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The Structure of 5′-Acetamido-3′-acetyl-5′-deoxythymidine Chloroform Solvate

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Abstract

The structure of a modified thymidine ($C_{14}H_{19}N_3O_6.CHCl_3$) has been determined by the single-crystal X-ray diffraction technique. The crystal is orthorhombic, space group $P2_12_12_1$, with four molecules in the unit cell: $a = 24{\cdot}177\ (3)$, $b = 16{\cdot}203\ (2)$, $c = 4{\cdot}992\ (0{\cdot}4)$ Å. The structure was refined by block-diagonal least squares (nucleoside) and by a restrained-parameter refinement technique (chloroform) to $R = 0{\cdot}084$ for the 1851 independent reflections and $R = 0{\cdot}078$ for the 1650 reflections with $I > 3\sigma(I)$. The pyrimidine ring is a slight boat. The sugar plane is puckered with C(2′) *endo*. The dihedral angle between the sugar and the base is 79°, with the glycosidic torsion angle $\varphi_{CN} = 65°$. The chloroform molecules are greatly disordered and occupy the channels parallel to the *c* axis but they are hydrogen bonded to O(2) in the base.

Introduction

The title compound was prepared as part of a series of potential anti-cancer agents. Although this compound does not appear to possess any significant anti-tumor activity, its N(5′) diazo derivative is currently being evaluated as an acceptable anti-cancer drug (Chapman, 1979). In addition to its biochemical properties, the crystallization of this compound presented an interesting structural problem in that crystallization requires the presence of chloroform as a component of the solvent system and always appears to incorporate chloroform in the crystal lattice.

Experimental

The crystals used in this analysis were provided by Dr T. Chapman of the Department of Chemistry, University of Pittsburgh. They were grown by slow evaporation at room temperature from a mixture of chloroform and petroleum ether as clear rectangular prisms elongated along the *c* axis. The space group was determined from oscillation and Weissenberg photographs which showed systematic absences for $h00$, $h = 2n + 1$; $0k0$, $k = 2n + 1$; $00l$, $l = 2n + 1$. The unit-cell parameters were obtained from a least-squares fitting of the setting angles on a Picker FACS-1 diffractometer† for 12 centered reflections. The crystal data are summarized in Table 1. An initial set of intensity data was collected with the crystal mounted on a glass fiber approximately parallel to the *c* axis. As the data were collected the crystal gradually turned opaque and the intensities of standard reflections decreased on the average by 10%. These conditions indicated a loss of chloroform of solvation. When difficulty developed later during an attempt to refine a disordered chloroform molecule, it was decided to recollect data from a crystal sealed in a thin-walled glass capillary. This data set was collected on a Picker FACS-1 diffractometer using graphite-monochromatized Cu $K\alpha$ radiation with a $\theta{:}2\theta$ scan technique at a rate of 1° min^{-1} over a 2° scan range. The Biocrystallography Laboratory's FACS-1 utilizes the Picker DOS operating system which has locally undergone extensive modifications. The background was measured for 20 s at each end of the scan range. Of the 1851 independent reflections within the range of $\sin\theta \leq 0{\cdot}8870$, 192 were considered unobserved by the criterion $I < 3\sigma(I)$. During this data collection the crystal showed no significant optical changes and the three standard reflections, which were measured after every 50 reflections, showed systematic fluctuations in intensities of only $\pm 1{\cdot}3\%$. The variation of the standard reflections was used to place the intensity data on a uniform scale. After the Lorentz and polarization factors were applied, intensities were converted to the absolute scale by Wilson's (1942) method. The absorption corrections‡ that were applied to the

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† Instrument located in Department of Medicinal Chemistry, School of Pharmacy, University of Pittsburgh.

‡ The original program was written by L. Templeton based on the analytical method of Alcock (1970).

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Table 1. *Crystal data for 5′-acetamido-3′-acetyl-5′-deoxythymidine chloroform solvate*

$C_{14}H_{19}N_3O_6.CHCl_3$	$M_r = 444{\cdot}7$
$a = 24{\cdot}177$ (3) Å	Data measured at ambient temperature (295 K)
$b = 16{\cdot}203$ (2)	
$c = 4{\cdot}992$ (0·4)	$\lambda(\text{Cu } K\bar{\alpha}_1\alpha_2) = 1{\cdot}54178$ Å
$V = 1955{\cdot}6$ Å^3	$\mu = 4{\cdot}32$ mm^{-1}
Space group $P2_12_12_1$	$Z = 4$

$\rho_o = 1{\cdot}42$ Mg m^{-3} by flotation in benzene and dibromomethane
$\rho_c = 1{\cdot}51$ (= 1·45 based on partial occupancy of chloroform)
Distances between parallel crystal faces (001), (320) and (320) are 0·48, 0·35 and 0·21 mm respectively.

structure amplitudes had an average value of 2·698, with maximum and minimum values of 3·882 and 2·165 respectively. No extinction correction was applied.

Structure determination and refinement

The structure was solved with the program *MULTAN* (Germain, Main & Woolfson, 1971). From the initial E map the positions of all 23 nucleoside nonhydrogen atoms were identified. Three cycles of isotropic block-diagonal least-squares refinement reduced the R value to 0·34. Subsequent difference Fourier calculations located all but four of the nucleoside H atoms and gave plausible positions for the Cl and C atoms of a disordered chloroform. However, refining the model using the function $\sum w(|F_o|-k|F_c|)^2$ where k is a single scale factor and $w = 1/(A + B|F_o| + C|F_o|^2)$ with $A = 2{\cdot}0$, $B = 1{\cdot}0$ and $C = 0{\cdot}052$ resulted in chemically unreasonable parameters for chloroform. A closer examination of difference Fourier maps revealed two possible orientations for the chloroform molecule.

In order to obtain meaningful coordinates for the disordered chloroform, a restrained-parameter refinement technique (Konnert, 1976)* was implemented. To the best of our knowledge this represents the first application of Konnert's program to a disordered small-molecule structure and some comments regarding the details are in order. The technique as applied in this study involves minimization of the function φ where

$$\varphi = \sum_{i=1}^{\text{NREF}} w_i(|F_{o_i}| - |F_{c_i}|)^2 + \sum_{i=1}^{\text{NBOND}} w_i(d_{oi} - d_{I_i})^2 + \sum_{i=1}^{\text{NANG}} w_i(d_{o_i} - d_{I_i})^2.$$

w represents the weight $(1/\sigma^2)$ of any term where $\sigma = 0{\cdot}03$ Å for bond distances and 0·04 Å for angle-defining distances (bond angles are characterized by the distance between next-nearest neighboring atoms; *i.e.* the angle between the bond vectors $B\rightarrow A$ and $B\rightarrow C$ is characterized by the distance between atoms A and C). σ's for the structure factor terms were taken from counting statistics. d_o represents the observed distance in the current model and d_I represents the 'ideal' distance for each bond and angle type. Ideal distances were obtained from the crystallographic literature (Schaefer & Marsh, 1969). Since the program system as distributed is designed for the refinement of proteins, some changes were made to accommodate the small molecule. The only change implemented for this particular application was the inclusion of a 'standard chloroform' model in the standard group dictionary; however, the success of the application was also dependent on two other program modifications which had been implemented earlier in this laboratory for the refinement of proteins. Those two modifications were:

(*A*) Inclusion of fixed-atom contributions to structure factors prior to obtaining gradients. That is $A_{\text{calc}} = A_{\text{calc}} + A_{\text{fix}}$ and $B_{\text{calc}} = B_{\text{calc}} + B_{\text{fix}}$ where A_{calc} and B_{calc} are evaluated based on the input atoms and A_{fix} and B_{fix} are generated by an auxiliary program; they represent contributions from atoms not to be refined. This option was originally implemented to allow inclusion of H atom contributions to structure factors during protein refinement.

(*B*) The ability to assign scattering factors of zero to certain atoms or residues. This option was originally implemented to remove effectively certain residue contributions from F_{calc}, thus enabling unbiased electron density maps to be calculated where residues were thought to be incorrectly positioned or erroneously sequenced without modifying the input atomic coordinate file.

With these modifications at hand, the refinement of the disordered chloroform proceeded as follows:

(1) With a conventional least-squares program (Shiono, 1970) structure factors based on only the nucleoside atoms were calculated and output to a file. This file was merged with the standard reflection data file used in the Konnert program, thus providing values of A_{fix} and B_{fix} for each reflection along with F_o and $\sigma(F_o)$.

(2) Current coordinates for the alternative atomic locations of the chloroforms were added to the test tripeptide coordinate input file (supplied as input with the Konnert program) as additional solvent 'residues'. This adds the chloroform atoms and their associated restraint information to the data file required by the refinement program *PROLSQ* and also 'fools' the program into thinking it is dealing with protein data.

(3) The protein refinement program *PROLSQ* is executed in normal fashion except that all atoms in the test tripeptide are assigned scattering factors of zero, thereby removing their contributions to F_{calc}, and the

* In Konnert's paper the distance terms minimized are $\sum_{i=1}^{\text{NDIS}} w_i(d_Q^2 - d_I^2)^2$. However, the actual program as distributed minimizes $\sum_{i=1}^{\text{NDIS}} w_i(d_o - d_I)^2$. Hence the discrepancy between the function in this work and in the original publication.

fixed-atom contributions from the nucleoside are added to A_{calc} and B_{calc}. It is required that van der Waals contact restraints are given zero weight in *PROLSQ* to avoid repulsion of the two nearly superimposed chloroform molecules as well as any accidental contacts they might make with the dummy tripeptide atoms. Additionally the option to freeze the tripeptide atoms during the refinement (input parameter in *PROLSQ*) is invoked, thereby preventing large oscillatory shifts due to poor distance agreement caused by referencing the tripeptide coordinates in the nucleoside cell.

Several refinement cycles were calculated with occupancies, coordinates, and scale factor as variables. The initial occupancies were set to 0·5 and isotropic thermal factors were set to 10 Å^2. After convergence several additional cycles were calculated with isotropic thermal factors replacing the occupancies as variables. The net result was a decrease in the R factor, an improvement in the chloroform geometry and a better estimate of the relative occupancies of the two disordered molecules. The refined coordinates of the chloroforms were then input into the conventional refinement program as fixed parameters. The occupancies were averaged within each molecule and all atoms within each molecule were assigned the appropriate mean value. Chloroform isotropic thermal factors were converted to anisotropic values and were refined for several cycles along with positional and thermal factors for the nucleoside. The combined refinement scheme resulted in an improved geometry for both the chloroform and nucleoside and resulted in a lower R factor as well.

One drawback of the Konnert program is that the normal equations are solved by conjugate-gradient iteration; therefore there is no inverse matrix available from which e.s.d.'s or correlation coefficients can be calculated. E.s.d.'s for positional parameters are in fact approximated in the program and range from 0·021 to 0·050 Å but they are not particularly accurate. It is noteworthy that several of the chloroform atomic coordinates are nearly identical and might be expected to produce large oscillations in coordinate shifts or a singular normal matrix; however, this did not occur and the refinement converged rapidly. We believe the stability can be attributed to the input parameter P_{del} in *PROLSQ* which adds a constant to all diagonal elements of the normal matrix. This effectively prevents very large shifts and insures that no zero diagonal elements are present. Additional stability may be attributed to the rescaling of all matrix elements such that all diagonal elements are equal. This feature is automatically invoked in the programs as distributed.

The final R value was 0·084 over all 1851 reflections. The atomic scattering factors for Cl, O, N and C were taken from *International Tables for X-ray Crystallography* (1968) and that for H was from Stewart, Davidson & Simpson (1965). The anomalous-dispersion factors, f' and f'', for Cl were taken from *International Tables* (1968). The maximum shift/error ratio in the final cycle of refinement for all non-hydrogen parameters was 0·63 for the nucleoside group. A difference Fourier synthesis at the end of the

Table 2. *Final atomic positions (and e.s.d.'s) of nonhydrogen atoms* ($\times 10^4$) *and hydrogen atoms* ($\times 10^3$) *and isotropic temperature factors*

An asterisk indicates an occupancy of 0·482 (1) and a prime, one of 0·366 (1).

	x	y	z	B_{eq}/B (Å^2)
N(1)	6247 (1)	3257 (2)	7629 (9)	3·7 (3)
C(2)	6773 (1)	3489 (2)	6742 (9)	2·9 (3)
N(3)	6978 (1)	4170 (2)	8033 (11)	4·0 (3)
C(4)	6734 (1)	4611 (3)	10071 (11)	3·2 (4)
C(5)	6177 (2)	4369 (3)	10750 (10)	3·1 (4)
C(6)	5967 (1)	3714 (3)	9546 (10)	3·4 (4)
C(7)	5860 (2)	4872 (3)	12782 (13)	4·6 (5)
O(2)	7016 (1)	3137 (2)	4967 (11)	5·4 (4)
O(4)	6989 (1)	5183 (2)	11138 (10)	3·9 (3)
C(1′)	5991 (2)	2523 (3)	6459 (11)	3·5 (4)
C(2′)	5788 (2)	1884 (3)	8484 (12)	4·1 (4)
C(3′)	5305 (2)	1497 (2)	6977 (11)	3·4 (4)
C(4′)	5062 (2)	2208 (2)	5431 (10)	3·0 (4)
O(1′)	5509 (1)	2775 (2)	4976 (7)	3·5 (3)
C(5′)	4615 (2)	2661 (3)	6917 (11)	4·1 (4)
N(5′)	4091 (1)	2213 (3)	6907 (8)	3·5 (4)
C(6′)	3810 (2)	2038 (3)	9103 (10)	3·8 (4)
C(7′)	3259 (2)	1626 (4)	8780 (14)	5·0 (6)
O(6′)	3993 (2)	2195 (3)	11343 (8)	5·0 (4)
O(3′)	5514 (1)	914 (2)	4995 (9)	4·7 (3)
C(*A*1)	5503 (3)	110 (3)	5560 (14)	4·6 (5)
C(*A*2)	5763 (3)	−384 (4)	3489 (20)	6·8 (7)
O(*A*)	5254 (4)	−142 (3)	7466 (15)	10·8 (7)
H(N3)	725 (2)	426 (3)	703 (14)	6 (2)
H(C6)	556 (2)	352 (3)	994 (14)	4 (2)
H1(C7)	598 (2)	446 (3)	1409 (13)	13 (2)
H2(C7)	545 (2)	469 (3)	1320 (14)	6 (2)
H3(C7)	596 (2)	536 (3)	1279 (14)	8 (2)
H(C1′)	621 (2)	240 (3)	515 (14)	5 (2)
H1(C2′)	570 (2)	228 (3)	1001 (14)	6 (2)
H2(C2′)	605 (2)	154 (3)	847 (14)	7 (2)
H(C3′)	504 (2)	124 (3)	819 (13)	11 (2)
H(C4′)	496 (2)	212 (3)	387 (13)	4 (2)
H1(C5′)	459 (2)	325 (3)	592 (14)	6 (2)
H2(C5′)	465 (2)	272 (3)	842 (13)	4 (2)
H(N5′)	395 (2)	201 (3)	552 (13)	2 (2)
H1(C7′)	321 (2)	153 (3)	701 (14)	5 (2)
H2(C7′)	322 (2)	120 (3)	965 (14)	6 (2)
H3(C7′)	298 (2)	201 (3)	933 (14)	7 (2)
H1(*A*2)	596 (2)	−3 (3)	227 (14)	4 (2)
H2(*A*2)	547 (2)	−67 (3)	248 (14)	7 (2)
H3(*A*2)	601 (2)	−78 (3)	432 (14)	6 (2)
C*(Cl)	2493	6460	1488	21 (5)
Cl(1*)	1826	6146	663	16 (2)
Cl(2*)	2955	5795	−149	29 (4)
Cl(3*)	2619	6491	4803	23 (3)
C′(Cl)	2480	6440	184	10 (2)
Cl(1′)	1838	6119	1469	10 (1)
Cl(2′)	2504	6411	−3278	16 (4)
Cl(3′)	3008	5858	1681	16 (2)
H(C*Cl)	254	701	76	5
H(C′Cl)	253	701	72	3

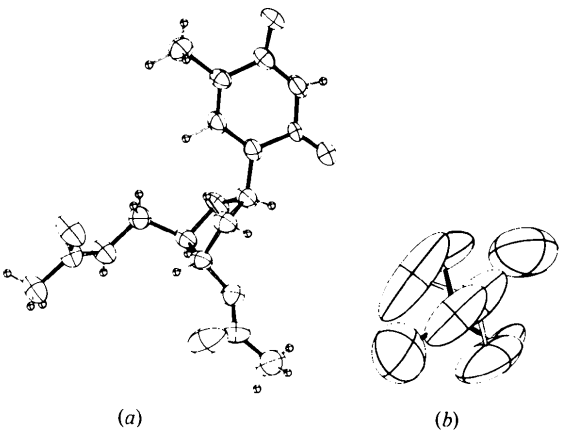
refinement was relatively clean. The two largest peaks in the map had densities of 0·35 and 0·32 e Å^{-3} which are located 1·99 and 2·10 Å from Cl(1′) and Cl(3*) respectively. The final atomic parameters with their estimated standard deviations are listed in Table 2.† It is noteworthy that the refined occupancies of the chloroform, in addition to minimizing the R factor, were also required to bring the calculated density into reasonable agreement with the observed value.

Description of the structure

An *ORTEP* (Johnson, 1965) drawing of the molecule is presented in Fig. 1. Although chloroform is disordered in the cell, the nucleoside molecule is normal in comparison with other structures. The molecular parameters and atomic numbering scheme are shown in Fig. 2. The bond lengths and angles are all in good agreement, with respect to the e.s.d.'s, in comparison with the average data published for thymidine and other thymidine derivatives (Young, Tollin & Wilson, 1969; Saenger & Suck, 1971; Suck, Saenger & Rohde, 1974). The pyrimidine ring resembles a slight boat (Table 3) with a maximum deviation of 0·035 Å and $\chi^2 = 151$. The displacements from the ring plane of the substituent atoms O(4), C(7) and C(1′) are also all significant.

In agreement with the tendency pointed out by Sundaralingam (1975), C(2′) in the sugar ring is puckered in the same direction as C(5′) (Table 3); that is, C(2′) *endo*: ^2_3T or $^2T_3$. Another variable parameter in sugars is the arrangement about C(4′)–C(5′) which is *trans-gauche*: g^- in this structure. Similar conformations were found by Rahman & Wilson (1972) and Harris & MacIntyre (1964). Both the amide and the ester groups in the two sugar-ring substituents are planar although the deviations in the amide are significantly smaller (Table 3). The difference in bond length between N(5′)–C(6′), 1·321 Å, and N(5′)–C(5′), 1·459 Å, is quite substantial and can be interpreted as delocalization of the N lone-pair electrons to the carbonyl. A similar condition is also found in the ester group where C(*A*1)–O(3′) is 1·333 Å in comparison with C(3′)–O(3′) at 1·459 Å. The three different types of angles within the sugar ring, C–C–C, C–C–O and C–O–C, have average values of 102·6, 105·9 and 110·3° respectively. The external angles, N(1)–C(1′)–O(1′) at 108·4° and C(5′)–C(4′)–O(1′) at 107·9°, are significantly smaller than N(1)–C(1′)–C(2′) and C(5′)–C(4′)–C(3′) with

† Lists of structure factors, thermal parameters and torsion angles have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 35351 (12 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.



(*a*) (*b*)

Fig. 1. Perspective views showing thermal ellipsoids at the 50% probability level for nonhydrogen atoms for (*a*) the main molecule, and (*b*) the disordered chloroform. The two figures are not on the same scale. H atoms are shown as spheres of arbitrary radii. In (*b*) one chloroform molecule is represented by dark solid lines and the other by light open lines.

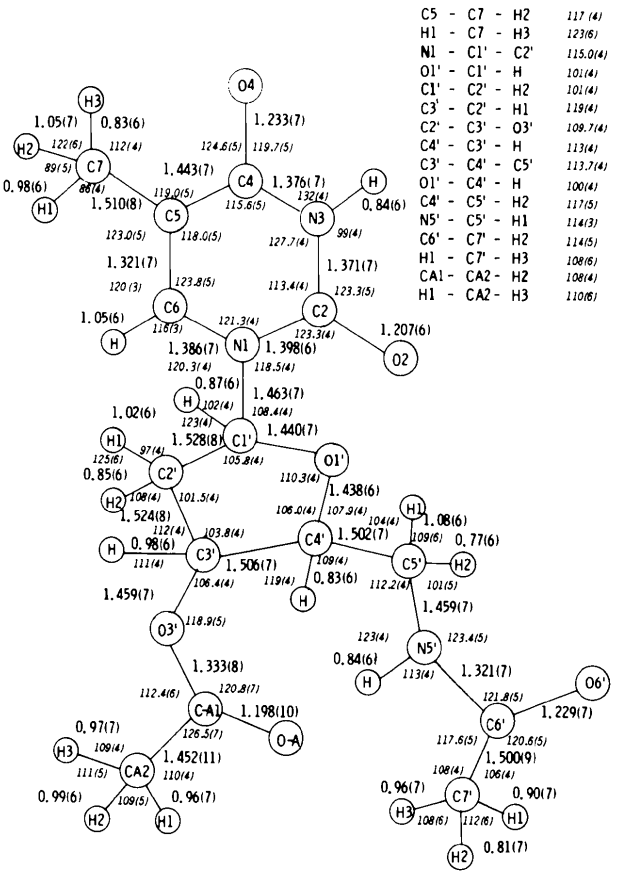


Fig. 2. Schematic representation of the molecule showing the atomic numbering scheme, the interatomic distances (Å), and the valence angles (°). The estimated standard deviations in parentheses refer to the least significant digit. Bond distances are presented in boldface type and the bond angles are in italic type.

Table 3. *Least-squares planes*

The coefficients ($\times 10^3$) are given for the planes which are expressed by the equation $Ax + By + Cz = D$, where x, y and z are in fractional unit-cell coordinates. The displacements of the atoms from the plane are in Å $\times 10^3$. Atoms used to define the plane are in boldface type. σ is the root-mean-square displacement of atoms defining the plane.

Plane	*A*	*B*	*C*	*D*	σ	Displacement
(1) Pyrimidine	9469	−9653	3500	5416	31	**N(1) 25 (4), N(3) −21 (5), C(2) −9 (5), C(4) 35 (5), C(5) −21 (5), C(6) −9 (9),** O(2) −61 (5), O(4) 98 (5), C(7) −95 (6), C(1′) 83 (5), C(2)[a] 3488 (5), O(2)[a] 3438 (5)
(2) Sugar	−7308	7524	4156	176	74	**C(1′) 28 (6), C(3′) −26 (5), C(4′) 43 (5), O(1′)−46 (4),** C(2′) 538 (6), C(5′) 1329 (6), N(1) 880 (5), O(3′) −1442 (5)
(3) Amide group	10645	−14536	179	1261	6	**C(6′) −5 (5), O(6′) 2 (6), N(5′) 2 (5), C(7′) 1 (7),** C(5′) −93 (5)
(4) Ester group	20652	984	2578	12776	39	**C(*A*1) 34 (7), C(*A*2) −10 (9), O(*A*) −13 (9), O(3′) −10 (5),** C(3′) 127 (5)

Dihedral angle: planes (1) and (2): 79·1°

Symmetry code: (*a*) $x, y, 1 + z$.

values of 115·0 and 113·7° respectively. This difference is common in other structures (Sundaralingam & Jensen, 1965).

The dihedral angle between the planes of the thymine base and the sugar ring is 79·1°. The torsion angle O(1′)–C(1′)–N(1)–C(6) of 64·7° is in the range of the *anti* conformation (Sundaralingam, 1975). A table of the torsion angles of the two side chains has been deposited.

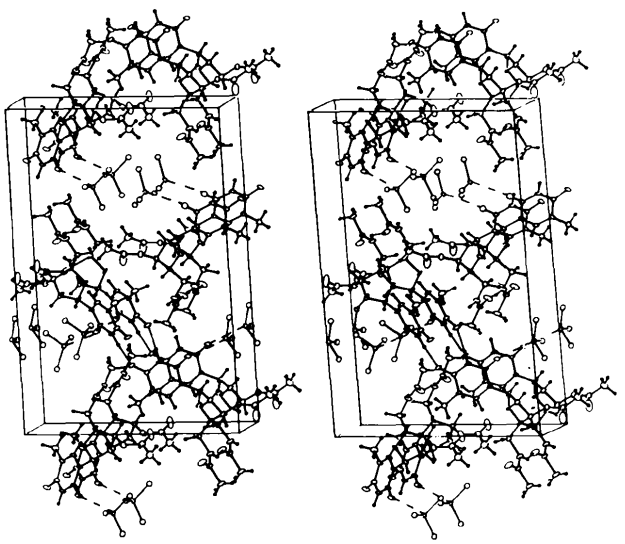


Fig. 3. Stereo packing diagram showing contents in the volume which extends along the *a* axis (vertical) from $-\frac{1}{2}$ to 1, along the *b* axis (horizontal) from 0 to 1 and along the *c* axis from −1 to 1. Covalent bonds are depicted with thick lines and the hydrogen bonds are represented by narrow lines. The hydrogen bond involving the chloroform molecule is represented by a dashed line. For clarity only the high-occupancy chloroform molecule is shown.

Molecular packing and hydrogen bonding

A stereoscopic *ORTEP* packing diagram is shown in Fig. 3. There are two N–H···O hydrogen bonds between nucleosides. The pyrimidine N(3)–H is hydrogen bonded to the O(4) in the molecule related by $(\frac{1}{2} - x, -y, \frac{1}{2} + z)$ and O(4) is bonded to N(3)–H of the pyrimidine related by $(\frac{1}{2} - x, -y, -\frac{1}{2} + z)$ with lengths of 2·09 (H···O) and 2·87 Å (N···O). This hydrogen bond connects the molecules in an infinite chain along the twofold screw axis. In the acetamide group N(5′)–H is hydrogen bonded to O(6′) of the molecule related by (−1 in *z*) which connects molecules along the *z* axis. The distances of the N–H···O hydrogen bond are 2·11 (H···O) and 2·79 Å (N···O). The pyrimidine ring is involved in a stacking interaction with a neighboring pyrimidine ring in a manner which is common in nucleosides (Bugg, Thomas, Sundaralingam & Rao, 1971). O(2) is 3·45 Å from the adjacent pyrimidine. There is a channel parallel to the *c* axis extending throughout the entire crystal. Chloroform is contained in this channel and forms only a weak hydrogen bond, $Cl_3CH\cdots O(2)$, with H···O = 2·13 and C···O = 3·05 Å; the second disordered position gives 2·15 and 3·05 Å. This explains the easy loss of chloroform from the crystal. This is similar to the situation observed in *N*,*N*′-ethylenebis(salicylideneiminato)cobalt(II)–monochloroform (Schaefer & Marsh, 1969). The two chloroform molecules chosen to

Table 4. *Bond lengths* (Å) *and angles* (°) *in chloroform*

C*(Cl)–Cl(1*)	1·74	Cl(1*)–C*(Cl)–Cl(2*)	107
C*(Cl)–Cl(2*)	1·75	Cl(1*)–C*(Cl)–Cl(3*)	114
C*(Cl)–Cl(3*)	1·69	Cl(2*)–C*(Cl)–Cl(3*)	111
C′(Cl)–Cl(1′)	1·76	Cl(1′)–C′(Cl)–Cl(2′)	113
C′(Cl)–Cl(2′)	1·73	Cl(1′)–C′(Cl)–Cl(3′)	109
C′(Cl)–Cl(3′)	1·75	Cl(2′)–C′(Cl)–Cl(3′)	113

explain the disorder are approximately related by rotation about the C—H bond. The elongation of the atoms in the molecule in the *ORTEP* drawing (Fig. 1*b*) is consistent with this disordered model. The bond lengths and angles for chloroform are given in Table 4.

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Salignone-D

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Abstract

$C_{18}H_{20}O_5$, $M_r = 316{\cdot}36$, is monoclinic, $P2_1$, with $a = 13{\cdot}928\ (4)$, $b = 9{\cdot}218\ (2)$, $c = 6{\cdot}119\ (2)$ Å, $\beta = 97{\cdot}45\ (3)°$, $V = 779{\cdot}0\ (4)$ Å^3, $Z = 2$, $d_c = 1{\cdot}349$ Mg m^{-3}, λ(Cu $K\alpha$) = 1·54178 Å. Full-matrix least-squares refinement (nonhydrogen atoms anisotropic, H atoms isotropic) based on 1441 reflexions led to a final R of 0·057. Salignone-D is a bisnorditerpene dilactone. The A and B rings are *trans* fused and exhibit flattened-chair and 1,2-diplanar conformations, respectively. The conformation of the δ-lactone ring is best described as 1,3-diplanar, while the five-membered γ-lactone is in an envelope conformation with C(5) as the flap. The molecule also contains a *cis*-fused epoxide function.

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Introduction

Nor- and bisnorditerpene dilactones, isolated from *Podocarpus* species, exhibit a variety of biological activities. Hallactone A and B (Russell, Fenemore & Singh, 1973) and nagilactone A (Hirotsu, Higuchi, Shimada, Hayashi & Sakan, 1975) are toxic to house-fly larvae; sellowin-A (Cambie & Russell, 1973) and podolactones A and B (Galbraith, Horn & Sasse, 1971) inhibit growth of pea stem hook segments; inumakilactone-A glucoside is an inhibitor of expansion