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The Structure of a 4-Demethoxythiodaunomycinone Derivative*

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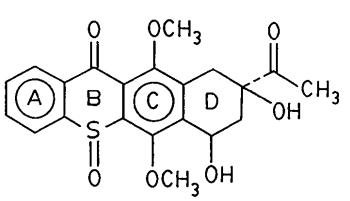
Abstract. $C_{21}H_{20}O_7S.CH_2Cl_2$, $M_r = 501{\cdot}388$, triclinic, $P\bar{1}$, $a = 9{\cdot}5708$ (18), $b = 11{\cdot}1965$ (16), $c = 11{\cdot}3634$ (20) Å, $\alpha = 75{\cdot}982$ (13), $\beta = 83{\cdot}323$ (15), $\gamma = 74{\cdot}629$ (19)°, $V = 1137{\cdot}39$ (33) Å^3, $Z = 2$, D_m (flotation) = 1·45, $D_x = 1{\cdot}46$ Mg m^{-3}, λ(Mo $K\alpha$) = 0·71069 Å, $\mu = 0{\cdot}16$ mm^{-1}, $F(000) = 520$, $T = 294$ K, $R = 0{\cdot}065$ for 3198 unique observed reflections. The molecule is a thio derivative of daunomycinone, but the multiple ring system of the present molecule is bent so that the two flat portions intersect along the S···CO line in the *B* ring with a dihedral angle of 40·1°. The crystal structure exhibits an intermolecular hydrogen bond between the sulfoxide oxygen and the 9-hydroxy group, and an intramolecular hydrogen bond between the 7- and 9-hydroxy groups. The structure includes a dichloromethane solvent molecule with some orientational disorder.

Introduction. Daunomycin is one of the most active and effective anticancer chemotherapeutic agents, but its clinical use is limited primarily by a dose-dependent cardiomyopathy. Studies (Goodman & Hochstein, 1977; Bachur, Gordon & Gee, 1978; Wong, Mi, Ren, Haque, Lam & Marat, 1984) have shown that the quinone moiety of the molecule may be enzymatically reduced and may subsequently autoxidize, resulting in the generation of oxygen radicals and hydrogen peroxide. These free radicals may in turn react with endogenous lipid and cause membrane damage, especially to heart cells which have relatively low levels of superoxide dismutase. Analogues of daunomycin are being sought which have reduced toxicity yet an improved therapeutic index. The title compound (I) is a derivative of daunomycinone (Arcamone, Franceschi, Orezzi, Cassinelli, Barbieri & Mondelli, 1964; Wong, Popien, Schwenk & Raa, 1971; Wong, Schwenk, Popien & Ho, 1973), a precursor in the synthesis of daunomycin. The sulfoxide portion of the ring system is expected to confer on the molecule a different oxidation–reduction potential from that of daunomycinone and it is thought that this will alter the free-radical formation process in the living cell with a concomitant decrease in the toxicity of the drug. Because the synthesis affords both α and β isomers (epimeric at S), the present study was undertaken to identify the isomer as α or β and to provide structural details of a compound representative of a series of possibly improved anticancer drugs.



(I)

Experimental. A yellow pinacoidal crystal of dimensions 0·28 × 0·36 × 0·48 mm was used for data collection on a Nicolet *R3m* automated diffractometer; orientation matrix and unit-cell parameters from 25 centered reflections; data collected by ω–2θ technique in the range $2 \le 2\theta \le 50°$ with scan speeds 4·0–29·30° min^{-1}; scan widths given by 2·00° + ($2\theta_{K\alpha_2}$–$2\theta_{K\alpha_1}$)°; 4016 independent reflections measured of which 3198 were considered observed with $I \ge 2{\cdot}5\sigma(I)$ where $\sigma(I) = SR(SC + BL + BR)^{1/2}$, SR = scan rate, SC = total scan count, BL, BR are left and right backgrounds; reciprocal space explored, $\pm h \pm k + l$; three standard reflections measured after every 45 collected data; minor intensity variation in standards; Lorentz and polarization corrections applied.

The structure was solved with *MULTAN*80 (Main, Fiske, Hull, Lessinger, Germain, Declercq & Woolfson, 1980), all non-H atoms located, full-matrix least-squares refinement on F; $\sum w(|F_o| - k|F_c|)^2$ minimized; 11 H atoms located by difference Fourier maps and refined isotropically; 13 H atoms placed in calculated positions of which four were refined; 30 of 32 non-H atoms were refined with anisotropic temperature factors.

The crystal contains a dichloromethane solvent molecule but only one Cl atom was refined anisotropically; the other Cl and C atoms were refined with isotropic thermal parameters and, in the case of the C atom, only the temperature factor was refined. The solvent molecule is disordered with 55% occupancy in

* 9-Acetyl-*cis*-7,9-dihydroxy-6,11-dimethoxy-7,8,9,10-tetrahydrobenzo[*b*]thioxanthen-12-one 5α-oxide dichloromethane solvate.

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Table 1. *Final positional parameters (fractional* $\times 10^4$*) and equivalent isotropic thermal parameters* ($Å^2 \times 10^3$) *with e.s.d.'s in parentheses*

Single primes denote 55% occupancy, double primes 45% occupancy.

$U_{eq} = \frac{1}{3}$(trace of diagonalized temperature-factor matrix).

	x	y	z	U_{eq}/U_{iso}
C(1)	1035 (6)	2028 (5)	9230 (5)	48
C(2)	1164 (7)	3101 (6)	9583 (5)	58
C(3)	1045 (8)	4230 (6)	8734 (5)	59
C(4)	835 (6)	4308 (5)	7531 (5)	47
C(4a)	741 (5)	3231 (4)	7180 (4)	37
S	400 (1)	3395 (1)	5632 (1)	35
C(5a)	1378 (5)	1841 (4)	5469 (4)	34
C(6)	2001 (5)	1724 (4)	4330 (4)	37
C(6a)	2753 (5)	543 (4)	4112 (4)	37
C(7)	3495 (6)	437 (5)	2864 (4)	45
C(8)	4622 (6)	−819 (5)	2888 (5)	50
C(9)	4038 (5)	−1944 (5)	3591 (5)	42
C(10)	3642 (7)	−1835 (5)	4899 (5)	42
C(10a)	2812 (5)	−536 (4)	5056 (4)	35
C(11)	2112 (5)	−417 (4)	6190 (4)	33
C(11a)	1402 (5)	763 (4)	6427 (4)	34
C(12)	777 (5)	916 (4)	7662 (4)	38
C(12a)	840 (5)	2087 (4)	8029 (4)	39
C(13)	2806 (7)	3534 (6)	3135 (6)	61
C(14)	5187 (6)	−3193 (5)	3590 (5)	47
C(15)	4881 (14)	−4158 (9)	3044 (14)	103
C(16)	1153 (8)	−2167 (6)	7193 (6)	52
O(1)	−1178 (4)	3443 (3)	5599 (4)	51
O(2)	283 (5)	102 (3)	8375 (3)	55
O(3)	2273 (4)	−1499 (3)	7107 (3)	41
O(4)	6308 (5)	−3380 (5)	4053 (5)	80
O(5)	2769 (4)	−1895 (4)	2999 (3)	48
O(6)	2452 (5)	684 (4)	1991 (3)	60
O(7)	1756 (4)	2781 (3)	3385 (3)	43
C(17′)*	2670	−2070	119	78 (4)
C(17″)*	3011	−2254	38	73 (5)
Cl(1)	3148 (4)	−3772 (3)	53 (3)	133
Cl(2′)	4148 (5)	−1422 (5)	−348 (4)	94 (1)
Cl(2″)	4796 (7)	−1983 (6)	−170 (5)	101 (2)

* Atoms in calculated positions.

one orientation and 45% in the other. Extinction correction (Coppens & Hamilton, 1970; Becker & Coppens, 1974; Thornley & Nelmes, 1974) was minor with a final g value of $0{\cdot}51 \times 10^4$. Final $R = 0{\cdot}065$, $wR = 0{\cdot}088$ for 3198 observed reflections, $R = 0{\cdot}078$, $wR = 0{\cdot}088$ for 4016 data where $w = (15{\cdot}0/|F_o|)^2$ for $|F_o| \geq 15{\cdot}0$, and $w = 1{\cdot}0$ for $|F_o| < 15{\cdot}0$; unobserved data assigned $w = 0$; the standard error was constant over ranges of F_o. The max. Δ/σ in the final cycle was 0·974 [for methyl H(15c)]; goodness of fit = 0·921; final max./min. residuals from difference map were 1·306 and −1·036 e $Å^{-3}$, with the maximum between Cl(1) and C(17′), while the minimum lies near Cl(2″). Atomic scattering factors from Cromer & Mann (1968) and Stewart, Davidson & Simpson (1965).* The non-H atom positional parameters and equivalent isotropic thermal factors are given in Table 1.*

Discussion. The bulk of the molecule (Fig. 1*a*) is formed by four six-membered rings of which two are aromatic, one is a heterocyclic sulfoxide and the fourth is a mostly saturated ring containing acetyl and hydroxyl substituents. Unlike the daunomycinone moiety of daunomycin (Neidle & Taylor, 1977) and other similar compounds (Von Dreele & Einck, 1977; Neidle & Sanderson, 1987) which exhibit overall planarity of three aromatic rings, *A*, *B* and *C*, the introduction of sulfur into the *B* ring of the present compound alters the geometry of the molecule significantly (bond lengths and angles, Table 2) resulting in a bent conformation (Fig. 1*b*). Ring *B* adopts a boat-like conformation with S and C(12) atoms deviating from the mean plane through C(4a), C(5a), C(11a) and C(12a) by 0·5934 and 0·3560 Å, respectively. The folding along the S···C(12) line in the molecule is common to similar multiple-ring compounds containing a sulfur heterocyclic ring (Chu, 1976; Chu & Yang, 1976; Wei & Einstein, 1978). The torsion angles of 4·8 (7)° for S–C(4a)–C(12a)–C(12) and −8·5 (6)° for S–C(5a)–C(11a)–C(12) indicate that the two essentially flat portions of the molecule composed of rings *A* and *C* and their immediate bonded

* Lists of structure factors, anisotropic thermal parameters, H-atom positional and thermal parameters, bond distances and angles involving H atoms and torsion angles have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 44628 (21 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

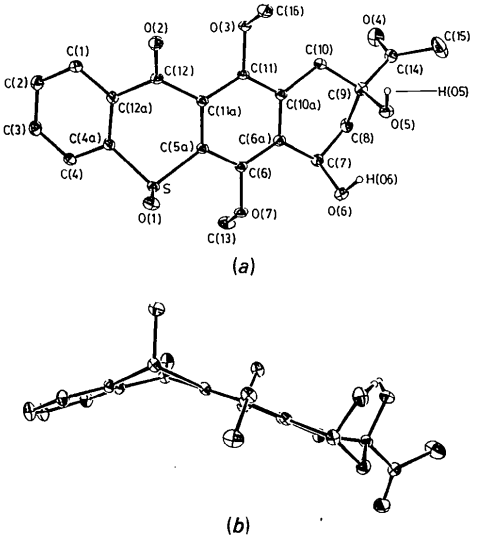

Fig. 1. *ORTEP* diagrams (Johnson, 1976) of (I): (*a*) top view, (*b*) side view with S in the foreground. Ellipsoids drawn at 50% probability level.

* Computation was carried out on the University of Manitoba Computer Services Department's Amdahl 580/5850 mainframe computer using locally written programs and *SHELXTL* (Sheldrick, 1983) for processing, and modified versions of the following programs for structure refinement and calculations: *ORFLS* (Busing, Martin & Levy, 1962); *FORDAP* (A. Zalkin, private communication); *ORFFE* (Busing, Martin & Levy, 1964); *ORTEP*II (Johnson, 1976).

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

C(1)–C(2)	1·394 (8)	C(9)–C(10)	1·517 (7)
C(1)–C(12a)	1·383 (7)	C(9)–C(14)	1·543 (7)
C(2)–C(3)	1·379 (8)	C(9)–O(5)	1·458 (6)
C(3)–C(4)	1·384 (8)	C(10)–C(10a)	1·506 (7)
C(4)–C(4a)	1·387 (7)	C(10a)–C(11)	1·406 (7)
C(4a)–S	1·785 (5)	C(11)–C(11a)	1·393 (6)
C(4a)–C(12a)	1·392 (7)	C(11)–O(3)	1·379 (5)
S–C(5a)	1·791 (5)	C(11a)–C(12)	1·494 (7)
S–O(1)	1·531 (4)	C(12)–C(12a)	1·487 (7)
C(5a)–C(6)	1·384 (7)	C(12)–O(2)	1·226 (6)
C(5a)–C(11a)	1·414 (6)	C(13)–O(7)	1·454 (6)
C(6)–C(6a)	1·396 (7)	C(14)–C(15)	1·477 (10)
C(6)–O(7)	1·380 (5)	C(14)–O(4)	1·214 (7)
C(6a)–C(7)	1·532 (7)	C(16)–O(3)	1·462 (7)
C(6a)–C(10a)	1·401 (6)	C(17')–Cl(1)	1·856 (3)
C(7)–C(8)	1·534 (8)	C(17') Cl(2')	1·753 (5)
C(7)–O(6)	1·430 (7)	C(17'')–Cl(1)	1·665 (3)
C(8)–C(9)	1·528 (7)	C(17'')–Cl(2'')	1·824 (6)

C(2)–C(1)–C(12a)	120·2 (5)	C(10)–C(9)–O(5)	109·7 (4)
C(1)–C(2)–C(3)	119·5 (5)	C(14)–C(9)–O(5)	112·1 (4)
C(2)–C(3)–C(4)	121·0 (5)	C(9)–C(10)–C(10a)	114·9 (4)
C(3)–C(4)–C(4a)	119·2 (5)	C(6a)–C(10a)–C(10)	121·6 (4)
C(4)–C(4a)–S	117·5 (4)	C(6a)–C(10a)–C(11)	119·9 (4)
C(4)–C(4a)–C(12a)	120·5 (5)	C(10)–C(10a)–C(11)	118·5 (4)
S–C(4a)–C(12a)	122·0 (4)	C(10a)–C(11)–C(11a)	121·7 (4)
C(4a)–S–C(5a)	97·8 (2)	C(10a)–C(11)–O(3)	117·5 (4)
C(4a)–S–O(1)	107·0 (2)	C(11a)–C(11)–O(3)	120·5 (4)
C(5a)–S–O(1)	106·7 (2)	C(5a)–C(11a)–C(11)	117·4 (4)
S–C(5a)–C(6)	117·1 (3)	C(5a)–C(11a)–C(12)	120·3 (4)
S–C(5a)–C(11a)	121·2 (4)	C(11)–C(11a)–C(12)	122·2 (4)
C(6)–C(5a)–C(11a)	121·2 (4)	C(11a)–C(12)–C(12a)	116·9 (4)
C(5a)–C(6)–C(6a)	121·0 (4)	C(11a)–C(12)–O(2)	122·7 (4)
C(5a)–C(6)–O(7)	118·5 (4)	C(12a)–C(12)–O(2)	120·3 (4)
C(6a)–C(6)–O(7)	120·3 (4)	C(1)–C(12a)–C(4a)	119·6 (4)
C(6)–C(6a)–C(7)	120·4 (4)	C(1)–C(12a)–C(12)	119·3 (4)
C(6)–C(6a)–C(10a)	118·7 (4)	C(4a)–C(12a)–C(12)	121·1 (4)
C(7)–C(6a)–C(10a)	120·9 (4)	C(9)–C(14)–C(15)	118·8 (6)
C(6a)–C(7)–C(8)	113·1 (4)	C(9)–C(14)–O(4)	120·1 (5)
C(6a)–C(7)–O(6)	109·8 (4)	C(15)–C(14)–O(4)	121·1 (7)
C(8)–C(7)–O(6)	113·2 (4)	C(11)–O(3)–C(16)	113·6 (4)
C(7)–C(8)–C(9)	110·8 (4)	C(10)–C(9)–C(14)	108·3 (4)
C(8)–C(9)–C(10)	110·1 (4)	C(6)–O(7)–C(13)	116·9 (4)
C(8)–C(9)–C(14)	109·7 (4)	Cl(1)–C(17')–Cl(2')	110·1 (2)
C(8)–C(9)–O(5)	106·9 (4)	Cl(1)–C(17'')–Cl(2'')	108·5 (2)

atoms are not strictly planar. However, the individual rings *A* and *C* more closely approximate planes, with average deviations from their respective least-squares planes of 0·0060 and 0·0132 Å. The lack of overall planarity in the molecule imparted by the S in the *B* ring may hinder the intercalative binding of this molecule into DNA. Relative to the intercalating portion of daunomycin, the tetracyclic fragment in (I) is approximately 3 Å thicker. This suggests that if this modified fragment used in a daunomycin-like drug is to intercalate, considerably more unwinding of the DNA helix would be required in order to accommodate the drug.

The ketone and sulfoxide oxygens lie on the same side of the bent *B* ring and extend upwards from the S and C(12) apices. The least-squares plane fitted to S, C(12), O(1) and O(2) shows an average deviation of 0·0095 Å and makes identical dihedral angles of 70·4° with rings *A* and *C*. The methoxy substituents on ring *C* which serve only as protecting groups in the synthesis lie in a plane perpendicular to the ring plane (dihedral angle 90·0°). Ring *D* adopts a half-chair conformation with C(8) deviating from the mean plane through the remaining five atoms (average deviation 0·076 Å) by 0·6314 Å. O(5) is *cis* to the O(6) hydroxyl group with an interatomic distance of 2·785 (6) Å and an O(5)···H(O6)–O(6) angle of 140 (8)°. This intramolecular hydrogen bond, which helps stabilize the half-chair conformation, is also found in the daunomycin structure (Neidle & Taylor, 1977).

All bonds and intraannular angles of rings *A*, *C* and *D* are not significantly different from those in daunomycin (Neidle & Taylor, 1977; Courseille, Busetta, Geoffre & Hospital, 1979). In ring *B*, the mean value of the two C–S bond lengths is 1·788 Å, and the C(4a)–S–C(5a) bond angle is 97·8 (2)°. The S–O bond length is 1·531 (4) Å, and the mean value of the two C–S–O bond angles is 106·9°. Except for the C–S–O bond angles, these values are very similar to the ones found in thioxanthone 10-oxide (Chu, 1976) where the mean value for the C–S–O angles is 108·2°. The smaller bond angle in the present molecule may be due, in part, to packing effects such as the intermolecular hydrogen bond formed between the O(1) (*x*, *y*, *z*) and O(5) (−*x*, −*y*, 1−*z*) atoms (see below). Although the S atom is considered sp^3 hybridized, all the angles involving S are smaller than the normal tetrahedral value.

Molecules in the crystal (Fig. 2) are infinitely stacked back-to-back in H-bonded dimers along the *a* axis. Each dimer is linked by two intermolecular hydrogen bonds between the O(1) (*x*, *y*, *z*) and O(5) (−*x*, −*y*, 1−*z*) atoms, where the O(1)···O(5) distance is 2·731 (5) Å and the O(1)···H(O5)–O(5) angle is 169 (6)°.

The dichloromethane solvent molecule is located in the vicinity of ring *A* (*x*, *y*, *z*) and ring *D* (−*x*, −*y*, 1−*z*). The structure analysis revealed that the molecule is disordered with Cl(1) in a fixed position and Cl(2) occupying two other positions resulting in two orientations of the molecule with 55 and 45% occupancies.

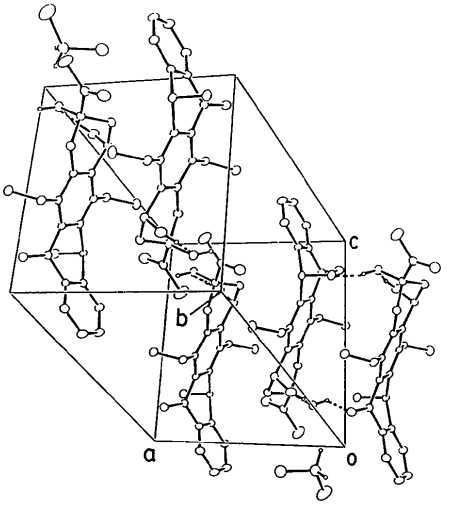

Fig. 2. Packing diagram of unit-cell contents with broken lines indicating hydrogen bonding.

Although the difference map indicated only one carbon peak, C(17) had to be assigned two positions with the same occupancies as the Cl(2) in order to satisfy the CH_2Cl_2 molecular geometry. The present geometry assignment of the solvent molecule is assumed to be the best one since it consumes the maximum extra electron density in that region of the cell while yielding a reasonable description of the disorder.

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Structure of Allocryptopine

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Abstract. 5,7,8,15-Tetrahydro-3,4-dimethoxy-6-methyl[1,3]benzodioxolo[5,6-*e*][2]benzazecin-14(6*H*)-one, $C_{21}H_{23}NO_5$, $M_r = 369{\cdot}40$, monoclinic, $P2_1/c$, $a = 18{\cdot}689$ (6), $b = 7{\cdot}253$ (3), $c = 14{\cdot}034$ (4) Å, $\beta = 108{\cdot}93$ (2)°, $V = 1799{\cdot}4$ (25) Å^3, $Z = 4$, $D_x = 1{\cdot}363$ Mg m^{-3}, $F(000) = 784$, λ(Mo $K\alpha$) = 0·71069 Å, $\mu = 0{\cdot}1052$ mm^{-1}, room temperature. Final $R = 0{\cdot}054$ for 1676 unique observed reflections. The skeleton of the molecule is similar to those of the other protopine-type alkaloids. The methyl of the methoxy group, which is *ortho* to the fused position, deviates far from the plane of the ring. This methyl group, the carbonyl O atom and the *N*-methyl group are on the same side of the ten-membered ring.

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