

Table 2. Hydrogen-bond lengths (Å) and angles (°)

D-H...A	D...A	H...A	D-H...A	Symmetry of A
Intramolecular				
O(1)-H(O1)...O(4)	2.722 (2)	1.81 (3)	158 (2)	
O(1P)-H(O1P)...O(4P)	2.756 (3)	1.98 (4)	159 (3)	
C(13)-H(131)...O(10)	3.133 (2)	2.44 (3)	126 (2)	
C(13P)-H(131P)...O(10P)	3.095 (4)	2.34 (3)	130 (2)	
Intermolecular				
C(11)-H(C11)...O(10)	3.286 (3)	2.36 (2)	155 (1)	$x\bar{y}, \frac{1}{2} + z$

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Hydrogen Bonding in Andrographolide: 3-{2-[Decahydro-6-hydroxy-5-(hydroxymethyl)-5,8a-dimethyl-2-methylene-1-naphthalenyl]ethylidene}dihydro-4-hydroxy-2(3H)-furanone

BY A. L. SPEK* AND A. J. M. DUISENBERG

Vakgroep Algemene Chemie, Afdeling Kristal- en Structuurchemie, University of Utrecht, Padualaan 8, 3584 CH Utrecht, The Netherlands

R. P. LABADIE

Department of Pharmacognosy, Pharmaceutical Laboratory, University of Utrecht, The Netherlands

AND S. RATNAYAKE, A. ABEYSEKERA AND K. T. D. DE SILVA

Department of Chemistry, University of Sri Jayewardenepura, Sri Lanka

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Abstract. $C_{20}H_{30}O_5$, $M_r = 350.45$, monoclinic, $P2_1$, $a = 6.559$ (1), $b = 8.017$ (1), $c = 18.004$ (2) Å, $\beta = 97.38$ (1)°, $U = 938.9$ (2) Å³, $Z = 2$, $D_x = 1.240$ g cm⁻³, $\lambda(\text{Cu K}\alpha) = 1.5418$ Å, $\mu = 6.7$ cm⁻¹, $F(000) = 380$, $T = 295$ K, $R = 0.044$ for 1894 observed reflections with $I > 2.5\sigma(I)$. The present study confirms the results of the previous structure determinations of andrographolide by Smith, Toder, Carroll & Donohue [*J. Cryst. Spectrosc. Res.* (1982), **12**, 309-319] and Fujita, Fujitani, Takeda, Takanishi, Yamada, Kido & Miura [*Chem. Pharm. Bull.* (1984), **32**, 2117-2125], but the present structure is more accurately determined and the hydrogen-bonding scheme clearly defined. The six-membered rings are in chair conformations. The furan ring is slightly puckered.

There are two separate systems of infinite chains of hydrogen bonds along the a and b axes, respectively.

Introduction. *Andrographis paniculata* Nees (Acanthaceae) is an annual herb common in Sri Lanka (Trimen, 1974) and India (Chopra, Nayar & Chopra, 1956). It is extensively used in the Ayurvedic system of medicine in Sri Lanka for fevers, dysentery, general debility, certain forms of dyspepsia and also as a stomachic, anthelmintic and a tonic (Jayaweera, 1981). A preparation of it with pepper is used in the treatment of malarial fever (*Ayurveda Pharmacopoeia*, 1979).

Reported pharmacological studies on the extracts and compounds of the plant indicate that *Andrographis* exhibit antibacterial (*Herbal Pharmacology in the Republic of China*, 1975), anthelmintic (Kaleysa Raj, 1975), male antifertility (Stamsuzzona, Rahman &

* Author to whom correspondence should be addressed.

Ahmed, 1979) and hypotensive (Garcia, Kintad, Fogas, Sison, Chua & Villanueva, 1950) activities. It has also been shown to be effective against snake venom by a mechanism other than the nicotinic receptor activity (Nagimuden, Ramasamy & Kamaswaran, 1978).

In our field search in Sri Lanka for plants with possible immunomodulatory activity, *Andrographis paniculata* turned out to be a promising plant. *In vitro* experiments on the effect of the aqueous plant extract on the alternative and classical pathways of the human complement showed a significant inhibitory effect (Abeysekera, Bamunuarachchi, De Silva & Labadie, 1984). Hence further studies were done using eight diterpenoids isolated from the plant. These diterpenoids showed a great deal of variation with regard to their effects on the alternative and classical pathways of the human complement activity. Some showed inhibition of both pathways. Andrographolide, which is the main crystalline diterpenoid, showed a significant effect only on the alternative pathway. The chemical structure of andrographolide has been reported (Cava, Chan, Stein & Willis, 1965). X-ray studies established the stereochemistry (Smith, Toder, Carroll & Donohue, 1982; Fujita, Fujitani, Takeda, Takanishi, Yamada, Kido & Miura, 1984), but left the hydrogen-bonding scheme uncertain due to relatively poor data. This paper reports the results of an analysis that allowed the determination of H-atom positions and the hydrogen-bonding scheme. Knowledge of the stereochemistry and hydrogen bonding can be important to explain the structure-activity relationship of these diterpenoids on the human complement activity.

Experimental. Andrographolide was isolated from a methanolic extract of *Andrographis paniculata* collected in Sri Lanka and was recrystallized from a methylene chloride/methanol mixture (m.p. 504 K). Enraf-Nonius CAD-4F diffractometer, Ni-filtered Cu $K\alpha$ radiation; plate-shaped (001) colourless transparent crystal 0.10 × 0.65 × 0.95 mm glued on a glass fibre. Cell dimensions from setting angles of 24 reflections ($40 < \theta < 42^\circ$). Space group from observed extinctions ($0k0: k = 2n + 1$). Total 6835 reflections; $\omega/2\theta$ scan; $\Delta\omega = (0.60 + 0.15 \tan \theta)^\circ$; $2.48 < \theta < 70^\circ$; $h - 7:7, k - 9:9, l - 21:21$. Three reference reflections measured every hour (400: r.m.s.d. 1%; 008: r.m.s.d. 1.7%; 040: r.m.s.d. 0.9%) showed a small decay of 2% over the 81.3 h of X-ray exposure time. Intensities were corrected for Lp and the small decay and averaged [$R_{\text{int}}(I) = 10.5\%$] into a unique set of 1910 reflections. Variance $\sigma^2(I)$ calculated based on counting statistics plus a term $(PI)^2$, where $P (= 0.015)$ is the instability constant as derived from the excess variance in the reference reflections (McCandlish, Stout & Andrews, 1975). Structure solved by direct methods using *SHELX84* (Sheldrick, 1984). The solution with the highest figure of merit showed all non-H atoms.

Table 1. *Positional and equivalent isotropic thermal parameters for the non-H atoms of andrographolide*

Numbers in parentheses are e.s.d.'s in the least significant digit.

$$U_{\text{eq}} = \frac{1}{3} \sum_i \sum_j U_{ij} a_i^* a_j^* \mathbf{a}_i \cdot \mathbf{a}_j$$

	<i>x</i>	<i>y</i>	<i>z</i>	$U_{\text{eq}}(\text{\AA}^2)$
O(1)	0.3806 (2)	0.6592 (7)	0.4153 (1)	0.0512 (3)
O(2)	0.8463 (3)	0.7658 (3)	0.4527 (1)	0.0569 (3)
O(3)	0.2503 (2)	0.7072 (2)	0.5212 (1)	0.0541 (3)
O(4)	1.6122 (3)	0.4354 (3)	0.9589 (1)	0.0596 (3)
O(5)	1.3796 (3)	0.1641 (3)	0.9297 (1)	0.0781 (3)
C(1)	1.0838 (4)	0.3198 (3)	0.7506 (1)	0.0451 (3)
C(2)	1.2486 (4)	0.2272 (3)	0.8023 (2)	0.0588 (3)
C(3)	1.2305 (4)	0.2635 (3)	0.8833 (1)	0.0524 (3)
C(4)	1.2465 (3)	0.4523 (3)	0.9033 (1)	0.0411 (3)
C(5)	1.0882 (3)	0.5481 (3)	0.8462 (1)	0.0355 (3)
C(6)	1.0836 (4)	0.7362 (3)	0.8607 (1)	0.0543 (3)
C(7)	0.8967 (4)	0.8157 (3)	0.8141 (2)	0.0605 (3)
C(8)	0.8932 (3)	0.7751 (3)	0.7322 (1)	0.0457 (3)
C(9)	0.8958 (3)	0.5903 (3)	0.7173 (1)	0.0327 (3)
C(10)	1.0930 (3)	0.5099 (3)	0.7614 (1)	0.0318 (3)
C(11)	0.8614 (3)	0.5456 (3)	0.6338 (1)	0.0393 (3)
C(12)	0.6570 (3)	0.5997 (3)	0.5956 (1)	0.0386 (3)
C(13)	0.6067 (3)	0.6251 (3)	0.5226 (1)	0.0352 (3)
C(14)	0.7363 (3)	0.6163 (3)	0.4598 (1)	0.0414 (3)
C(15)	0.5717 (4)	0.5972 (4)	0.3927 (1)	0.0584 (3)
C(16)	0.3951 (3)	0.6680 (3)	0.4899 (1)	0.0391 (3)
C(17)	0.8977 (4)	0.8909 (3)	0.6803 (2)	0.0671 (3)
C(18)	1.2822 (3)	0.5768 (3)	0.7288 (1)	0.0486 (3)
C(19)	1.4673 (3)	0.5149 (3)	0.9040 (1)	0.0478 (3)
C(20)	1.1835 (4)	0.4715 (4)	0.9821 (1)	0.0585 (3)

Refinement on *F* by blocked full-matrix least squares with a locally modified Eclipse S/230 implementation of *SHELX76* (Sheldrick, 1976) converged at $R = 0.044$, $wR = 0.056$; $w = 1/\sigma^2(F)$; $S = 0.28$; 1894 observed reflections with $I > 2.5\sigma(I)$; 345 refined parameters [all positional parameters except for *y* of O(1), anisotropic thermal parameters for the non-H atoms and individual isotropic thermal parameters for the H atoms and a scale factor]; $\langle \Delta/\sigma \rangle = 0.1$. Max. and min. residual densities in final difference Fourier map 0.23 and -0.21 e \AA^{-3} .

The reflection $\bar{1}02$ was left out of the final refinement cycles. The final values of the refined parameters are given in Table 1.* Scattering factors from Cromer & Mann (1968). Geometry calculations carried out on the Cyber-855 of the University of Utrecht with the program *PLATO* (Spek, 1982).

Discussion. Fig. 1 gives a view of the molecule with the atom numbering. Bond distances and angles are given in Table 2. The present results agree with those reported by Smith, Toder, Carroll & Donohue (1982) within the error ranges. The two central six-membered rings adopt the chair conformation with puckering parameters

* Lists of structure factors, anisotropic thermal parameters, H-atom parameters and a complete list of bond distances and angles have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 43597 (16 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

(Cremer & Pople, 1975) for ring [C(1), C(2), ..., C(10)]: $Q = 0.553(2) \text{ \AA}$, $\theta = 175.7(3)$, $\phi = 230(3)^\circ$ and for ring [C(5), C(6), ..., C(10)]: $Q = 0.597(2) \text{ \AA}$, $\theta = 175.8(2)$, $\phi = 121(3)^\circ$. The five-membered ring is only slightly puckered with $Q(2) = 0.210(3) \text{ \AA}$ and $\phi = 61.3(8)^\circ$.

Details on the hydrogen-bond geometry are assembled in Table 3. The two extreme sides of the molecule are each involved with two oxygen functions in separate systems of infinite chains of hydrogen-bonded molecules. One chain involves O(3) and O(2) with hydrogen bonds that link molecules in the a direction.

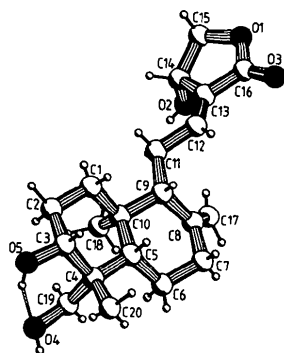


Fig. 1. PLUTO drawing (Spek, 1982) of andrographolide with atom numbering.

Table 2. Data on the geometry of andrographolide

(a) Bond distances (Å)

O(1)—C(15)	1.454 (4)	C(5)—C(10)	1.561 (3)
O(1)—C(16)	1.336 (3)	C(6)—C(7)	1.533 (4)
O(2)—C(14)	1.413 (3)	C(7)—C(8)	1.507 (4)
O(3)—C(16)	1.207 (2)	C(8)—C(9)	1.506 (3)
O(4)—C(19)	1.430 (3)	C(8)—C(17)	1.320 (4)
O(5)—C(3)	1.442 (3)	C(9)—C(11)	1.534 (3)
C(1)—C(2)	1.526 (4)	C(9)—C(10)	1.567 (3)
C(1)—C(10)	1.537 (3)	C(10)—C(18)	1.536 (3)
C(2)—C(3)	1.507 (4)	C(11)—C(12)	1.491 (3)
C(3)—C(4)	1.556 (3)	C(12)—C(13)	1.329 (3)
C(4)—C(5)	1.565 (3)	C(13)—C(14)	1.501 (3)
C(4)—C(19)	1.531 (3)	C(13)—C(16)	1.477 (3)
C(4)—C(20)	1.536 (3)	C(14)—C(15)	1.521 (3)
C(5)—C(6)	1.531 (3)		

(b) Bond angles ($^\circ$)

C(15)—O(1)—C(16)	110.3 (2)	C(10)—C(9)—C(11)	114.1 (2)
C(2)—C(1)—C(10)	113.1 (2)	C(8)—C(9)—C(10)	110.0 (2)
C(1)—C(2)—C(3)	111.0 (2)	C(1)—C(10)—C(5)	108.2 (2)
O(5)—C(3)—C(4)	112.5 (2)	C(1)—C(10)—C(9)	109.1 (2)
C(2)—C(3)—C(4)	113.6 (2)	C(1)—C(10)—C(18)	108.6 (2)
O(5)—C(3)—C(2)	108.8 (2)	C(5)—C(10)—C(9)	107.2 (2)
C(3)—C(4)—C(5)	107.8 (2)	C(5)—C(10)—C(18)	115.1 (2)
C(5)—C(4)—C(19)	113.0 (2)	C(9)—C(10)—C(18)	108.5 (2)
C(5)—C(4)—C(20)	108.8 (2)	C(9)—C(11)—C(12)	113.2 (2)
C(3)—C(4)—C(19)	110.9 (2)	C(11)—C(12)—C(13)	126.5 (2)
C(3)—C(4)—C(20)	107.0 (2)	C(14)—C(13)—C(16)	107.8 (2)
C(19)—C(4)—C(20)	109.0 (2)	C(12)—C(13)—C(14)	130.2 (2)
C(6)—C(5)—C(10)	111.3 (2)	C(12)—C(13)—C(16)	122.1 (2)
C(4)—C(5)—C(6)	113.4 (2)	O(2)—C(14)—C(15)	109.4 (2)
C(4)—C(5)—C(10)	116.8 (2)	C(13)—C(14)—C(15)	100.9 (2)
C(5)—C(6)—C(7)	110.4 (2)	O(2)—C(14)—C(13)	111.9 (2)
C(6)—C(7)—C(8)	110.9 (2)	O(1)—C(15)—C(14)	107.0 (2)
C(7)—C(8)—C(9)	112.8 (2)	O(1)—C(16)—C(13)	109.3 (2)
C(9)—C(8)—C(17)	124.3 (2)	O(1)—C(16)—O(3)	121.6 (2)
C(7)—C(8)—C(17)	122.8 (2)	O(3)—C(16)—C(13)	129.1 (2)
C(8)—C(9)—C(11)	113.6 (2)	O(4)—C(19)—C(4)	113.8 (2)

Table 3. Hydrogen-bond geometry (Å and $^\circ$)

Symmetry operations: (i) = $1+x, y, z$; (ii) = $3-x, \frac{1}{2}+y, 2-z$.

D—H...A	D...A	D—H	H...A	$\angle D-H...A$
O(2)—H(2)...O(3 ⁱ)	2.815 (2)	0.705 (7)	2.130 (7)	164.5 (6)
O(4)—H(4)...O(5 ⁱⁱ)	2.713 (3)	0.730 (10)	2.013 (9)	159.9 (6)
O(5)—H(5)...O(4)	2.670 (3)	0.839 (7)	1.902 (6)	151.5 (7)

The second chain involves an infinite alternation of one intramolecular [O(5)—H(5)...O(4)] and one intermolecular [O(4)—H(4)...O(5)] hydrogen bond and links molecules in the b -screw-axis direction. This results in an infinite two-dimensional slab of hydrogen-bonded molecules perpendicular to the c axis. The furan ring O(1) atom is not involved in hydrogen bonding.

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