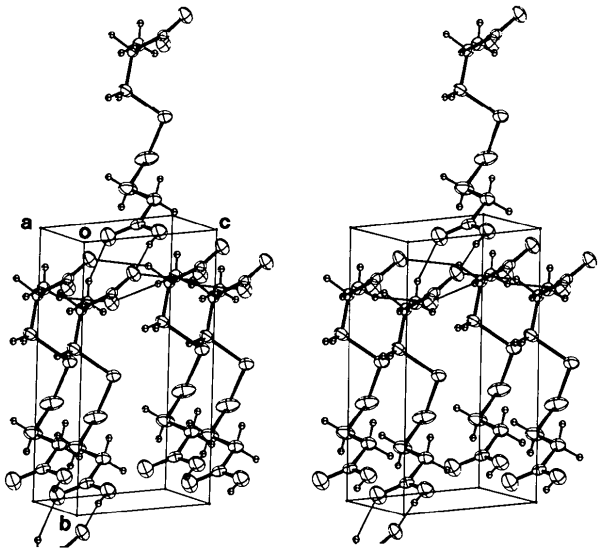

Fig. 2. A stereoview of the molecular packing and hydrogen-bonding interactions in the crystal.

and Sγ(1)···H(1Cα2) are 3·341 (3) and 2·89 (5) Å, respectively, and the angle Sγ(1)···H(1Cα2)—Cα(2) is 111 (4)°. There is no other short contact with S; the reason for the occurrence of the type of short S···S and S···X contacts (X = electrophiles or nucleophiles; Rosenfield, Parthasarathy & Dunitz, 1977) with S atoms in only some selected structures is not yet clear.

We thank Professor H. A. Scheraga for the compound and for a discussion on short contacts to S atoms. We thank Mr Craig Schmidt for his participation in this work as a summer participant and Ms J. Mann for technical help. Partial financial support by grants NIH CA 23704 and GM 24864 is gratefully acknowledged.

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The Structure of Phyllanthose Hexaacetate, $C_{24}H_{34}O_{15}$*

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(*Received* 2 *February* 1984; *accepted* 13 *December* 1984)

Abstract. *O*-6-Deoxy-β-D-glucopyranosyl-(1→2)-6-deoxy-α-D-glucopyranose hexaacetate. $M_r = 562{\cdot}52$, monoclinic, $P2_1$, $a = 13{\cdot}077$ (7), $b = 9{\cdot}306$ (5), $c = 12{\cdot}009$ (6) Å, $\beta = 92{\cdot}33$ (2)°, $V = 1460$ (1) Å^3, $Z = 2$, $D_m = 1{\cdot}24$, $D_x = 1{\cdot}28$ Mg m^{-3}, Cu $K\alpha$, $\lambda = 1{\cdot}5418$ Å, $\mu = 0{\cdot}882$ mm^{-1}, $F(000) = 596$, room temperature, final $R = 0{\cdot}049$ for 1930 reflections. The molecules exist as discrete monomers in the crystal. The bond

* The present contribution is part 106 of Antineoplastic Agents. For part 105 refer to Pettit, Gaddimidi & Cragg (1985).

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lengths and angles in the pyranose rings are normal. The two C—O glycosidic bond lengths are not equal [1·427 (5), 1·394 (6) Å], the shorter involving the anomeric carbon. A conformational analysis has been carried out and a postulate of the most likely conformation in solution is put forward.

Introduction. Isolation of the antineoplastic glycosides phyllanthostatins 1–3 and phyllanthoside (see Fig. 1) from the Euphorbiaceae tree *Phyllanthus acuminatus* Vahl was recently summarized (Pettit, Cragg, Gust, Brown & Schmidt, 1982; Pettit, Cragg, Gust & Brown, 1982). Phyllanthostatin 1 (1*a*) and phyllanthoside (1*b*) were found to have identical aglycone units bonded *via* ester linkages to diacetylated isomers of a new 6-deoxy-D-glucose disaccharide. Phyllanthostatin 3 (2*a*) was shown to contain the same parent disaccharide, but to have a diol group replacing the aglycone epoxide at C(7)–C(14). Because these very important glycosides resisted crystallization for X-ray studies, structural assignments were based on extensive chemical and spectral studies. More recently, methanolysis (Pettit, Cragg, Niven & Nassimbeni, 1983) of phyllanthostatin 3 (2*a*) afforded phyllanthocindiol methyl ester (2*b*). The resulting X-ray crystal structure of ester (2*b*) was described in our preceding contribution (Nassimbeni, Niven, Cragg & Pettit, 1984). The disaccharide methanolysis product (phyllanthose, 3*a*) was acetylated to yield *O*-6-deoxy-β-D-glucopyranosyl-(1→2)-6-deoxy-α-D-glucopyranose hexaacetate (3*b*, phyllanthose hexaacetate). In order to confirm the structure of phyllanthose and in turn the parent *P. acuminatus* glycosides an X-ray crystal structure determination of phyllanthose acetate (3*b*) was undertaken. By this means the unique 1→2 linked di-6-deoxy-D-glucose structure of phyllanthose and structures assigned to the phyllanthostatins and phyllanthoside were unequivocally verified.

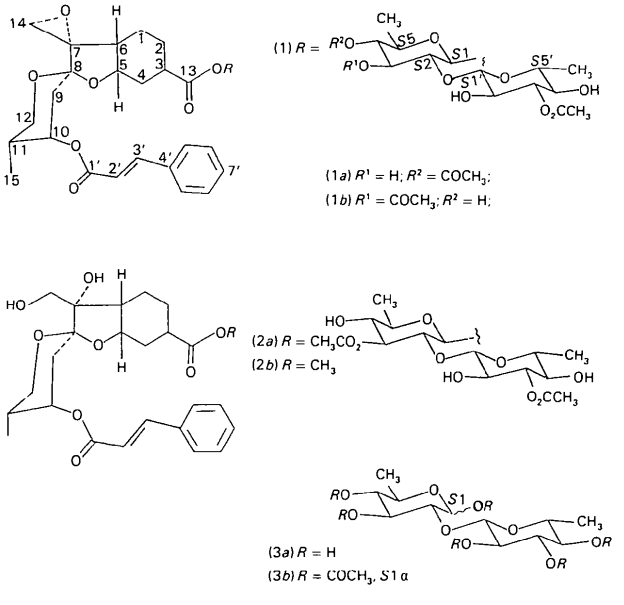

Fig. 1. Antineoplastic glycosides: diagrammatic representation.

Experimental. Single crystal obtained by slow evaporation of an acetone solution in hexane-saturated atmosphere. D_m by flotation. Preliminary photography established space group as $P2_1$. Accurate cell constants by least squares from settings of 25 high-order reflections ($15 \leq \theta \leq 16°$), Philips PW 1100 four-circle diffractometer, graphite-monochromated Cu $K\alpha$ radiation; three reference reflections monitored every 50 measured reflections to ascertain crystal stability, intensities corrected for Lorentz–polarization, not for absorption. Crystal data and experimental details of data collection are listed in Table 1. Structure solved by direct methods using multisolution tangent refinement procedures of *SHELX* (Sheldrick, 1978). Best *E* map (reliability index $R_A = 0{\cdot}129$) gave recognizable molecular fragment of 21 of the 39 non-hydrogen atoms in asymmetric unit. Subsequent weighted difference syntheses yielded remaining non-hydrogen atoms. Hydrogen atoms placed at 1·00 Å from parent carbon atoms; positions of methine hydrogens dictated by geometry of molecule, methyl hydrogens treated as rigid groups. Owing to large number of independent atoms, final refinements (on *F*) were with blocked-matrix technique, non-hydrogen atoms anisotropic, hydrogen atoms isotropic.* In final difference map max. residual peak 0·23 e Å^{-3}, max. $\Delta/\sigma = 0{\cdot}48$, for atomic coordinates, min. peak height −0·25 e Å^{-3}. Details of final refinements are given in Table 1. Complex neutral-atom scattering factors from Cromer & Mann (1968) for C and O, from Stewart, Davidson & Simpson (1965) for H, with dispersion corrections from Cromer & Liberman (1970). Table 2 lists the final fractional atomic coordinates and temperature factors for all the non-hydrogen atoms. All computations were performed on a Univac 1100/81 with *PARST* (Nardelli, 1983*a*) for molecular geometry, *EENY* (Motherwell, 1974*b*) for energy calculations and *PLUTO* (Motherwell, 1974*a*) for illustrations.

Discussion.

Molecular structure. A perspective view of the molecule with atomic numbering is shown in Fig. 2.

* Anisotropic temperature factors, bond lengths and angles, conformational parameters, hydrogen-atom coordinates, analyses of variance and a list of structure factors have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 39973 (14 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 1. *Crystal data, experimental and refinement parameters*

Data collection	
Crystal dimensions (mm)	0·15 × 0·25 × 0·50
Scan mode	ω–2θ
Scan width (°θ)	1·70
Scan speed (°θs^{-1})	0·057
Range scanned (2θ) (°)	10–120
Range of indices (h, k, l)	±14, +10, +13
Stability of standard reflections (%)	0·08
Number of reflections collected	2299
Number of observed reflections, N (with $I_{rel} > 2\sigma I_{rel}$)	1930
Final refinement	
Number of variables, NP	377
R	0·049
$wR = \sum w^{1/2}\|\|F_o\| - \|F_c\|\| / \sum w^{1/2}\|F_o\|$	0·042
w	$(\sigma^2 F)^{-1}$
S	2·02
U (methyl H) (Å^2)	0·166 (10)
U (methine H) (Å^2)	0·036 (6)

Table 2. *Fractional atomic coordinates* (×10^4) *and thermal parameters* (Å^2 × 10^3) *for non-hydrogen atoms*

	x	y	z	U_{eq}*
C(1)	−3410 (4)	8276 (6)	7029 (4)	46 (2)
C(2)	−2615 (3)	7967 (6)	7974 (3)	39 (2)
C(3)	−3109 (4)	7314 (6)	8981 (4)	42 (2)
C(4)	−3946 (4)	8344 (6)	9308 (4)	47 (2)
C(5)	−4738 (4)	8422 (7)	8349 (4)	52 (2)
C(6)	−5689 (5)	9298 (8)	8595 (6)	78 (3)
C(1′)	−1160 (4)	7580 (6)	6878 (4)	39 (2)
C(2′)	−136 (3)	6807 (6)	6967 (4)	40 (2)
C(3′)	538 (4)	7453 (6)	6097 (4)	42 (2)
C(4′)	32 (4)	7321 (6)	4943 (4)	40 (2)
C(5′)	−1036 (4)	8010 (7)	4926 (4)	44 (2)
C(6′)	−1633 (5)	7725 (8)	3831 (4)	62 (2)
O(1′)	−1823 (2)	7020	7648 (2)	41 (1)
O(5)	−4249 (3)	9061 (4)	7421 (3)	53 (1)
O(5′)	−1601 (2)	7337 (4)	5790 (2)	40 (1)
O(11)	−3734 (2)	6913 (4)	6575 (3)	43 (1)
C(11)	−3990 (4)	6895 (8)	5453 (4)	52 (2)
O(12)	−4037 (3)	7990 (6)	4904 (3)	67 (2)
C(12)	−4144 (5)	5402 (8)	5051 (5)	76 (3)
O(31)	−2350 (3)	7200 (4)	9885 (3)	53 (1)
C(31)	−2040 (5)	5837 (9)	10157 (5)	56 (3)
O(32)	−2341 (3)	4779 (5)	9698 (4)	72 (2)
C(32)	−1274 (6)	5860 (9)	11127 (5)	96 (4)
O(41)	−4430 (3)	7813 (5)	10290 (3)	47 (1)
C(41)	−4512 (5)	8725 (6)	11152 (5)	62 (3)
O(42)	−4129 (5)	9906 (7)	11160 (4)	121 (3)
C(42)	−5132 (7)	8108 (13)	12053 (6)	76 (3)
O(21′)	358 (3)	7091 (4)	8042 (3)	50 (1)
C(21′)	606 (5)	5954 (10)	8698 (5)	71 (3)
O(22′)	347 (4)	4736 (6)	8485 (4)	96 (2)
C(22′)	1237 (7)	6391 (12)	9693 (6)	120 (4)
O(31′)	1497 (3)	6661 (4)	6103 (3)	52 (2)
C(31′)	2371 (5)	7412 (9)	6302 (5)	59 (3)
O(32′)	2372 (4)	8679 (7)	6487 (5)	96 (2)
C(32′)	3281 (5)	6472 (9)	6222 (6)	85 (3)
O(41′)	659 (2)	8107 (4)	4184 (3)	47 (1)
C(41′)	1160 (5)	7381 (9)	3409 (5)	62 (3)
O(42′)	1021 (5)	6130 (6)	3256 (5)	121 (3)
C(42′)	1855 (5)	8308 (9)	2783 (6)	76 (1)

* $U_{eq} = \frac{1}{3}$(trace of the orthogonalized U_{ij} matrix).

The C—C distances in the two pyranose rings are in the range 1·516 (7)–1·536 (8) Å, in good agreement with those observed for related structures (Jeffrey & French, 1978); more interesting are the glycosidic C—O linkages: C(2)—O(1′) is significantly longer than C(1′)—O(1′), the shortening of the latter being characteristically associated with the anomeric carbon C(1′) (Jeffrey & French, 1978; Taga, Sumiya, Osaki, Utamura & Koizumi, 1981). The ring C—O bonds have a mean value of 1·429 (10) Å while the exocyclic C—O lengths (excluding the glycosidic linkage), having a mean of 1·446 (5) Å, are longer than the average value of 1·426 Å obtained for 23 non-acetylated glucosyl residues (Avenel, Neuman & Gillier-Pandraud, 1976).

The C(1′)—O(1′)—C(2) bridge angle of 115·4 (3)° is in the lower range of the equivalent angles in six other 1–2 linked disaccharides (Kanters, Roelofsen, Doesburg & Koops, 1976) [C—O—C bridge angle in range 114·3 (8)–122·1 (5)° – mean118 (1)°]; however, a comparison based on a similar-type linkage may not be valid as the angle in question is likely to have some dependence on the steric and hydrogen-bonding features, which are frequently different. In support of this view, the C(1′)—O(1′)—C(2) angle here is similar to a remarkably constant value (113·0–113·8°) in seven methyl glycosides (Jeffrey & French, 1978). The interior and exterior ring angles are in the range 106·6 (5)–114·9 (4)°, consistent with an expected high degree of tetrahedrality.

The angles at the oxygen atoms linked to the acetate groups have a mean of 117 (1)°, which is similar to the mean value of 118 (1)° observed in β-D-(1→4)-xylobiose hexaacetate (Leung & Marchessault, 1973). The O—C(=O)—CH_3 angles of the side groups are 110·7 (7)–112·7 (6)°, which are similar to those previously observed in β-D-(1→4)-xylobiose hexaacetate (Leung & Marchessault, 1973) and 3′-*O*-acetyl-4-thiothymidine (Saenger & Suck, 1971). According to Schweizer & Dunitz (1982) the expected value for the O—CO—C angle is 111°.

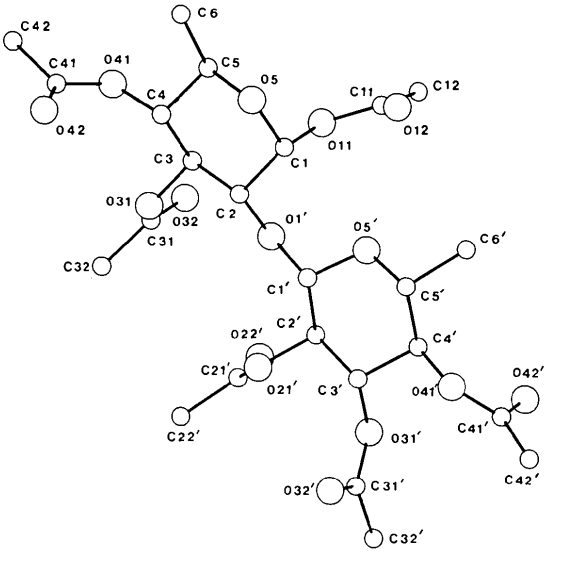

Fig. 2. Phyllanthose acetate: perspective view and atomic numbering.

There is neither hydrogen bonding nor any other particular short interatomic contact within the crystal structure, and the molecular packing is unremarkable.

Conformational analysis. The molecular conformations of the two pyranose rings in the crystal have been examined in terms of asymmetry parameters (Nardelli, 1983*b*) and puckering parameters (Cremer & Pople, 1975).* Both rings are $^4C_1$. The predicted conformations of both α- and β-glucopyranoses are $^4C_1$ (Stoddard, 1981). In addition the conformational angles Φ and Ψ, as previously defined (Sundararajan & Rao, 1969), are 24 (2) and −43 (1)° respectively.

Planarity of each of the acetate groups allows the torsion angles $H-C_{(ring)}-O-C_{(acetate)}$ to be used as a measure of the acetate orientation with respect to the adjacent $C-H_{(ring)}$. In the six cases, the relevant torsion angles are in the range 12·8 (8) to −25·7 (7)°. Similarly low values have been obtained in the studies of the related xylan diacetate (Gabbay, Sundararajan & Marchessault, 1972).

We have attempted to predict the most likely free molecule and possibly solution conformation of the compound by carrying out an energy-minimization procedure based upon simple calculation of the van der Waals energy using empirical atom-pair potentials (Giglio, 1969). Atomic coordinates used in the energy analysis were obtained from the refined crystal structure.

Numerous energy maps were calculated with the five torsion angles $\tau_1 - \tau_5$ (as defined in Table 3) varying simultaneously over the complete angular range 0–360° in 20° increments. These five torsion angles encompassing the linkage of the two rings and the acetate groups closest to the linkage can be considered as those resulting in the most significant energy changes with conformational variations.

There was found to be essentially only one region of the five-dimensional space that yields molecular energies below 83·68 kJ mol^{-1}: $80 < \tau_1 < 160$, $80 < \tau_2 < 300$, $60 < \tau_3 < 160$, $200 < \tau_4 < 260$, $100 < \tau_5 < 260°$. (The relevant torsion-angle values for the molecule in the crystal are within this range.) The lowest minimum, $E = 11{\cdot}17$ kJ mol^{-1}, corresponds to $\tau_1 \rightarrow \tau_5$, 95, 166, 128, 208, 194° respectively. Interestingly, the molecule in the crystal ($E = 26{\cdot}32$ kJ mol^{-1}) yields, on energy minimization ($E = 12{\cdot}80$ kJ mol^{-1}), a conformation differing by as much as 27° in τ_1, 15° in τ_2, 4° in τ_3, 15° in τ_4 and 20° in τ_5. It is possible that the difference between the two conformations arises because not all acetates nor the ring conformations were allowed to vary in the energy model. Hence, from the results we believe that the most favourable solution conformation of this disaccharide is similar to that determined in the crystal structure analysis.

* See deposition footnote.

Table 3. *Torsion angles allowed to vary in the conformational analysis*

τ_1	C(1′)–C(2′)–O(21′)–C(21′)
τ_2	C(2′)–C(1′)–O(1′)–C(2)
τ_3	C(1′)–O(1′)–C(2)–C(1)
τ_4	C(2)–C(3)–O(31)–C(31)
τ_5	C(2)–C(1)–O(11)–C(11)

For very necessary financial assistance the ASU-CRI chemists are pleased to thank Mary Dell Pritzlaff, the Olin Foundation (Spencer T. and Ann W.), the Fannie E. Rippel Foundation, Eleanor W. Libby, the Donald Ware Waddell Foundation, Pearl Spear and Robert B. Dalton; also Contract NO1-CM-97297 with the Division of Cancer Treatment, NCI, National Institutes of Health, DHW. The UCT chemists are grateful for financial assistance from the University of Cape Town and the CSIR, Pretoria.

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