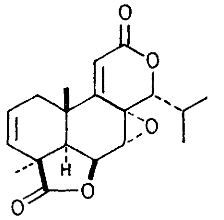
X-Ray Determination of the Structure of Podolide, an Antileukemic Norditerpene Dilactone

By **Robert F. Bryan** * and **Peter M. Smith**, Department of Chemistry, University of Virginia, Charlottesville, Virginia 22901, U.S.A.

The crystal structure of podolide, (I), $C_{19}H_{22}O_5$, an antileukemic norditerpene dilactone isolated from *Podocarpus gracilior*, has been determined by *X*-ray diffraction methods. Crystals are monoclinic, space group $P2_1$, with $a = 12.165(3)$, $b = 7.771(1)$, $c = 9.708(4)$ Å, $\beta = 113.76(3)°$, and $Z = 2$. The structure was solved by direct methods and refined by least-squares methods to R 0.045 for 1 975 independent reflections measured by counter diffractometry. The molecule has a double bond at C(2)–C(3), an epoxide α at C(7)–C(8), and an isopropyl substituent α at C(14). Rings A and B have slightly distorted 1,2-diplanar conformations, the pyran ring C has a near 1,3-diplanar conformation, while the γ-lactone is a C(5) envelope.

CONTINUING their search for tumour inhibitors from plant sources, Kupchan *et al.* isolated podolide,[1] an active antileukemic agent, from an alcoholic extract of the leaves and twigs of *Podocarpus gracilior*, Pilg. The characterization of podolide as the norditerpene dilactone (I) by a combination of chemical, spectral, and *X*-ray diffraction methods has been briefly reported,[1] and we give here the details and results of the *X*-ray structure determination which established the relative stereochemistry of (I).



(I)

Because Mo-K_α radiation was used for the measurement of the diffracted intensities, the absolute configuration of podolide could not be determined by the anomalous scattering method,[2] but an assignment of absolute configuration consistent with that accepted for related molecules[3] has been made[1] based on the observation of a negative Cotton effect in the c.d. spectrum of (I).

The crystal structure determination was carried out by use of direct methods of phase determination (MULTAN),[4] and led to the location of all atoms in the molecule, including hydrogen. Atomic co-ordinates and thermal parameters are given in Table 1, and bond distances and valence angles in Table 2. The molecular structure, as found in the crystal, is illustrated by the stereoscopic diagram[5] in Figure 1. The endocyclic torsion angles defining the conformation of the ring system are given, together with the numbering scheme adopted, in Figure 2. The displacements of atoms from selected mean planes in the molecule are given in Table 3.

The results of the *X*-ray study confirm that podolide is a norditerpene dilactone having the same ring system as the other norditerpene and bisnorditerpene dilactones

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[1] S. M. Kupchan, R. L. Baxter, M. F. Ziegler, P. M. Smith, and R. F. Bryan, *Experientia*, 1975, **31**, 137.

[2] J. M. Bijvoet, A. F. Peerdeman, and A. J. van Bommel, *Nature*, 1951, **169**, 271.

[3] S. Itô, M. Sunagawa, M. Kodama, H. Honma, and T. Takahashi, *Chem. Comm.*, 1971, 91.

[4] G. Germain, P. Main, and M. M. Woolfson, *Acta Cryst.*, 1971, **A27**, 368.

[5] C. K. Johnson, Oak Ridge National Laboratory Report, ORNL 3794, Oak Ridge, Tennessee, U.S.A., 1965.

TABLE 1

(*a*) Positional parameters (fractional co-ordinates × 10^4) and anisotropic thermal parameters * for non-hydrogen atoms, with standard deviations in parentheses

Atom	x/a	y/b	z/c	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
C(1)	6 854(3)	5 367(4)	2 775(4)	60(2)	99(4)	148(5)	−14(3)	32(3)	18(4)
C(2)	8 085(3)	4 751(6)	3 000(7)	71(3)	200(8)	627(17)	22(5)	134(6)	178(10)
C(3)	8 479(3)	3 104(5)	3 405(4)	62(3)	163(7)	290(8)	6(4)	78(4)	21(6)
C(4)	7 749(2)	1 836(4)	3 866(3)	52(2)	114(4)	121(4)	14(3)	23(2)	0(4)
C(5)	6 571(2)	2 580(3)	3 833(3)	52(2)	84(4)	77(3)	6(2)	21(2)	−3(3)
C(6)	5 826(2)	962(3)	3 699(3)	61(2)	75(4)	111(4)	11(3)	35(2)	16(3)
C(7)	4 491(2)	1 215(3)	3 032(3)	59(2)	68(3)	127(4)	−1(3)	33(2)	10(3)
C(8)	3 962(2)	2 906 †	2 470(3)	50(2)	58(3)	97(3)	−4(2)	26(2)	−1(3)
C(9)	4 774(2)	4 356(3)	2 458(3)	47(2)	60(3)	70(3)	−8(2)	18(2)	0(3)
C(10)	5 987(2)	3 858(3)	2 525(3)	47(2)	73(4)	82(3)	−2(2)	22(2)	6(3)
C(11)	4 305(2)	5 935(3)	2 238(3)	56(2)	65(4)	103(4)	−10(3)	27(2)	4(3)
C(12)	3 051(2)	6 242(3)	2 014(3)	68(2)	71(4)	124(4)	3(3)	36(3)	9(3)
C(14)	2 697(2)	3 206(3)	1 353(3)	50(2)	64(4)	109(4)	−2(2)	27(2)	−5(3)
C(15)	1 716(2)	1 891(4)	1 177(4)	59(3)	76(4)	152(5)	−9(3)	3(3)	−9(4)
C(16)	592(3)	2 341(5)	−222(5)	63(3)	170(7)	238(7)	−28(4)	8(3)	5(6)
C(17)	1 442(4)	1 654(6)	2 549(5)	116(4)	236(9)	227(7)	−73(5)	96(4)	−25(7)
C(18)	7 287(3)	267(4)	2 839(3)	83(3)	112(5)	126(5)	20(3)	40(3)	10(4)
C(19)	8 542(3)	1 090(6)	5 430(4)	83(3)	275(9)	135(5)	76(5)	12(3)	27(6)
C(20)	5 693(3)	3 067(4)	942(3)	74(3)	149(5)	75(3)	15(3)	30(2)	−1(4)
O(1)	2 664(2)	7 647(3)	2 118(3)	83(2)	70(3)	267(5)	13(2)	69(3)	0(3)
O(2)	2 300(2)	4 870(2)	1 714(2)	58(2)	70(3)	168(3)	−3(2)	43(2)	−3(3)
O(3)	4 148(2)	2 342(3)	3 990(2)	81(2)	111(3)	113(3)	11(2)	50(2)	22(3)
O(4)	6 188(2)	−195(2)	2 770(2)	76(2)	79(3)	158(3)	10(2)	43(2)	−16(3)
O(5)	7 767(2)	−504(3)	2 177(3)	120(3)	190(5)	223(5)	18(3)	95(3)	−50(4)

(*b*) Positional praameters (fractional co-ordinates × 10^3) and isotropic thermal parameters for H atoms ‡

Atom	x/a	y/b	z/c	B(Å^2)	Atom	x/a	y/b	z/c	B(Å^2)
H(1a)	690(3)	589(4)	369(3)	4.1(7)	H(16b)	20(4)	330(5)	−6(5)	6.7(10)
H(1b)	658(3)	610(5)	185(3)	4.5(7)	H(16c)	78(4)	253(7)	−114(5)	10.4(14)
H(2)	855(3)	565(5)	284(4)	6.7(10)	H(17a)	107(4)	80(8)	260(6)	11.8(16)
H(3)	916(3)	281(5)	359(4)	6.0(9)	H(17b)	200(4)	185(6)	359(5)	9.1(12)
H(5)	665(2)	313(4)	477(3)	2.2(5)	H(17c)	80(5)	230(8)	248(6)	12.6(17)
H(6)	604(2)	38(3)	474(3)	2.4(6)	H(19a)	806(3)	18(6)	569(4)	7.4(11)
H(7)	405(2)	25(4)	269(3)	3.9(7)	H(19b)	881(3)	185(6)	620(4)	6.8(10)
H(11)	480(2)	684(4)	225(3)	2.4(6)	H(19c)	923(3)	58(5)	535(4)	4.9(8)
H(14)	271(2)	324(4)	35(3)	2.0(5)	H(20a)	629(3)	250(5)	84(4)	5.4(9)
H(15)	205(2)	89(4)	94(3)	3.2(6)	H(20b)	549(5)	399(8)	17(7)	12.4(20)
H(16a)	−3(4)	150(5)	−37(4)	7.5(11)	H(20c)	503(4)	257(6)	47(4)	8.0(12)

* Exponent in the form $-[h^2\beta_{11} + k^2\beta_{22} + l^2\beta_{33} + 2hk\beta_{12} + 2hl\beta_{13} + 2kl\beta_{23}]$ and individual β_{ij} are given × 10^4. † Co-ordinate held fixed to define the origin. ‡ Hydrogen atoms are numbered according to the carbon atom to which they are attached.

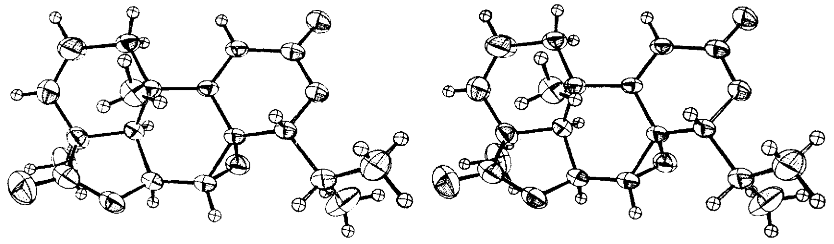

FIGURE 1 Stereoscopic view of the molecular structure in the conformation found in the crystal; thermal ellipsoids drawn to 50% probability level

thus far isolated from the various *Podocarpus* species.[6] As in the podolactones,[7] sellowins A and B,[8] inumakilactones A and B,[9] nagilactone E,[10] and epoxynagilactone F,[11] podolide has an epoxy functionality α at C(7)–C(8). A double bond occurs at C(9)–C(11) in ring C, but, unique among the related compounds thus far reported, podolide has a double bond in ring A at C(2)–C(3).* The configuration at C(14) is *S*, with the isopropyl group equatorial (α). The C(4) methyl group is α, that at C(10) β, in the pattern of substitution common to the series.

Bond distances show expected features. Exclusive of

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* Podolactone D[7] is the only other member of this class with unsaturation reported in ring A, having a double bond replacing the epoxide functionality found at this site in the other podolactones.

[6] For a recent review, see K. S. Brown, jun., and W. E. Sanchez, *Biochem. Syst. Ecol.*, 1974, **2**, 11.

[7] M. N. Galbraith, D. H. S. Horn, J. M. Sasse, and D. Adamson, *Chem. Comm.*, 1970, 170; M. N. Galbraith, D. H. S. Horn, and J. M. Sasse, *ibid.*, 1971, 1362; *Experientia*, 1972, **28**, 253.

[8] W. E. Sanchez, K. S. Brown, jun., T. Nishida, L. J. Durham, and A. M. Duffield, *Anales, Acad. Bras. Ciencias*, 1971, **42**, Suppl. 77.

[9] T. Hayashi, H. Kakisawa, S. Itô, Y. P. Chen, and H.-Y. Hsu, *Tetrahedron Letters*, 1972, 3385; S. Itô, M. Kodama, M. Sunagawa, T. Takahashi, H. Inamura, and O. Honda, *ibid.*, 1968, 2065; see also refs. 3 and 7.

[10] Y. Hayashi, J. Yokoi, Y. Watanabe, T. Sakan, Y. Masuda, and R. Yamamoto, *Chem. Letters*, 1972, 759.

[11] D. J. Watts, Dissertation, Indiana University, 1969; see also ref. 6.

bonds to the carbon atoms of the epoxy group, the mean C(sp^3)–C(sp^3) bond distance is **1.534(5)** Å. The shortness of C(15)–C(17) [1.509(5) Å] is probably attributable to the effects of thermal motion, while the two longest bonds in this group are to the methyl substituents at the tertiary carbon atoms. The mean C(sp^3)–C(sp^2) bond distance is 1.509(5) Å, and only C(10)–C(18) deviates significantly from this value, probably reflecting steric strain at the tertiary atom.

TABLE 2

Bond distances (Å) and angles (deg.), with standard deviations in parentheses

(*a*) Bond distances not involving hydrogen

C(sp^3)–C(sp^3)		C(sp^2)–C(sp^2)	
C(1)–C(10)	1.530(3)	C(2)–C(3)	1.368(6)
C(4)–C(5)	1.534(3)	C(9)–C(11)	1.334(3)
C(4)–C(19)	1.547(5)	C(11)–C(12)	1.471(4)
C(5)–C(10)	1.542(3)		
C(5)–C(6)	1.525(3)	C(sp^3)–O	
C(10)–C(20)	1.557(4)	C(6)–O(4)	1.462(3)
C(14)–C(15)	1.527(4)	*C(7)–O(3)	1.455(3)
C(15)–C(16)	1.531(5)	*C(8)–O(3)	1.467(3)
C(15)–C(17)	1.509(5)	C(14)–O(2)	1.472(3)
*C(6)–C(7)	1.499(3)		
*C(7)–C(8)	1.468(3)	C(sp^2)–O	
*C(8)–C(14)	1.501(3)	C(12)–O(2)	1.356(3)
		C(18)–O(4)	1.359(3)
C(sp^3)–C(sp^2)			
C(1)–C(2)	1.503(5)	C(sp^2)–O	
C(4)–C(3)	1.509(5)	C(12)–O(1)	1.209(3)
C(4)–C(18)	1.531(4)	C(18)–O(5)	1.190(4)
*C(8)–C(9)	1.501(3)		
C(10)–C(9)	1.501(3)		

(*b*) C–H bond distances

C(1)–H(1a)	0.96(3)	C(16)–H(16a)	0.96(4)
C(1)–H(1b)	1.00(3)	C(16)–H(16b)	0.93(4)
C(5)–H(5)	0.97(3)	C(16)–H(16c)	1.02(4)
C(6)–H(6)	1.04(3)	C(17)–H(17a)	0.82(7)
*C(7)–H(7)	0.90(3)	C(17)–H(17b)	0.98(5)
C(14)–H(14)	0.98(3)	C(17)–H(17c)	0.91(5)
C(15)–H(15)	0.95(3)	C(19)–H(19a)	1.01(4)
C(2)–H(2)	0.95(4)	C(19)–H(19b)	0.90(4)
C(3)–H(3)	0.81(5)	C(19)–H(19c)	0.96(3)
C(11)–H(11)	0.93(3)	C(20)–H(20a)	0.89(5)
C(20)–H(20b)	0.99(7)	C(20)–H(20c)	0.85(4)

(*c*) Bond angles not involving hydrogen

C(sp^3) endocyclic		C(sp^3) exocyclic	
C(2)–C(1)–C(10)	111.2(3)	C(3)–C(4)–C(19)	109.1(3)
C(3)–C(4)–C(5)	113.8(3)	C(18)–C(4)–C(19)	105.1(3)
C(4)–C(5)–C(10)	112.1(2)	C(5)–C(4)–C(19)	111.7(3)
C(5)–C(10)–C(1)	107.7(2)	C(3)–C(4)–C(18)	115.6(3)
C(6)–C(5)–C(10)	113.6(2)	C(1)–C(10)–C(20)	109.2(2)
*C(5)–C(6)–C(7)	115.6(2)	C(1)–C(10)–C(9)	114.3(2)
C(5)–C(10)–C(9)	108.7(2)	C(9)–C(10)–C(20)	103.2(2)
*C(6)–C(7)–C(8)	120.9(3)	C(5)–C(10)–C(20)	113.9(2)
*C(7)–C(8)–C(9)	118.9(2)	*C(8)–C(14)–C(15)	120.3(2)
*C(8)–C(14)–O(2)	107.7(2)	C(15)–C(14)–O(2)	107.4(2)
*C(9)–C(8)–C(14)	111.4(2)	*C(8)–C(14)–O(2)	107.7(2)
C(5)–C(4)–C(18)	101.0(2)	C(14)–C(15)–C(16)	109.0(3)
C(4)–C(5)–C(6)	102.1(2)	C(14)–C(15)–C(17)	115.1(3)
C(5)–C(6)–O(4)	104.1(2)	C(16)–C(15)–C(17)	112.0(3)
*C(7)–C(8)–O(3)	59.4(2)	*C(6)–C(7)–O(3)	110.0(2)
*C(8)–C(7)–O(3)	60.3(2)	*C(9)–C(8)–O(3)	113.4(2)
		*C(14)–C(8)–O(3)	118.1(2)
C(sp^2) endocyclic		*C(14)–C(8)–C(7)	125.1(2)
C(1)–C(2)–C(3)	123.6(4)	*C(7)–C(6)–O(4)	111.0(2)
C(2)–C(3)–C(4)	121.1(3)		
C(8)–C(9)–C(11)	116.8(2)	C(sp^2) exocyclic	
C(9)–C(11)–C(12)	121.6(3)	C(4)–C(18)–O(5)	128.4(3)
C(11)–C(12)–O(2)	118.2(3)	O(4)–C(18)–O(5)	121.8(3)
C(4)–C(18)–O(4)	109.8(3)	C(10)–C(9)–C(11)	126.5(2)
C(8)–C(9)–C(10)	116.4(3)	C(11)–C(12)–O(1)	123.3(3)
		O(1)–C(12)–O(2)	118.5(3)
Angles at O			
C(6)–O(4)–C(18)	110.0(2)	*C(7)–O(3)–C(8)	60.3(2)
C(14)–O(2)–C(12)	119.0(2)		

TABLE 2 (*Continued*)

(*d*) Bond angles involving hydrogen

H–C(sp^3)–H		H–C(sp^2)–C	
H(1a)–C(1)–H(1b)	118(3)	H(2)–C(2)–C(1)	112(2)
		H(2)–C(2)–C(3)	125(2)
H–C(sp^3)–C		H(3)–C(3)–C(2)	122(2)
H(1a)–C(1)–C(2)	109(2)	H(3)–C(3)–C(4)	115(2)
H(1b)–C(1)–C(2)	105(2)	H(11)–C(11)–C(12)	121(2)
H(1a)–C(1)–C(10)	104(2)	H(11)–C(11)–C(9)	117(2)
H(1b)–C(1)–C(10)	109(2)		
H(5)–C(5)–C(4)	114(2)	H–C–O	
H(5)–C(5)–C(10)	109(2)	H(6)–C(6)–O(4)	108(2)
H(5)–C(5)–C(6)	106(2)	*H(7)–C(7)–O(3)	117(2)
H(6)–C(6)–C(5)	112(2)	H(14)–C(14)–O(2)	111(2)
*H(6)–C(6)–C(7)	106(2)		
*H(7)–C(7)–C(8)	120(2)	Methyl groups	
*H(7)–C(7)–C(6)	115(2)	Mean H–C–H	105
*H(14)–C(14)–C(8)	107(2)	Mean C–C–H	114
H(14)–C(14)–C(15)	103(2)		

* Atoms involved in the epoxide ring. Estimated standard deviations include contributions from the unit-cell parameter errors and the effects of correlations between the parameters of an individual atom, but not those arising from correlations between the parameters of different atoms. No corrections have been applied for the effects of thermal motion.

TABLE 3

Displacements (Å) of atoms from selected least-squares mean planes; atoms not included in the calculation of the planes are italicized.

Plane (*a*): C(4), C(18), O(4), O(6)

C(4) 0.00, C(18) 0.00, O(4) 0.00, C(6) 0.00, *C(5) −0.56, C(3) −0.78, C(7) −0.76, O(5) 0.01*

Plane (*b*): C(8), C(9), C(11), C(12)

C(8) 0.00, C(9) 0.00, C(11) 0.00, C(12) 0.00, *C(10) −0.16, C(14) −0.82, O(2) −0.29, O(1) 0.27*

Plane (*c*): C(6)—(9)

C(6) −0.01, C(7) 0.02, C(8) −0.02, C(9) 0.01, *C(5) 0.18, C(10) −0.54, O(3) 1.25*

Plane (*d*): C(1)—(4)

C(1) 0.02, C(2) −0.04, C(3) 0.04, C(4) −0.02, *C(5) 0.16, C(10) −0.62*

Plane (*e*): C(11), C(12), O(1), O(2)

C(11) −0.003, O(1) −0.003, C(12) 0.009, O(2) −0.003

Plane (*f*): C(4), O(4), O(5), C(18)

C(4) −0.001, O(4) −0.001, C(18) 0.003, O(5) −0.008

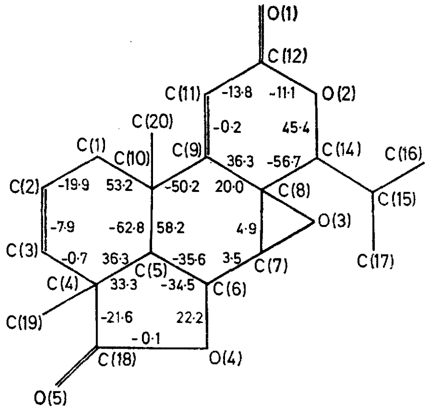

FIGURE 2 Numbering scheme for podolide with endocyclic torsion angles (deg.) in the crystal structure

The epoxide functionality produces a psuedo-olefin effect with a significant contraction in the length of C(7)–C(8) to 1.468(3) Å, and in the flanking bonds C(6)–C(7) and C(8)–C(14) to 1.499(3) and 1.501(3) Å, respectively. The contraction in the flanking bonds apparently operates in a *trans*-sense since C(8)–C(9) is of normal length. The effect is noted also in the increased valence angles at C(7) and C(8), the endocyclic angles in ring B being 120.9(3) and 118.9(3)°, respectively. However, the most striking manifestation of the steric equivalence of the epoxy-linkage and an olefinic bond is shown by the remarkable similarity in equivalent torsion angles in rings A and B and the resultant high degree of stereochemical symmetry in the fused system comprising these rings and the γ-lactone. To an excellent approximation, and despite the different states of hybridization of C(1) and C(9), this fused system has a plane of symmetry passing through C(20), C(10), and the mid-point of the C(18)–O(4) bond. The maximum difference between any pair of related torsion angles is only 5°, and the average deviation from the mean in any pair only 1°. This symmetry of torsion angles, which is not suggested by a Dreiding model of the structure, seems to be stabilized by the two 1,6-interactions H(11) · · · H(1a) (2.47 Å) and H(11) · · · H(1b) (2.41 Å), with the locking of these three atoms constraining C(1), C(10), C(9), and C(11) to a near plane (ϕ 17°).

The conformation of both rings A and B is close to the 1,2-diplanar (sofa) arrangement calculated for cyclohexenes[12] as being little more than 1 kcal mol^{-1} higher in energy than the favoured monoplanar (half-chair) form. Compared to the ideal model suggested[12] for unsubstituted cyclohexene,* the sum of the deviations in bond angle, $\Sigma|\Delta\theta|$, is 10° for ring A, and 18° for ring B. The maximum deviation from the calculated value for a given torsion angle is 8°, the sums of the torsion angle differences, $\Sigma|\Delta\phi|$, being 36° for ring A and 29° for ring B.

A 1,2-diplanar conformation is calculated[12] to be the least favourable for a cyclohexane, and its adoption in ring B emphasizes the steric influence of the epoxy-group, and demonstrates that in this class of norditerpenes low-energy conformations of a cyclohexene type are to be expected where epoxy-groups are present.

The γ-lactone ring is a C(5) envelope (Δ_{av} 36.4°, ϕ_m 36.1°).[13] This is the conformation usually favoured by saturated γ-lactones.[14-17] The β-carbon atom, C(5), is displaced from the plane of the other four atoms of the ring by 0.56 Å. Save for the elongation of C(4)–C(18) already mentioned, the geometry of the ring is comparable to those found for other sesquiterpene lactones.

The conformation of the δ-lactone ring is intermediate between 1,2- and a 1,3-diplanar cyclohexene form[12] with $\Sigma|\Delta\phi|$ being 52° for the former and 33° for the latter. C(14) and O(2) are 0.82 and 0.29 Å below the plane C(8)—(12) containing the double bond. The pattern of torsion angles in the ring is similar to those found for the pyran systems in vernolepin *p*-bromobenzenesulphonate[18] and allamdin.[19] Each ring contains a sequence O–C(sp^2)–C(sp^2)–C with the corresponding torsion angles less than 20° followed by a sequence 35 ± 2, −58 ± 6, 47 ± 4°, or its reverse.

Figure 3 shows the molecular packing. Most short intermolecular contacts are of the normal van der Waals type with the shorter H · · · H distances >2.5 Å, but there are two abnormally short O · · · H approaches involving carbonyl oxygen atoms [O(5) · · · H(14) 2.49 Å and O(1) · · · H(7) 2.54 Å] which suggest strong dipolar-type interactions between the polarized hydrogen atoms and contributing resonance forms of the type $^{-}O^{+}{=}C{-}O^{-}$ in the lactone. The clear distinction between C(sp^3)–O and C(sp^2)–O bond distances in the lactone ring supports the presence of such resonance forms.

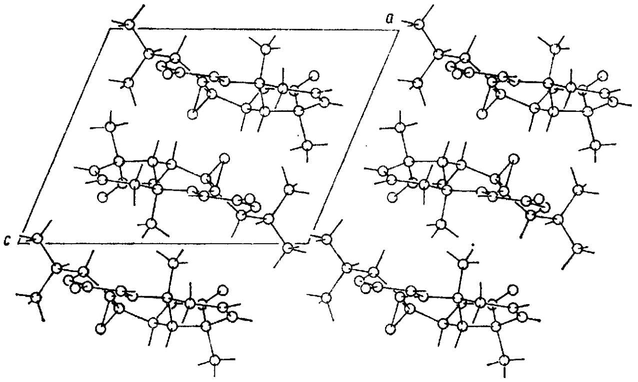

FIGURE 3 View of the molecular packing in the crystal structure of podolide seen in projection down *b*

EXPERIMENTAL

Crystal Data.—$C_{19}H_{22}O_5$, M = 330.4. Monoclinic, a = 12.165(3), b = 7.771(1), c = 9.708(4) Å, β = 113.76(3)°, U = 839.9 Å^3, D_m = 1.32, Z = 2, D_c = 1.306, $F(000)$ = 352. Space group $P2_1$ from systematic absences $0k0$ with k odd. Mo-K_α radiation, λ = 0.71069 Å; μ(Mo-K_α) = 1 cm^{-1}.

Preliminary measurements of the unit-cell dimensions and the determination of the space-group symmetry were made from 25° precession photographs of the reciprocal lattice taken with Mo-K_α radiation. The cell parameters were refined by a least-squares fit of the preliminary values to the values of $\pm 2\theta$ for 17 general reflections carefully measured on the diffractometer.

Intensity Measurements.—These were made by standard diffractometric methods from a single crystal mounted with b^* parallel to the ϕ-axis of a Picker four-circle instrument.

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* None of the models for substituted cyclohexenes in ref. 12 matches the pattern in this structure, but the energy differences between substituted and unsubstituted conformations of this type are very small, *ca.* 0.3 kcal mol^{-1}.

[12] R. Bucourt and D. Hainaut, *Bull. Soc. chim. France*, 1965, 1366.

[13] H. J. Geise, C. Altona, and C. Romers, *Tetrahedron*, 1967, **23**, 439.

[14] J. Fridrichsons and A. McL. Mathieson, *Acta Cryst.*, 1962, **15**, 119.

[15] J. D. M. Asher and G. A. Sim, *J. Chem. Soc.*, 1965, 1584.

[16] J. D. M. Asher and G. A. Sim, *J. Chem. Soc.*, 1965, 6041.

[17] J. A. Hamilton, A. T. McPhail, and G. A. Sim, *J. Chem. Soc.*, 1962, 708.

[18] A. T. McPhail and G. A. Sim, *J. Chem. Soc. (B)*, 1971, 198.

[19] S. M. Kupchan, A. L. Dessertine, B. T. Blaylock, and R F. Bryan, *J. Org. Chem.*, 1974, **39**, 2477

Monochromatic Mo-K_α radiation was used with scintillation counting and pulse-height analysis. Scan ranges of 2.5° in 2θ were used with a scan rate of 2° min^{-1}. Background corrections were made from a carefully determined curve of intensity *vs.* setting angle. Some 2 200 reciprocal lattice points were surveyed out to 2θ 60°, and scattered intensity significantly above background $[I > 3.0\sigma(I)]$ detected at 1 975 of them. *E* values and structure amplitudes derived from these intensities were used in the analysis. No absorption corrections were applied and errors due to absorption are expected to be insignificant given the crystal and radiation used. The stability of the experimental conditions was monitored by comparison of the consistency in the intensity of two reference reflections measured after every 50 measurements. The variation about the mean was $<2\%$ in each case.

Structure Determination and Refinement.—The structure was solved by direct methods of phase determination (MULTAN).[4] Initial phases were obtained for 300 $E(hkl) > 1.34$ with $10\bar{2}$, $43\bar{1}$, and 821 used to define the origin, and $43\bar{1}$ to specify the enantiomorph. Symbols were assigned to four other phases: 4,10,2; $85\bar{4}$; 11,0,5; and 011, and symbolic addition by hand used to reduce the number of phase sets calculated to eight, of which that with highest *FOM* (1.19) yielded an *E* map showing 18 of the 24 atomic sites (*R* 0.34). The remaining non-hydrogen atoms were found from a three-dimensional difference electron-density map.

Refinement of the parameters was by block-diagonal least-squares methods giving *R* 0.13 when individual isotropic thermal parameters were assumed, and *R* 0.079 when vibrational ellipsoids were adopted. All 19 hydrogen positions were then determined from a difference electron-density map, and these atoms were included in the refinement process with isotropic thermal parameters. With a Hughes-type weighting scheme,[20] *R* was 0.045 at convergence. Scattering factors for carbon and oxygen were taken from ref. 21, and for hydrogen from ref. 22. Except for the phase determination, where a CDC 6400 computer was used, all calculations were carried out on an XDS Sigma 2 computer, used to control the diffractometer, with local programs.

Observed and calculated structure amplitudes and Tables of the shorter intra- and inter-molecular distances are listed in Supplementary Publication No. SUP 21356 (16 pp., 1 microfiche).*

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[20] E. W. Hughes, *J. Amer. Chem. Soc.*, 1941, **63**, 1737.

[21] H. P. Hanson, F. Herman, J. D. Lea, and S. Skillman, *Acta Cryst.*, 1964, **17**, 1040.

[22] R. F. Stewart, E. R. Davidson, and W. T. Simpson, *J. Chem. Phys.*, 1965, **42**, 3175.