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PLANT ANTITUMOUR AGENTS—XV

ISOLATION AND X-RAY CRYSTAL STRUCTURE OF A NEW ANTILEUKAEMIC QUASSINOID UNDULATONE FROM *HANNOA UNDULATA*[1]

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Abstract—The structure of Undulatone, a new antileukaemic quassinoid from *Hannoa undulata* was determined by spectral means and confirmed by single crystal X-ray analysis of the methanol solvate.

As a continuation of our work on antineoplastic agents from plants, we wish to report on the isolation and X-ray crystal structure of a new antileukaemic quassinoid undulatone (1) from *Hannoa undulata*.[2] Although a number of 6-oxygenated quassinoids are known,[3] this is the first example of ester substitution at C(6) combined with the well known ester moiety at C(15). In addition to 1, a known quassinoid ailanthinone (2)[3] was also isolated from this plant.

Fractionation of the alcoholic extract of the dried plant guided by assay in 9KB and P388 leukaemia systems,[4] showed that the antitumour activity was concentrated successively in the chloroform layer of a chloroform-water partition and the methanol layer of an aqueous methanol–petroleum partition. Column chromatography of the residue from the aqueous methanol layer on SilicAR CC-7 using chloroform with increasing amounts of methanol yielded an active fraction containing a mixture of 1 and 2. Further chromatography of this mixture on a Waters Associated Prep LC/System 500 using a gradient of 1% methanol in methylene chloride to 4% methanol in methylene chloride followed by fractional crystallization from methanol gave 1 (0.002%) and 2 (0.001%). These two quassinoids were inseparable by TLC using a variety of different solvent systems and their homogeneity had to be established by analytical HPLC.

The molecular composition of undulatone (1) was found to be $C_{27}H_{34}O_{11}$ by combustion analysis and high resolution mass spectrometry. A comparison of the spectral properties (IR, UV, PMR and MS) of 1 and 2 suggested that the former was a quassinoid similar to 2 but with an additional unsaturated ester moiety. The IR spectrum of 1 showed the presence of CO absorptions at 1740 (δ-lactone and acetate ester), 1700 (α,β-unsaturated ester), and 1680 cm^{-1} (α,β-unsaturated ketone). The UV spectrum showed maxima at 222 (ϵ 17,100) and 240 nm (sh, ϵ 13,800) which confirmed the presence of α,β-unsaturated ester and ketone moieties in undulatone. The presence of a 2-methyl-2-butenoate ester was indicated by the loss of 100 amu in the mass spectrum and the presence of peaks at *m/e* 83 $[O{\equiv}C(Me)C{=}CHMe]^+$ and 55 $(MeC{=}CHMe)^+$. In the PMR spectrum of 1, the doublet due to the C(25) Me and the singlet due to the C(23) Me appeared at δ 1.81 (J = 6 Hz) and 1.84 respectively. The quartet due to the vinyl proton at C(24) appeared at δ 7.02 (J = 6 Hz) which is characteristic of a *trans* 2-methyl-2-butenoate (tiglate) ester.[5] The singlet due to the acetate Me appeared at δ 2.08.

The location and stereochemistry of the two ester moieties in 1 were established by PMR and mass spectra. The PMR spectrum of 1 was similar to that of 2 and displayed a doublet at δ 5.56 (J = 10 Hz) assignable to the proton at C(15) bearing an ester function. In addition the presence of a doublet of doublets at the same position (δ 5.56, J = 2, 10 Hz) suggested that the second ester function was probably located at C(6). In agreement with this assignment the C(7) proton appeared as a doublet at δ 4.62 (J = 2 Hz) rather than a triplet as in 2 and this doublet collapsed to a singlet upon irradiation of the signal at δ 5.56. If it be assumed from biogenetic considerations that the stereochemistry of ring junctions in 1 is the same as in 2, then the large coupling constant ($J_{6,5} = J_{15,14} = 10$ Hz) of protons at C(6) and C(15) would suggest that these protons are axial and the two ester functions must therefore be equatorial. That the tiglate ester was located at C(6) was indicated by the mass spectral fragment ion 3 at *m/e* 345.[6] The acetate ester must therefore be located at C(15).

Partial hydrolysis of 1 gave desacetylundulatone (4). The PMR and mass spectra of 4 also supported the above conclusions. In the PMR spectrum of 4, the doublet (*J* = 10 Hz) due to the proton at C(15) now appeared at a higher field at δ 4.71 while the doublet of doublets (J = 2, 11 Hz) due to the proton at C(6) still appeared at δ 5.56. The Me group at C(13) was considerably deshielded and appeared as a doublet (J = 6 Hz) at δ 1.24. The mass spectrum of 4 showed the same fragment ion 3 at *m/e* 345.

Unequivocal proof that the structure and relative stereochemistry of undulatone are as represented by 1 was provided by single-crystal X-ray analysis of the methanol solvate. The absolute configuration, also represented by 1, follows from the experimentally proven triterpenoid biogenetic origin of quassinoids.[3a]

The solid state conformation and atom numbering scheme are shown in Fig. 1, and the packing of these units in the crystal is illustrated in Fig. 2. Fractional atomic co-ordinates and thermal parameters are in Tables 1 and 2; interatomic distances, valency and torsion angles are in Tables 3 and 4.

Means of chemically equivalent bonds in 1 compare well with accepted values:[7] $C(sp^3)$–$C(sp^3)$ 1.538, $C(sp^3)$–$C(sp^2)$ 1.513, $C(sp^2)$–$C(sp^2)$ 1.453, $C(sp^2)$=$C(sp^2)$ 1.329, $C(sp^3)$–O 1.436, $C(sp^2)$–O 1.346 and C=O 1.189 Å. The C(39)–O(40) bond length of 1.311(12) Å in the methanol of solvation is foreshortened probably as a consequence of some disordering of this molecule which is readily lost from the crystals when they are exposed to the open atmosphere.

The structure of 1 closely resembles that of glaucarubin *p*-bromobenzoate[8] (5) and so it is not surprising to find that the overall shapes of these molecules are quite similar with the largest differences occurring in the A ring and δ-lactone ring conformations. The presence of the 2-keto-Δ^3 moiety in ring A of 1 might be expected to result in an approximately planar delocalized C–CO–C=C–C system which consequently would produce an envelope conformation with C(10) as the out-of-plane atom. However, structural information for this type of system, derived from X-ray analyses on the analogous 3-keto-Δ^4 moiety of steroid molecules,[9] clearly shows that in those compounds the C–CO–C=C–C units are not conformationally rigid as manifested by the fact that their C(3)–C(4) ring A torsion angle often departs significantly from 0°, and the associated ring shapes consequently vary between half-chair and envelope forms. Analysis of the deviations of the torsion angles (ω_{ij}) in ring A of 1 from ideal half-chair (ΔC_2–HC $= |\omega_{2,3}| + |\omega_{1,2} - \omega_{3,4}| + |\omega_{1,10} - \omega_{4,5}| = 31.7°$) and ideal envelope ($\Delta C_s$–E $= |\omega_{2,3}| + |\omega_{3,4}| + |\omega_{1,2} + \omega_{4,5}| + |\omega_{1,10} + \omega_{5,10}| = 45.2°$) conformations indicates that the ring adopts an intermediate form which lies slightly closer to the former type. This conformation may be alternatively described in terms of C(5) and C(10) displacements of 0.272 and 0.580 Å to the α and β sides, respectively, of the C(1)—C(4) least-squares plane. Adoption of this intermediate form serves not only to alleviate non-bonded interactions between C(17) and O(30) but also to produce a more acceptable O(28)...O(31) intramolecular hydrogen bonded geometry. In 5, ΔC_2–HC $= |\omega_{3,4}| + |\omega_{2,3} - \omega_{4,5}| + |\omega_{1,2} - \omega_{5,10}| = 13°$ for ring A which thus approximates to a half-chair form with the C_2 axis bisecting the C(3)–C(4) bond rather than the C(2)–C(3) bond as in 1.

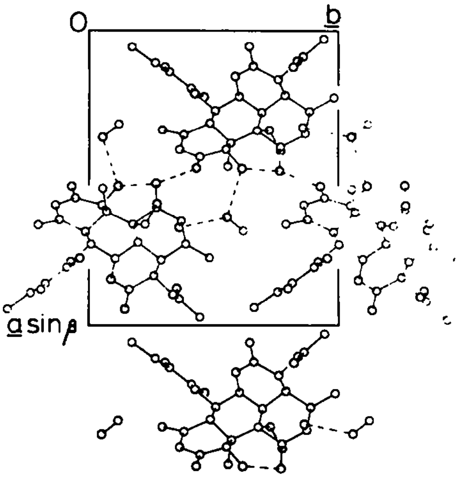


Fig. 2. Crystal structure of undulatone methanol solvate, viewed in projection along the *c*-axis; O–H...O hydrogen bonds are denoted by broken lines.

The cyclohexane B and C rings in combination with the tetrahydrofuran ring formed by their C(8)...C(11) epoxymethano bridge make a fairly rigid structural unit and thus the conformations of these rings in 1 and 5 are not substantially different. Detailed analysis of the endocyclic torsion angles characterizing the B and C ring conformations of these two compounds indicates that both rings consistently adopt chair forms. Ring B in 1 is best described as a flattened chair form in which the approximate plane of symmetry passes through C(6) and C(9) ($\Delta C_s^{6,9} = |\omega_{8,9} + \omega_{9,10}| + |\omega_{7,8} + \omega_{5,10}| + |\omega_{5,6} + \omega_{6,7}| = 22.3°$; the alternative choice of C(5)...C(8) as the symmetry plane direction is only slightly poorer ($\Delta C_s^{5,8} = |\omega_{7,8} + \omega_{8,9}| + |\omega_{6,7} + \omega_{9,10}| + |\omega_{5,6} + \omega_{5,10}| = 31.5°$). In ring C of 1 atoms C(9) and C(13) lie in the symmetry plane ($\Delta C_s^{9,13} = |\omega_{8,9} + \omega_{9,11}| + |\omega_{8,14} + \omega_{11,12}| + |\omega_{13,14} + \omega_{12,13}| = 3.0°$) of a chair form which is more puckered at C(9) and more flattened at C(13) than a regular cyclohexane ring; corresponding calculations for 5 yield $\Delta C_s^{6,9} = 48°$, $\Delta C_s^{5,8} = 20°$ in ring B, and $\Delta C_s^{9,13} = 14°$ in ring C. The small variations between the B ring conformations of 1 and 5 probably result from conformational transmission

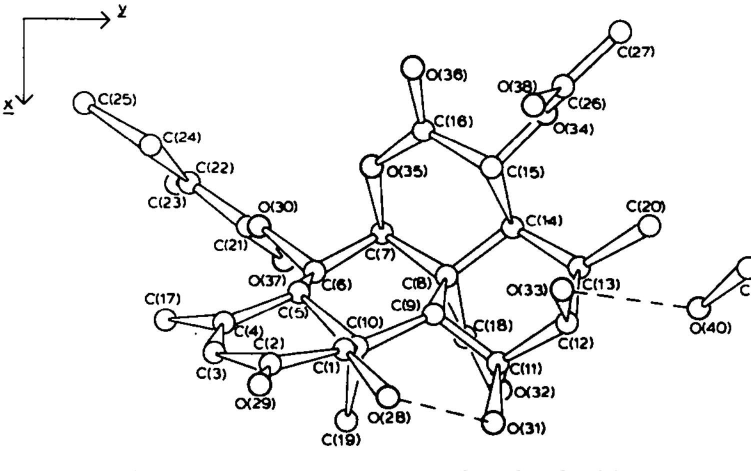


Fig. 1. Atom numbering scheme and conformation of undulatone.

Table 1. Fractional atomic coordinates ($\times 10^4$) and anisotropic thermal parameters* ($\times 10^3$) for non-hydrogen atoms, with estimated standard deviations in parentheses

Atom	x	y	z	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
C(1)	4060(3)	5492(-)	3434(8)	43(3)	46(3)	40(3)	2(3)	7(2)	-9(2)
C(2)	4300(4)	4426(6)	4068(10)	54(3)	44(4)	45(3)	6(3)	10(3)	0(3)
C(3)	4059(5)	3622(6)	2620(11)	65(4)	37(4)	71(4)	7(3)	17(3)	1(4)
C(4)	3551(4)	3791(5)	821(10)	48(3)	40(4)	55(3)	-3(3)	19(3)	-14(3)
C(5)	3151(4)	4846(5)	343(9)	39(3)	37(3)	40(3)	-3(3)	15(2)	-10(3)
C(6)	2732(4)	5055(6)	-1805(10)	42(3)	50(4)	40(3)	-11(3)	12(2)	-11(3)
C(7)	2260(4)	6032(6)	-1985(9)	44(3)	60(4)	31(3)	-4(3)	2(3)	1(3)
C(8)	2794(4)	6944(6)	-1206(9)	54(3)	42(4)	36(3)	5(3)	14(2)	4(3)
C(9)	3413(4)	6757(5)	806(8)	37(3)	41(3)	29(2)	-4(3)	13(2)	-6(3)
C(10)	3838(4)	5681(5)	1144(9)	36(3)	38(3)	44(3)	-5(3)	20(2)	-12(3)
C(11)	3977(4)	7692(6)	701(9)	51(3)	41(3)	40(3)	-8(3)	13(3)	-2(3)
C(12)	3518(5)	8675(6)	1063(10)	54(4)	46(4)	47(3)	-13(3)	9(3)	4(3)
C(13)	2756(5)	8848(6)	-606(11)	70(4)	40(4)	58(4)	-1(4)	15(3)	4(3)
C(14)	2215(5)	7871(6)	-1036(9)	71(4)	44(4)	33(3)	2(4)	-2(3)	5(3)
C(15)	1688(4)	7588(6)	487(11)	41(3)	42(4)	58(4)	10(3)	1(3)	0(3)
C(16)	1223(4)	6592(7)	-40(12)	39(3)	63(5)	81(5)	-3(4)	20(3)	-5(4)
C(17)	3388(5)	2927(6)	-612(13)	74(5)	45(4)	86(5)	9(4)	13(4)	-27(4)
C(18)	3408(5)	7232(5)	-2587(9)	69(4)	72(4)	36(3)	-16(4)	17(3)	-2(3)
C(19)	4618(4)	5534(4)	183(10)	40(3)	50(4)	66(3)	-8(3)	26(2)	-20(3)
C(20)	2285(6)	9816(6)	-186(15)	83(5)	52(4)	95(6)	2(4)	-2(5)	18(4)
C(21)	1970(4)	4091(4)	-4539(10)	52(3)	72(5)	47(3)	-17(4)	13(3)	-15(3)
C(22)	1408(5)	3232(5)	-5202(11)	52(4)	88(5)	64(4)	-15(4)	2(3)	-26(4)
C(23)	1217(8)	3066(8)	-7511(15)	134(8)	169(10)	77(6)	-67(8)	7(6)	-51(6)
C(24)	1119(5)	2641(5)	-3951(14)	63(4)	78(5)	87(5)	-24(4)	21(4)	-21(5)
C(25)	550(7)	1728(7)	-4374(18)	108(7)	96(7)	142(8)	-45(6)	31(6)	-47(6)
C(26)	903(5)	8580(5)	2381(12)	52(4)	79(5)	74(4)	7(4)	15(3)	-19(4)
C(27)	275(7)	9428(7)	2191(19)	97(5)	69(6)	158(3)	25(5)	37(5)	-25(6)
O(28)	4710(3)	6146(3)	4504(7)	52(2)	54(3)	52(2)	-1(2)	-1(2)	-9(2)
O(29)	4693(4)	4279(4)	5747(7)	84(3)	62(3)	53(3)	12(3)	-9(2)	8(3)
O(30)	2136(3)	4245(3)	-2539(6)	50(2)	51(2)	46(2)	-13(2)	13(2)	-12(2)
O(31)	4776(3)	7646(3)	2022(7)	39(2)	51(2)	64(2)	-10(2)	9(2)	-11(2)
O(32)	4109(3)	7702(3)	-1309(6)	70(2)	63(3)	49(2)	-20(3)	28(2)	-4(2)
O(33)	3316(3)	8595(3)	3010(6)	60(2)	39(2)	44(2)	-5(2)	9(2)	-6(2)
O(34)	1054(3)	8343(4)	537(7)	55(2)	59(3)	76(3)	15(2)	1(2)	-8(2)
O(35)	1570(2)	5870(3)	-950(6)	41(2)	49(2)	69(2)	-3(2)	16(2)	-7(2)
O(36)	572(3)	6427(5)	433(10)	78(3)	80(3)	153(4)	-10(3)	55(2)	-31(3)
O(37)	2277(3)	4602(5)	-5644(7)	94(3)	120(4)	49(2)	-51(3)	20(2)	-18(3)
O(38)	1251(4)	8195(6)	3870(8)	82(3)	160(6)	72(3)	29(4)	9(2)	-19(4)
C(39)	3168(6)	11166(9)	5070(15)	91(5)	105(6)	127(6)	14(5)	32(4)	-37(5)
O(40)	3644(4)	10507(5)	4378(12)	70(3)	93(3)	212(5)	-3(3)	12(4)	-87(3)

*In the form: $B\sin^2\theta/\lambda^2 = 2\pi^2(U_{11}h^2a^{*2} + U_{22}k^2b^{*2} + U_{33}l^2c^{*2} + 2U_{12}hka^*b^* + 2U_{13}hla^*c^* + 2U_{23}klb^*c^*)$

Table 2. Calculated hydrogen atom fractional coordinates

Atom	x	y	z	*Atom*	x	y	z	*Atom*	x	y	z
H(1)	351	565	390	H(14)	183	799	-248	H(20B)	263	1052	16
H(3)	429	289	301	H(15)	207	750	189	H(20C)	207	969	115
H(5)	267	490	118	H(18A)	358	656	-328	H(24)	124	281	-237
H(6)	318	508	-269	H(18B)	308	772	-375	H(28)	474	672	355
H(7)	200	617	-350	H(19A)	509	608	78	H(31)	498	826	286
H(9)	310	685	197	H(19B)	448	567	-131	H(33)	344	930	352
H(12)	394	929	111	H(19C)	491	482	50	H(40)	424	1074	479
H(13)	295	900	-191	H(20A)	175	997	-132				

Table 3. Interatomic distances (Å) and angles (deg.), with estimated standard deviations in parentheses

(a) Bond lengths

C(1)–C(2)	1.493(8)	C(8)–C(14)	1.556(11)	C(15)–O(34)	1.434(8)
C(1)–C(10)	1.549(8)	C(8)–C(18)	1.553(10)	C(16)–O(35)	1.322(9)
C(1)–O(28)	1.438(6)	C(9)–C(10)	1.569(9)	C(16)–O(36)	1.186(9)
C(2)–C(3)	1.445(11)	C(9)–C(11)	1.543(10)	C(18)–O(32)	1.423(9)
C(2)–O(29)	1.206(9)	C(10)–C(19)	1.553(8)	C(21)–C(22)	1.462(12)
C(3)–C(4)	1.348(10)	C(11)–C(12)	1.537(10)	C(21)–O(30)	1.350(8)
C(4)–C(5)	1.536(10)	C(11)–O(31)	1.418(8)	C(21)–O(37)	1.193(9)
C(4)–C(17)	1.486(11)	C(11)–O(32)	1.430(8)	C(22)–C(23)	1.557(13)
C(5)–C(6)	1.508(9)	C(12)–C(13)	1.514(10)	C(22)–C(24)	1.309(12)
C(5)–C(10)	1.579(9)	C(12)–O(33)	1.435(8)	C(24)–C(25)	1.506(15)
C(6)–C(7)	1.486(10)	C(13)–C(14)	1.548(11)	C(26)–C(27)	1.497(14)
C(6)–O(30)	1.455(8)	C(13)–C(20)	1.540(12)	C(26)–O(34)	1.366(9)
C(7)–C(8)	1.509(10)	C(14)–C(15)	1.521(10)	C(26)–O(38)	1.170(10)
C(7)–O(35)	1.457(7)	C(15)–C(16)	1.517(11)	C(39)–O(40)	1.311(12)
C(8)–C(9)	1.544(8)				

(b) Valency angles

C(2)–C(1)–C(10)	115.8(4)	C(9)–C(11)–O(31)	114.1(5)
C(2)–C(1)–O(28)	107.0(5)	C(9)–C(11)–O(32)	105.0(5)
C(10)–C(1)–O(28)	114.2(4)	C(12)–C(11)–O(31)	110.1(5)
C(1)–C(2)–C(3)	118.1(6)	C(12)–C(11)–O(32)	108.7(5)
C(1)–C(2)–O(29)	118.8(6)		
C(3)–C(2)–O(29)	123.1(7)	C(11)–C(12)–C(13)	110.7(6)
C(2)–C(3)–C(4)	122.0(7)	C(11)–C(12)–O(33)	107.3(5)
C(3)–C(4)–C(5)	119.6(6)	C(13)–C(12)–O(33)	113.6(6)
C(3)–C(4)–C(17)	117.7(7)	C(12)–C(13)–C(14)	111.1(6)
C(5)–C(4)–C(17)	122.7(6)	C(12)–C(13)–C(20)	110.0(7)
C(4)–C(5)–C(6)	117.2(6)	C(14)–C(13)–C(20)	115.9(7)
C(4)–C(5)–C(10)	108.4(5)	C(8)–C(14)–C(13)	109.7(6)
C(6)–C(5)–C(10)	110.7(5)	C(8)–C(14)–C(15)	107.0(6)
C(5)–C(6)–C(7)	111.1(6)	C(13)–C(14)–C(15)	116.7(6)
C(5)–C(6)–O(30)	109.6(5)	C(14)–C(15)–C(16)	111.8(6)
C(7)–C(6)–O(30)	108.0(5)	C(14)–C(15)–O(34)	110.7(6)
C(6)–C(7)–C(8)	114.1(5)	C(16)–C(15)–O(34)	106.1(5)
C(6)–C(7)–O(35)	105.4(5)	C(15)–C(16)–O(35)	119.4(6)
C(8)–C(7)–O(35)	112.8(5)	C(15)–C(16)–O(36)	121.4(7)
C(7)–C(8)–C(9)	114.0(6)	O(35)–C(16)–O(36)	119.1(8)
C(7)–C(8)–C(14)	109.7(6)	C(8)–C(18)–O(32)	105.4(5)
C(7)–C(8)–C(18)	111.9(5)	C(22)–C(21)–O(30)	114.2(6)
C(9)–C(8)–C(14)	110.4(5)	C(22)–C(21)–O(37)	123.6(6)
C(9)–C(8)–C(18)	101.4(5)	O(30)–C(21)–O(37)	122.1(7)
C(14)–C(8)–C(18)	109.1(6)	C(21)–C(22)–C(23)	113.7(8)
C(8)–C(9)–C(10)	117.4(5)	C(21)–C(22)–C(24)	122.6(7)
C(8)–C(9)–C(11)	96.6(5)	C(23)–C(22)–C(24)	123.7(9)
C(10)–C(9)–C(11)	118.5(5)	C(22)–C(24)–C(25)	129.4(9)
C(1)–C(10)–C(5)	103.7(4)	C(27)–C(26)–O(34)	109.7(8)
C(1)–C(10)–C(9)	107.2(4)	C(27)–C(26)–O(38)	126.5(9)
C(1)–C(10)–C(19)	111.5(5)	O(34)–C(26)–O(38)	123.7(8)
C(5)–C(10)–C(9)	108.5(5)	C(6)–O(30)–C(21)	116.0(5)
C(5)–C(10)–C(19)	110.2(5)	C(11)–O(32)–C(18)	109.0(5)
C(9)–C(10)–C(19)	115.2(5)	C(15)–O(34)–C(26)	116.4(6)
C(9)–C(11)–C(12)	110.5(5)	C(7)–O(35)–C(16)	124.5(6)

(c) Intermolecular separations < 3.50 Å.

O(31)...O(29$^{\mathrm{I}}$)	2.67	O(27)...O(36$^{\mathrm{IV}}$)	3.31	C(39)...O(28$^{\mathrm{I}}$)	3.39
O(33)...O(40)	2.69	C(2)...O(37$^{\mathrm{II}}$)	3.33	O(29)...C(19$^{\mathrm{II}}$)	3.47
O(40)...O(28$^{\mathrm{I}}$)	2.75	O(31)...C(17$^{\mathrm{III}}$)	3.33	O(33)...C(18$^{\mathrm{II}}$)	3.47
O(40)...O(29$^{\mathrm{I}}$)	3.16	C(12)...O(29$^{\mathrm{I}}$)	3.34	O(28)...C(18$^{\mathrm{II}}$)	3.49

Table 3. (*Contd*)

$O(33)\ldots O(29^{I})$	3.29	$C(5)\ldots O(37^{II})$	3.35	$O(32)\ldots C(3^{III})$	3.49
$C(1)\ldots O(37^{II})$	3.30				

Roman numeral superscripts refer to the following transformations of the coordinates of Table 1:

I	$1 - x,\ \frac{1}{2} + y,\ 1 - z$	III	$1 - x,\ \frac{1}{2} + y,\ - z$
II	$x,\ y,\ 1 + z$	IV	$- x,\ \frac{1}{2} + y,\ - z$

Table 4. Torsion angles (deg.), σ range 0.5–1.2°

C(10)-C(1)-C(2)-C(3)	-19.2	C(9)-C(8)-C(18)-O(32)	-30.0
C(10)-C(1)-C(2)-O(29)	160.0	C(14)-C(8)-C(18)-O(32)	86.5
O(28)-C(1)-C(2)-C(3)	-147.7	C(8)-C(9)-C(10)-C(1)	-153.5
O(28)-C(1)-C(2)-O(29)	31.4	C(8)-C(9)-C(10)-C(5)	-42.0
C(2)-C(1)-C(10)-C(5)	52.6	C(8)-C(9)-C(10)-C(19)	81.9
C(2)-C(1)-C(10)-C(9)	167.3	C(11)-C(9)-C(10)-C(1)	91.1
C(2)-C(1)-C(10)-C(19)	-66.0	C(11)-C(9)-C(10)-C(5)	-157.4
O(28)-C(1)-C(10)-C(5)	177.6	C(11)-C(9)-C(10)-C(19)	-33.5
O(28)-C(1)-C(10)-C(9)	-67.7	C(8)-C(9)-C(11)-C(12)	72.6
O(28)-C(1)-C(10)-C(19)	59.0	C(8)-C(9)-C(11)-O(31)	-162.8
C(1)-C(2)-C(3)-C(4)	-7.5	C(8)-C(9)-C(11)-O(32)	-44.4
O(29)-C(2)-C(3)-C(4)	173.4	C(10)-C(9)-C(11)-C(12)	-161.3
C(2)-C(3)-C(4)-C(5)	-5.4	C(10)-C(9)-C(11)-O(31)	-36.6
C(2)-C(3)-C(4)-C(17)	176.0	C(10)-C(9)-C(11)-O(32)	81.7
C(3)-C(4)-C(5)-C(6)	168.4	C(9)-C(11)-C(12)-C(13)	-65.1
C(3)-C(4)-C(5)-C(10)	42.2	C(9)-C(11)-C(12)-O(33)	59.4
C(17)-C(4)-C(5)-C(6)	-13.1	O(31)-C(11)-C(12)-C(13)	167.9
C(17)-C(4)-C(5)-C(10)	-139.3	O(31)-C(11)-C(12)-O(33)	-67.6
C(4)-C(5)-C(6)-C(7)	171.1	O(32)-C(11)-C(12)-C(13)	49.6
C(4)-C(5)-C(6)-O(30)	51.8	O(32)-C(11)-C(12)-O(33)	174.0
C(10)-C(5)-C(6)-C(7)	-63.9	C(9)-C(11)-O(32)-C(18)	27.8
C(10)-C(5)-C(6)-O(30)	176.9	C(12)-C(11)-O(32)-C(18)	-90.4
C(4)-C(5)-C(10)-C(1)	-61.9	O(31)-C(11)-O(32)-C(18)	150.0
C(4)-C(5)-C(10)-C(9)	-175.8	C(11)-C(12)-C(13)-C(14)	48.4
C(4)-C(5)-C(10)-C(19)	57.5	C(11)-C(12)-C(13)-C(20)	178.1
C(6)-C(5)-C(10)-C(1)	168.2	O(33)-C(12)-C(13)-C(14)	-72.4
C(6)-C(5)-C(10)-C(9)	54.4	O(33)-C(12)-C(13)-C(20)	57.3
C(6)-C(5)-C(10)-C(19)	-72.3	C(12)-C(13)-C(14)-C(8)	-47.5
C(5)-C(6)-C(7)-C(8)	57.7	C(12)-C(13)-C(14)-C(15)	74.3
C(5)-C(6)-C(7)-O(35)	-66.7	C(20)-C(13)-C(14)-C(8)	-174.1
O(30)-C(6)-C(7)-C(8)	177.9	C(20)-C(13)-C(14)-C(15)	-52.3
O(30)-C(6)-C(7)-O(35)	53.6	C(8)-C(14)-C(15)-C(16)	-53.9
C(5)-C(6)-O(30)-C(21)	-154.3	C(8)-C(14)-C(15)-O(34)	-172.0
C(7)-C(6)-O(30)-C(21)	84.5	C(13)-C(14)-C(15)-C(16)	-177.1
C(6)-C(7)-C(8)-C(9)	-43.3	C(13)-C(14)-C(15)-O(34)	64.8
C(6)-C(7)-C(8)-C(14)	-167.8	C(14)-C(15)-C(16)-O(35)	32.6
C(6)-C(7)-C(8)-C(18)	71.0	C(14)-C(15)-C(16)-O(36)	-151.2
O(35)-C(7)-C(8)-C(9)	77.0	O(34)-C(15)-C(16)-O(35)	153.4
O(35)-C(7)-C(8)-C(14)	-47.3	O(34)-C(15)-C(16)-O(36)	-30.3
O(35)-C(7)-C(8)-C(18)	-168.7	C(14)-C(15)-O(34)-C(26)	-140.7
C(6)-C(7)-O(35)-C(16)	150.6	C(16)-C(15)-O(34)-C(26)	97.8
C(8)-C(7)-O(35)-C(16)	25.4	C(15)-C(16)-O(35)-C(7)	-17.5
C(7)-C(8)-C(9)-C(10)	37.0	O(36)-C(16)-O(35)-C(7)	166.2
C(7)-C(8)-C(9)-C(11)	163.9	C(8)-C(18)-O(32)-C(11)	1.[illegible]
C(14)-C(8)-C(9)-C(10)	161.1	O(30)-C(21)-C(22)-C(23)	179.7
C(14)-C(8)-C(9)-C(11)	-72.0	O(30)-C(21)-C(22)-C(24)	-2.6
C(18)-C(8)-C(9)-C(10)	-83.4	O(37)-C(21)-C(22)-C(23)	-2.1
C(18)-C(8)-C(9)-C(11)	43.5	O(37)-C(21)-C(22)-C(24)	175.6
C(7)-C(8)-C(14)-C(13)	-169.9	C(22)-C(21)-O(30)-C(6)	176.5
C(7)-C(8)-C(14)-C(15)	62.6	O(37)-C(21)-O(30)-C(6)	-1.7

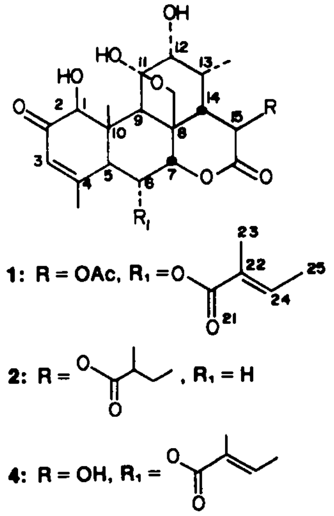
Table 4. (*Contd*)

C(9)-C(8)-C(14)-C(13)	63.5	C(21)-C(22)-C(24)-C(25)	-179.2
C(9)-C(8)-C(14)-C(15)	-63.9	C(23)-C(22)-C(24)-C(25)	-1.7
C(18)-C(8)-C(14)-C(13)	-47.1	C(27)-C(26)-O(34)-C(15)	175.8
C(18)-C(8)-C(14)-C(15)	-174.5	O(38)-C(26)-O(34)-C(15)	-1.1
C(7)-C(8)-C(18)-O(32)	-151.9		

The torsion angle A-B-C-D is defined as positive if, when viewed along the bond B-C, atom A must be rotated clockwise to eclipse atom D.

effects due to the different forms adopted by ring A in each of these compounds (*vide supra*) since the largest torsion angle difference (8°) occurs around the C(5)-C(10) bond. In both 1 and 5 the tetrahydrofuran ring, presumably formed biogenetically by the linkage of a hydroxymethyl group at C(8) to C(11), adopts an envelope conformation in which C(9) is the out-of-plane atom. One factor contributing to the pronounced flattening of ring B around C(8) and C(9) is the epoxymethano linkage the presence of which not only produces puckering of ring C centered about C(9) but also results in flattening around C(12) owing to the reflex effect.[10] Ring B is further flattened to relieve severe β-face interactions between the bridge atoms and the Me group at C(10) such that the resulting conformation possesses acceptable C(10)...C(19) and C(19)...O(32) separations of 3.30 and 3.08 Å, respectively, in contrast to those of *ca.* 2.75 and 2.62 Å measured on a Dreiding molecular model.

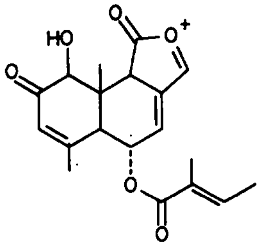
It has been noted elsewhere[11] that while the preferred conformation of a δ-lactone ring containing a planar C-CO-O-C moiety appears to be a half-chair form a boat form may be adopted in response to the imposition of certain steric constraints. Fusion of the δ-lactone to rings B and C in 1 results in a large endocyclic torsion angle of −53.9° about the C(14)-(C(15) bond, a feature which renders impossible any shape approaching a boat form since such a conformation would demand small values for both the C(8)-C(14)-C(15)-C(16) and C(15)-C(16)-O(35)-C(17) torsion angles. Moreover, the latter of these two ring angles assumes a value of −17.5° in 1 and consequently the atoms comprising the C-O-CO-C moiety are not coplanar. To obtain the best description of the δ-lactone ring conformation in 1 the endocyclic torsion angles were analyzed in terms of their deviations from symmetry-related values for half-chair (ΔC_2-HC = $|\omega_{16,35}| + |\omega_{7,35} - \omega_{15,16}| + |\omega_{7,8} - \omega_{14,15}|$) and flattened chair ($\Delta C_s - \mathrm{C} = |\omega_{7,35} + \omega_{16,35}| + |\omega_{7,8} + \omega_{15,16}| + |\omega_{8,14} + \omega_{14,15}|$) forms; the approximate equality of the calculated deviations (ΔC_2-HC = 31.2, ΔC_s-C = 31.4°) indicates that the ring adopts an intermediate conformation. Corresponding deviations for 5 (ΔC_2-HC = 9°, ΔC_s-C = 51°) demonstrate that the δ-lactone ring in that compound lies much closer to a half-chair form probably in order to minimize the more severe non-bonded interactions involving the methyl group at C(13) and the bulkier substituent at C(15), although some contribution to the observed conformation may also arise from the effects of intermolecular H-bonding involving the C(15) side chain in crystals of 5. An intermediate δ-lactone ring confor-



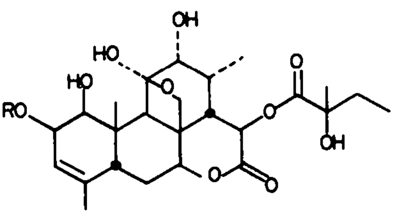
1: R = OAc, R_1 =

2: R = , R_1 = H

4: R = OH, R_1 =



3: (*m/e* 345)



5: R = p-$\mathrm{BrC_6H_4CO}$

mation similar to that found in **1** has been encountered in 17β-hydroxy-17α-methyl-2-oxa-5α-androstan-3-one[12] (ΔC_s-C = 21.1, ΔC_2-HC = 38°).

In each of the secondary ester side chains the atoms are, as expected, approximately coplanar. By use of the observed values of −140.7 and 97.8° for the C(14)–C(15)–O(34)–C(26) and C(16)–C(15)–O(34)–C(26) torsion angles, respectively, the C(26)–O(34)–C(15)–H(15) torsion angle is calculated to be −21.5°; a corresponding calculation for the C(21)–O(30)–C(6)–H(6) torsion angle yields a value of −34.9°. Both of these calculated values are in good accord with those found at other secondary ester groups.[13]

All of the OH groups in **1** as well as that of the methanol of solvation participate in O–H...O hydrogen bonds for which the geometrical details are provided in Table 5. Hydroxy groups on C(1) and C(11) are linked by an intramolecular O(28)–H(28)...O(31) H-bond (O...O 2.61 Å). The OH group on C(11) is then further involved, as a hydrogen donor, in an O(31)–H(31)...O(29) intermolecular H-bond (O...O 2.67 Å) to an adjacent molecule of **1** related by the 2_1 screw axis at $x = \frac{1}{2}$. The H-bonding scheme is completed by the involvement of the methanol of solvation which also bridges molecules of **1** related by the 2_1 screw axis at $x = \frac{1}{2}$ through O(33)–H(33)...O(40) and O(40)–H(40)...O(28) H-bonds (O...O 2.70 and 2.75 Å, respectively). The net effect of these interactions leads to a region containing a maximum number of H-bonds lying around one of the 2_1 screw axes (at $x = \frac{1}{2}$) and a region involving only weak van der Waals type interactions around the other 2_1 screw axis (at $x = 0$).

Table 5. Geometries involving the hydrogen-bonding scheme

A—B...C	B...C (Å)	A—B...C (°)
C(1)—O(28)...O(31)	2.61	104.1
C(11)—O(31)...O(29^{I})	2.67	118.2
C(12)—O(33)...O(40)	2.70	110.7
C(39)—O(40)...O(28^{I})	2.75	108.0
O(33)...O(40)...O(28^{I})		119.4
O(28)...O(31)...O(29^{I})		106.7

The Roman numeral suberscript refers to the transformation $1 - x, \frac{1}{2} + y, 1 - z$ of the coordinates of Table 1.

EXPERIMENTAL

M.ps were determined using a Kofler hot-stage microscope and are uncorrected. IR spectra were measured in $CHCl_3$ soln with a Perkin-Elmer 267 spectrophotometer. PMR spectra were recorded on a Varian Model HA-100 in $CDCl_3$ using TMS as an internal standard; chemical shifts are expressed in δ units. Mass spectra were determined using an Associated Electrical Industries MS-902 instrument. UV absorption spectra were obtained in MeOH soln using a Cary 14 spectrophotometer. Optical rotations were determined on a Perkin-Elmer 141 automatic polarimeter. Microanalyses were carried out by Micro-Tech Laboratories, Skokie, Illinois.

Extraction and isolation of undulatone (**1**) *and ailanthinone* (**2**). Milled root bark of *Hannoa undulata* (Guillem. and Perr.) Planch. (19.0 kg) was extracted by continuous percolation with 95% aqueous EtOH (56 l) during 2 days at 50°. This extract was evaporated to dryness *in vacuo* at 40° and the residue (1.4 kg) was partitioned between MeOH-water (1:9) and $CHCl_3$ (7.5 l each). The aqueous phase was reextracted with $CHCl_3$ (7.5 l) and the combined $CHCl_3$ layers were evaporated to a thick syrup *in vacuo*. This syrup (0.4 kg) was then partitioned between petroleum ether (b.p. 35–55°) and 10% water in MeOH (2.5 l each). Distillation followed by freeze-drying of the aqueous MeOH phase yielded a solid (0.3 kg).

A portion of the above residue (95 g) was chromatographed on SilicAR CC-7 (1.8 kg) using 1% MeOH in $CHCl_3$ as eluent (9 l). Fractions of 50 ml each were collected and combinations were made based on 9KB activity and TLC [silica gel F-254; $CHCl_3$-acetone-MeOH (7:1:0.5)]. The active fractions from this column and a similar column chromatography on the remainder of the residue from aqueous MeOH yielded 10.5 g of a crude mixture containing **1** and **2**, both having an R_f 0.63 in the above TLC system.

Partial purification of the above mixture was accomplished in 7 runs on a Waters Associates Prep LC/System 500 using one 30 × 5.7 cm Prep Pak-500 column, 100 ml/min flow rate and collecting 100 ml fractions. The mixture was injected in CH_2Cl_2 soln and eluted with a gradient of 1% MeOH in CH_2Cl_2(4 l) to 4% MeOH in CH_2Cl_2(4 l). Fractions were monitored by analytical HPLC for the presence of **1** and **2**. Analytical liquid chromatography (HPLC) was carried out using a Waters Associates M 6000 pump; a C-18/Corasil (37-50μ, 1 m × 2.1 mm) column; a Schoeffel Spectroflow Monitor SF 770 detector set at 254 nm, 0.1 AUFS; a solvent system consisting of 30% MeOH in a solution of 0.5% $NH_4H_2PO_4$ in water; and a flow rate of 2 ml/min.

Fraction A (4.3 g), consisting of **1** and **2** (inseparable by TLC) was fractionally crystallized from aqueous MeOH. Due to its low solubility in aqueous MeOH, pure **1** (0.4 g, 0.0021%) with an HPLC retention time of 5 min was the first crop of needles; m.p. 232–235°; $[\alpha]_D^{23°C}$ + 205.9° (*c* 0.1455, MeOH); IR ($CHCl_3$) 3300 (broad OH), 1740 (δ-lactone and acetate ester), 1700 (α,β-unsaturated ester) and 1680 (α,β-unsaturated ketone) cm^{-1}; UV (MeOH) 222 (ϵ 17,100) and 240 (shoulder; ϵ 13,800) nm; PMR ($CDCl_3$) δ 1.07 [d, 3, J = 6 Hz, C(13)], 1.29 [s, 3, C(10)], 1.81 [d, 3, J = 6 Hz, C(25)], 1.84 [s, 3, C(23)], 2.01 [s, 3, C(4)], 2.08 (s, 3, OAc), 2.76 [s, 1, C(9)], 3.58 [m, 1, C(12)], 3.74, 4.14 (d, 1, J = 8 Hz, CH_2O), 4.18 [s, 1, C(1)], 4.62 [d, 1, J = 2 Hz, C(7)], 5.56 [d of d, 2, J = 2, 10 Hz, C(6), C(15)], 6.10 [s, 1, C(3)] and 7.02 [q, 1, J = 6 Hz, C(24)]. (Found: C, 57.81; H, 6.29; *m/e* 534.2080. Required for $C_{27}H_{34}O_{11} \cdot 1.5\ H_2O$: C, 57.75; H, 6.64; *m/e* 534.2099). Other major ions were observed at *m/e* (% relative intensity) 375 (18), 345 (37), 317 (18), 245 (99), 217 (35), 201 (41), 151 (31), 135 (24), 83 (100) and 55 (63).

A later crop of needles from the fractional crystallization yielded pure **2**[3] (0.2 g, 0.0010%) m.p. 232–235° with an HPLC retention time of 3.75 min. The identity of **2** was confirmed by m.p., $[\alpha]_D$, IR, UV, PMR and high-resolution mass spectrometry.

15-*Desacetylundulatone* (**4**). A mixture of **1** (150 mg, 0.28 mmol) and 1% KOH in MeOH was stirred at 0° under N_2 for 45 min. The mixture was acidified with conc HCl (0.6 ml) and evaporated to dryness *in vacuo*. The residue was chromatographed on silica gel using 1% MeOH in $CHCl_3$ to give unchanged **1** (137 mg, 91%) and 15-desacetylundulatone (**4**, 9 mg, 75% based on recovered **1**).

An analytical sample of **4** was prepared by crystallization from CH_2Cl_2-hexane; m.p. 180–182°; IR ($CHCl_3$) 3300 (broad OH), 1740 (δ lactone), 1700 (α,β-unsaturated ester) and 1680 (α,β-unsaturated ketone) cm^{-1}; UV (MeOH) 223 (ϵ 17,600) and 240 (shoulder; ϵ 14,100) nm; PMR ($CDCl_3$) δ 1.24 [d, 3, J = 6 Hz, C(13)], 1.30 [s, 3, C(10)], 1.83 [d, 3, J = 6 Hz, C(25)], 1.86 [s, 3, C(23)], 2.03 [s, 3, C(4)], 2.69 [s, 1, C(9)], 3.58 [m, 1, C(12)], 3.78, 4.13 (d, 2, J = 8 Hz, CH_2O), 4.12 [s, 1, C(1)], 4.56 [d, 1, J = 2 Hz, C(7)], 4.71 [d, 1, J = 10 Hz, C(15)], 5.56 [d of d, 1, J = 2, 11 Hz, C(6)], 6.14 [s, 1, C(3)], 7.03 [d, 1, J = 7 Hz, C(24)]. (Found: *m/e* 492.1993. Required for $C_{25}H_{32}O_{10}$: *m/e* 492.1995).

Crystal data. $C_{27}H_{34}O_{11} \cdot CH_3OH$, $M = 566.6$, Monoclinic, $a = 16.215(6)$, $b = 13.139(5)$, $c = 6.822(3)$ Å, $\beta = 101.90(5)°$, $U = 1422$ Å^3, $Z = 2$, $D_c = 1.323\ g\ cm^{-3}$ $F(000) = 604$. Cu-K_α radiation, $\lambda = 1.5418$ Å, μ(Cu-K_α) = 8.8 cm^{-1}, Space group $P2_1(C_2^2)$ from systematic absences, $0k0$ when $k \neq 2n$, and the fact that undulatone is a chiral molecule.

Crystallographic measurements. Crystals grown from MeOH quickly lose solvent of crystallization once they are removed from the mother liquor, and for all crystallographic measurements individual crystals were sealed inside thin-walled glass capillaries. Preliminary unit-cell dimensions and space group information were obtained from oscillation and Weissenberg photographs taken with Cu–K_α radiation and from precession photographs taken with Mo–K_α radiation ($\lambda = 0.7107$ Å). For intensity measurements a single crystal of dimensions *ca.* $0.22 \times 0.34 \times 0.90$ mm was oriented to rotate with the long dimension parallel to the ϕ axis of an Enraf-Nonius CAD 3 automated diffractometer (Ni-filtered Cu–K_α radiation; 3° take-off angle). Refined unit-cell parameters were calculated by least-squares treatment of the θ, χ and ϕ angles for 40 high order reflections widely separated in reciprocal space. One octant of data to $\theta = 67°$ was surveyed by the θ–2θ scan technique with scan-widths of $(1.20 + 0.50 \tan \theta)°$; stationary background measurements were taken at each end of the scan range for times equal to half the duration of the scan. The intensity $0\,3\,\bar{1}$ reflection, checked periodically during data collection to monitor crystal and instrument stability, showed no significant variation. From a total of 2667 independent intensity measurements only those 1860 for which $I > 2.0\sigma(I)$, where $\sigma^2(I) =$ (scan count + total background count), were corrected for the usual Lorentz and polarization effects prior to their use in the structure analysis. Absorption corrections, determined from the ϕ-dependence of the $2\,0\,\bar{4}$ reflection measured at $\chi = 90°$, were also applied to these data.

Structure analysis. The structure was solved by direct phase determining methods using MULTAN[14] with the highest 246 E values, the program being allowed to select five unknowns in addition to the three origin- and enantiomorph-defining reflections. The E-map evaluated by use of that set of phases which yielded the lowest residual allowed placement of 31 of the 38 non-hydrogen undulatone atoms. A difference Fourier synthesis, phased by this partial structure, provided positions for the remaining 7 non-hydrogen atoms of the quassinoid and when structure factors were evaluated for this model R was 0.256. Positional and isotropic thermal parameters were refined by several cycles on full-matrix least-squares calculations to $R = 0.155$. Examination of a difference Fourier map revealed positions for the C and O atoms of the MeOH of solvation as well as for all the H atoms save those on the Me groups, and with the inclusion of these atoms, all with $U = 0.044$ Å^2, into the next structure-factor calculation R decreased to 0.125. Further least-squares adjustment of positional and anisotropic thermal parameters of the non-H atoms converged at $R = 0.074$.[15]

Atomic scattering factors used in all the structure-factor calculations were those for C and O from Ref. 16 and for H Ref. 17. In the least-squares calculations $\Sigma w\Delta^2$ was minimized; the weighting scheme used, $\sqrt{w} = 1$ when $|F_o| \leq 12.5$ and $\sqrt{w} = 12.5/|F_o|$ when $|F_o| > 12.5$, showed only random variations of $(w\Delta^2)$ when analyzed in ranges of $|F_o|$.

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