.9448 (2)	6.1 (1)
C(17)	0.4938 (5)	0.5511 (4)	0.7439 (2)	4.7 (1)
C(18)	0.4478 (6)	0.4863 (6)	0.6889 (2)	7.7 (1)

Table 2. Bond lengths (Å) and angles (°) with e.s.d.'s in parentheses

|			
C(1)–C(2)	1.385 (7)	O(11)–C(17)	1.366 (5)
C(2)–C(3)	1.358 (8)	C(13)–O(13)	1.209 (5)
C(3)–C(4)	1.391 (8)	C(15)–O(15)	1.202 (6)
C(4)–C(4A)	1.385 (6)	C(17)–O(17)	1.198 (6)
C(4A)–C(5)	1.494 (6)	C(1)–C(12A)	1.402 (6)
C(5)–C(5A)	1.461 (5)	C(4A)–C(12A)	1.385 (6)
C(5A)–C(6)	1.413 (5)	C(5)–O(5)	1.244 (5)
C(6)–C(6A)	1.397 (5)	C(5A)–C(11A)	1.403 (5)
C(6A)–C(7)	1.508 (5)	C(6)–O(6)	1.344 (5)
C(7)–C(8)	1.524 (5)	C(6A)–C(10A)	1.377 (5)
C(8)–C(9)	1.528 (6)	C(7)–O(7)	1.467 (5)
C(9)–C(10)	1.529 (6)	C(9)–O(9)	1.415 (5)
C(10)–C(10A)	1.505 (5)	C(9)–C(13)	1.527 (6)
C(10A)–C(11)	1.400 (5)	C(11)–O(11)	1.390 (4)
C(11)–C(11A)	1.394 (5)	C(12)–O(12)	1.213 (5)
C(11A)–C(12)	1.491 (6)	C(13)–C(14)	1.496 (6)
C(12)–C(12A)	1.490 (6)	C(15)–C(16)	1.489 (7)
O(7)–C(15)	1.346 (5)	C(17)–C(18)	1.481 (7)
C(1)–C(2)–C(3)	121.4 (5)	C(10A)–C(11)–C(11A)	122.3 (3)
C(1)–C(12A)–C(4A)	119.4 (4)	C(11)–C(11A)–C(12)	121.4 (3)
C(2)–C(1)–C(12A)	118.9 (4)	C(11)–O(11)–C(17)	116.6 (3)
C(2)–C(3)–C(4)	120.4 (5)	C(11A)–C(11)–O(11)	120.6 (3)
C(3)–C(4)–C(4A)	119.0 (5)	C(11A)–C(12)–C(12A)	117.0 (3)
C(4)–C(4A)–C(5)	119.5 (4)	C(12A)–C(12)–O(12)	120.2 (4)
C(4A)–C(5)–C(5A)	119.3 (3)	O(7)–C(15)–O(15)	122.2 (4)
C(4A)–C(12A)–C(12)	122.1 (4)	O(9)–C(9)–C(13)	109.7 (3)
C(5)–C(4A)–C(12A)	119.5 (4)	O(11)–C(17)–O(17)	121.8 (4)
C(5)–C(5A)–C(6)	119.3 (3)	O(13)–C(13)–C(14)	122.5 (4)
C(5A)–C(5)–O(5)	121.3 (4)	O(15)–C(15)–C(16)	126.9 (4)
C(5A)–C(6)–C(6A)	120.7 (3)	O(17)–C(17)–C(18)	128.6 (4)
C(5A)–C(11A)–C(11)	117.7 (3)	C(1)–C(12A)–C(12)	118.5
C(6)–C(5A)–C(11A)	120.0 (3)	C(4)–C(4A)–C(12A)	120.9
C(6)–C(6A)–C(7)	118.5 (3)	C(4A)–C(5)–O(5)	119.3
C(6A)–C(6)–O(6)	118.6 (3)	C(5)–C(5A)–C(11A)	120.6
C(6A)–C(7)–C(8)	115.5 (3)	C(5A)–C(6)–O(6)	120.7
C(6A)–C(10A)–C(10)	121.4 (3)	C(6)–C(6A)–C(10A)	119.5
C(7)–C(6A)–C(10A)	121.9 (3)	C(6A)–C(7)–O(7)	104.6
C(7)–C(8)–C(9)	111.2 (3)	C(6A)–C(10A)–C(11)	119.6
C(7)–O(7)–C(15)	117.7 (3)	C(8)–C(9)–O(9)	109.5
C(8)–C(7)–O(7)	109.5 (3)	C(9)–C(13)–C(14)	119.4
C(8)–C(9)–C(10)	109.2 (3)	C(10)–C(9)–C(13)	111.5
C(8)–C(9)–C(13)	110.1 (3)	C(10A)–C(11)–O(11)	116.8
C(9)–C(10)–C(10A)	109.7 (3)	C(11A)–C(12)–O(12)	122.7
C(9)–C(13)–O(13)	118.1 (4)	O(7)–C(15)–C(16)	110.9
C(10)–C(9)–O(9)	106.7 (3)	O(11)–C(17)–C(18)	109.6
C(10)–C(10A)–C(11)	118.9 (3)		
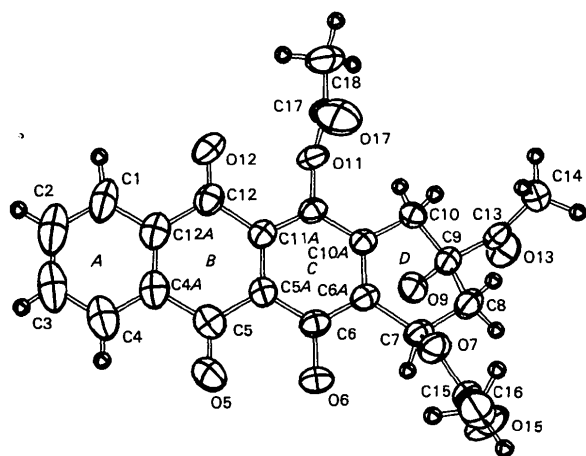
Fig. 1. ORTEP view (Johnson, 1976), with nonhydrogen-atom thermal ellipsoids drawn at the 50% probability level. The view is looking down onto the plane of the chromophore.
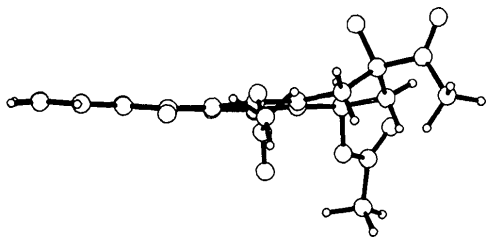

Fig. 2. Computer-drawn view looking along the plane of the chromophore.

The two carbonyl bond lengths C(5)–O(5) and C(12)–O(12) are significantly different. This is likely to be a consequence of only one carbonyl oxygen atom [O(5)] being involved in intramolecular hydrogen bonding, which would tend to lengthen the C(5)–O(5) bond. The other carbonyl oxygen atom O(12) deviates significantly [by 0.191 (3) Å] from the least-squares plane of ring C, whereas O(5) is 0.062 (3) Å out of this plane. These differences may be due to the mono-hydroxyquinoid nature of the structure compared with the more symmetrical dihydroxyquinoid feature of daunomycin itself.

The D ring of (I) is in a half-chair conformation with ring atom C(9) deviating from the least-squares plane of the other five atoms ($\chi^2 = 56$) by 0.723 (4) Å. In daunomycin itself (Neidle & Taylor, 1977; Courseille, Busetta, Geoffre & Hospital, 1979) and its 4-hydroxy analogue carminomycin (Von Dreele & Einck, 1977), the half-chair form has C(8) as the major out-of-plane atom. The N-bromoacetyl derivative has a C(9) deviation, as found here. Theoretical studies have indicated the acetyl group at C(9) is in an equatorial

position, and is *cis* to the equatorially-substituted acetyl group at C(7) (Fig. 2).

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Structure of 3,4-Dihydroxy-*trans*-cinnamic Acid (Caffeic Acid) and its Lack of Solid-State Topochemical Reactivity

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Abstract. $C_9H_8O_4$, $M_r = 180 \cdot 16$, monoclinic, $P2_1/n$, $a = 6 \cdot 6953$ (7), $b = 5 \cdot 7960$ (5), $c = 21 \cdot 193$ (2) Å, $\beta = 93 \cdot 83$ (1)°, $V = 820 \cdot 6$ (1) Å^3, $Z = 4$, $D_x = 1 \cdot 46$ Mg m^{-3}, Cu $K\alpha$ radiation (graphite crystal monochromator, $\lambda = 1 \cdot 54184$ Å), μ(Cu $K\alpha$) = $0 \cdot 943$ mm^{-1}, $T = 290$ K, $F(000) = 376$, final $R = 0 \cdot 044$ for 884 'observed' reflections and 150 variables. The geometry about the double bond is *trans*, torsion angle $-178 \cdot 9$ (3)°. The interplanar angle between the phenyl ring and the carboxyl group is $4 \cdot 33$ (8)°. O—H⋯O hydrogen bonds link the molecules to form dimers. Even though the crystal structure predicts that inversion-related molecules should undergo solid-state topochemical dimerization, the material is in fact photostable and a reason for this is presented.

Introduction. According to Schmidt (1964), the crystallographic short axis (SA) may be used to classify *trans*-cinnamic acids into three structural types, the photoactive α (SA > $5 \cdot 1$ Å) and β (SA < $4 \cdot 1$ Å) and the photostable γ ($4 \cdot 7 < SA < 5 \cdot 1$ Å) forms. The reactivity of the α and β forms is ascribed to the fact that parallel double bonds are at a centre-to-centre separation of < $4 \cdot 2$ Å. Many simple acids conform to these topochemical rules (Schmidt, 1964). However, the crystal chemistry of more complicated structures such as 3,4-dimethoxycinnamic acid (Desiraju, Kamala, Kumari & Sarma, 1984) and its 1:1 complex with 2,4-dinitrocinnamic acid (Desiraju & Sarma, 1983; Sarma & Desiraju, 1985) cannot be readily described in terms of such geometrical criteria.

Further, there has been much discussion as to what exactly constitutes a deviation from topochemical 2+2 photoreactivity, since there are cases like 2-benzylidenecyclopentanone (Kearsley & Desiraju, 1985) which is photostable even though parallel double bonds