

be published elsewhere (van Beek, Wehman-Ooyevaar, Grove, Smeets, Spek & van Koten, 1992).

Data were collected by A. J. M. Duisenberg. This work was supported in part (WJJS, JAMvB and ALS) by the Netherlands Foundation for Chemical Research (SON) with financial aid from the Netherlands Organization for Scientific Research (NWO).

#### References

- BEEK, J. A. M. VAN, WEHMAN-OOYEVAAR, I. C. M., GROVE, D. M., SMEETS, W. J. J., SPEK, A. L. & VAN KOTEN, G. (1992). *Organometallics*. Submitted.
- CROMER, D. T. & LIBERMAN, D. (1970). *J. Chem. Phys.* **53**, 1891–1898.
- CROMER, D. T. & MANN, J. B. (1968). *Acta Cryst.* **A24**, 321–324.
- SHELDRIK, G. M. (1976). *SHELX76*. Program for crystal structure determination. Univ. of Cambridge, England.
- SHELDRIK, G. M. (1986). *SHELXS86*. Program for crystal structure solution. Univ. of Göttingen, Germany.
- SMEETS, W. J. J., SPEK, A. L., VAN BEEK, J. A. M. & VAN KOTEN, G. (1992). *Acta Cryst.* Submitted.
- SPEK, A. L. (1982). *The EUCLID Package*. In *Computational Crystallography*, edited by D. SAYRE. Oxford: Clarendon Press.
- SPEK, A. L. (1988). *J. Appl. Cryst.* **21**, 578.
- WALKER, N. & STUART, D. (1983). *Acta Cryst.* **A39**, 158–166.
- ZEIJDEN, A. A. H. VAN DER, VAN KOTEN, G., WOUTERS, J. M. A., WIJSMULLER, W. F. A., GROVE, D. M., SMEETS, W. J. J. & SPEK, A. L. (1988). *J. Am. Chem. Soc.* **110**, 5354–5361.

*Acta Cryst.* (1992). **C48**, 747–749

## Structure of 4'-Demethylepipodophyllotoxin

BY FRANK V. SICHERI, W. B. DERRY, R. S. GUPTA AND D. S.-C. YANG

*Department of Biochemistry, McMaster University, Hamilton, Ontario, Canada L8N 3Z5*

(Received 12 March 1991; accepted 10 September 1991)

**Abstract.** [5*R*-(5 $\alpha$ ,5 $\beta$ ,8 $\alpha$ ,9 $\beta$ )]-5,8,8a,9-Tetrahydro-9-hydroxy-5-(4-hydroxy-3,5-dimethoxyphenyl)furo-[3',4':6,7]naphtho[2,3-*d*]-1,3-dioxol-6(5*aH*)-one, C<sub>21</sub>H<sub>20</sub>O<sub>8</sub>, *M<sub>r</sub>* = 400.38, orthorhombic, *P*2<sub>1</sub>2<sub>1</sub>2<sub>1</sub>, *a* = 11.483 (1), *b* = 19.345 (3), *c* = 8.459 (1) Å, *V* = 1879.0 (5) Å<sup>3</sup>, *Z* = 4, *D<sub>m</sub>* = 1.35 (9), *D<sub>x</sub>* = 1.415 g cm<sup>-3</sup>, λ(Cu *K*α) = 1.54178 Å, μ = 8.78 cm<sup>-1</sup>, *F*(000) = 840, *T* = 296 K, final *R* = 0.040 and *wR* = 0.05 for 1333 unique reflections. The title compound, synthesized from podophyllotoxin, was demethylated at the C4' position, and epimerized at the C4 position while maintaining chirality at all other stereo centres. The chair conformation of the cyclohexyl ring was not affected by the synthetic modification.

**Experimental.** The title compound (DMEP) was synthesized from podophyllotoxin (POD) according to the method of Kuhn, Keller-Juslen & von Wartburg (1969). DMEP was crystallized from a 4/1 ethanol/water solution by slow evaporation at 277 K. A rod-like crystal, having approximate dimensions of 0.3 × 0.3 × 0.2 mm, was mounted on a glass fibre. Measurements were made on a Rigaku AFC-6R diffractometer with graphite-monochromated Cu *K*α radiation and a 12 kW rotating anode generator. Intensities were measured at 296 K using ω-2θ scans to a maximum 2θ value of 120.1°. Cell constants were obtained from a least-squares refinement of the

setting angles of 24 reflections in the range 50.13 < 2θ < 76.48°. *h,k,l* ranged from 0,0,0 to 12,21,9. Of 1650 reflections collected, 1621 were unique (*R<sub>int</sub>* = 0.142) (22 were systematically absent). Number of unobserved reflections = 288 defined by *I* ≤ 3.0σ(*I*). The intensities of three representative reflections (2̄9̄2̄, 2̄9̄2̄ and 0,1̄0,1̄) remained constant throughout data collection and thus no decay correction was applied. The data were corrected for Lorentz and polarization effects. An empirical absorption correction (North, Phillips & Mathews, 1968) was applied, based on azimuthal scans of several reflections, with transmission factors ranging from 0.91 to 1.00. The structure was solved by direct methods using *MITHRIL* (Gilmore, 1984). Refinement of the two enantiomorphs did not reveal statistically significant differences; hence, enantiomorph selection was made by knowledge of the precursor compound's stereochemistry. H atoms were generated using optimum bonding geometry and included in *F<sub>c</sub>*. H-atom thermal parameters and positions were not refined. Non-H atoms were refined anisotropically. Parameters were refined on *F*, with function minimized: Σ*w*(|*F<sub>o</sub>*| - |*F<sub>c</sub>*|)<sup>2</sup>, where *w* = 4*F<sub>o</sub>*<sup>2</sup>/σ<sup>2</sup>(*F<sub>o</sub>*<sup>2</sup>), σ<sup>2</sup>(*F<sub>o</sub>*<sup>2</sup>) = [*S*<sup>2</sup>(*C* + *R*<sup>2</sup>*B*) + (*pF<sub>o</sub>*<sup>2</sup>)<sup>2</sup>]/*Lp*<sup>2</sup>, *S* = scan rate, *C* = total integrated peak count, *R* = ratio of scan time to background counting time, *B* = total background count, *Lp* = Lorentz-polarization factor, *p* = *p* factor.

Table 1. Positional parameters and equivalent isotropic thermal parameters ( $\text{\AA}^2$ ) with *e.s.d.*'s in parentheses

$$B_{\text{eq}} = (8\pi^2/3) \sum_{i=1}^3 \sum_{j=1}^3 U_{ij} a_i^* a_j^* a_i \cdot a_j$$

	x	y	z	$B_{\text{eq}}$
O(22)	0.1534 (4)	-0.3619 (2)	0.6555 (5)	7.0 (2)
O(23)	-0.0312 (4)	-0.3172 (2)	0.6753 (5)	8.3 (3)
O(24)	0.1311 (3)	-0.1460 (2)	-0.2062 (4)	5.3 (2)
O(25)	-0.0579 (3)	-0.1296 (2)	-0.1672 (4)	4.9 (2)
O(26)	0.2318 (3)	-0.3142 (2)	0.0499 (4)	4.6 (2)
O(27)	-0.1917 (3)	0.0461 (1)	0.2081 (4)	4.4 (2)
O(28)	-0.0169 (3)	0.0958 (1)	0.3791 (4)	4.5 (2)
O(29)	0.1633 (3)	0.0175 (2)	0.4634 (5)	5.1 (2)
C(1)	0.0457 (7)	-0.3703 (3)	0.7302 (8)	7.4 (4)
C(2)	0.0200 (5)	-0.2934 (3)	0.5388 (6)	5.1 (3)
C(3)	-0.0242 (4)	-0.2501 (2)	0.4284 (6)	4.7 (2)
C(4)	0.0449 (4)	-0.2327 (2)	0.2980 (6)	3.5 (2)
C(5)	-0.0069 (3)	-0.1842 (2)	0.1763 (5)	3.2 (2)
C(6)	0.0566 (4)	-0.1970 (2)	0.0213 (6)	3.5 (2)
C(7)	0.0328 (4)	-0.1539 (2)	-0.1222 (6)	4.0 (2)
C(8)	0.2258 (4)	-0.1841 (2)	-0.1309 (7)	4.8 (2)
C(9)	0.1879 (4)	-0.1919 (2)	0.0400 (6)	3.7 (2)
C(10)	0.2323 (4)	-0.2504 (2)	0.1390 (7)	3.9 (2)
C(11)	0.1576 (4)	-0.2601 (2)	0.2855 (6)	3.5 (2)
C(12)	0.2011 (4)	-0.3042 (2)	0.4036 (6)	4.1 (2)
C(13)	0.1304 (5)	-0.3198 (3)	0.5267 (6)	4.9 (3)
C(14)	-0.0072 (4)	-0.1090 (2)	0.2316 (6)	3.2 (2)
C(15)	0.0813 (4)	-0.0820 (2)	0.3265 (6)	3.7 (2)
C(16)	0.0793 (4)	-0.0130 (2)	0.3731 (6)	3.5 (2)
C(17)	-0.0126 (4)	0.0284 (2)	0.3289 (5)	3.3 (2)
C(18)	-0.1014 (4)	0.0012 (2)	0.2381 (5)	3.2 (2)
C(19)	-0.0985 (4)	-0.0670 (2)	0.1887 (6)	3.3 (2)
C(20)	-0.2824 (4)	0.0230 (2)	0.1074 (7)	4.8 (2)
C(21)	0.2625 (6)	-0.0212 (3)	0.502 (1)	7.2 (4)

Table 2. Intramolecular distances ( $\text{\AA}$ ) and angles ( $^\circ$ ) involving non-H atoms with *e.s.d.*'s in parentheses

O(22)—C(1)	1.399 (8)	C(4)—C(11)	1.402 (6)
O(22)—C(13)	1.386 (6)	C(5)—C(6)	1.520 (6)
O(23)—C(1)	1.431 (7)	C(5)—C(14)	1.528 (5)
O(23)—C(2)	1.375 (7)	C(6)—C(7)	1.499 (7)
O(24)—C(7)	1.343 (5)	C(6)—C(9)	1.520 (6)
O(24)—C(8)	1.460 (6)	C(8)—C(9)	1.517 (7)
O(25)—C(7)	1.204 (5)	C(9)—C(10)	1.497 (6)
O(26)—C(10)	1.446 (5)	C(10)—C(11)	1.519 (7)
O(27)—C(18)	1.376 (5)	C(11)—C(12)	1.405 (6)
O(27)—C(20)	1.417 (6)	C(12)—C(13)	1.354 (7)
O(28)—C(17)	1.372 (5)	C(14)—C(15)	1.395 (6)
O(29)—C(16)	1.364 (5)	C(14)—C(19)	1.375 (6)
O(29)—C(21)	1.401 (6)	C(15)—C(16)	1.392 (5)
C(2)—C(3)	1.353 (7)	C(16)—C(17)	1.377 (6)
C(2)—C(13)	1.371 (7)	C(17)—C(18)	1.382 (6)
C(3)—C(4)	1.400 (7)	C(18)—C(19)	1.383 (5)
C(4)—C(5)	1.515 (6)		
C(1)—O(22)—C(13)	104.7 (4)	C(8)—C(9)—C(10)	120.8 (4)
C(1)—O(23)—C(2)	104.4 (4)	O(26)—C(10)—C(9)	110.6 (4)
C(7)—O(24)—C(8)	109.8 (4)	O(26)—C(10)—C(11)	108.5 (3)
C(18)—O(27)—C(20)	117.7 (3)	C(9)—C(10)—C(11)	111.0 (4)
C(16)—O(29)—C(21)	118.2 (4)	C(4)—C(11)—C(10)	122.4 (4)
O(22)—C(1)—O(23)	108.4 (5)	C(4)—C(11)—C(12)	120.2 (5)
O(23)—C(2)—C(3)	128.8 (5)	C(10)—C(11)—C(12)	117.0 (4)
O(23)—C(2)—C(13)	109.5 (5)	C(11)—C(12)—C(13)	118.0 (4)
C(3)—C(2)—C(13)	121.7 (5)	O(22)—C(13)—C(2)	109.6 (5)
C(2)—C(3)—C(4)	118.7 (4)	O(22)—C(13)—C(12)	128.5 (5)
C(3)—C(4)—C(5)	117.5 (4)	C(2)—C(13)—C(12)	121.9 (5)
C(3)—C(4)—C(11)	119.5 (4)	C(5)—C(14)—C(15)	122.0 (4)
C(5)—C(4)—C(11)	123.0 (4)	C(5)—C(14)—C(19)	118.9 (4)
C(4)—C(5)—C(6)	107.2 (3)	C(15)—C(14)—C(19)	119.1 (4)
C(4)—C(5)—C(14)	112.5 (4)	C(14)—C(15)—C(16)	120.6 (4)
C(6)—C(5)—C(14)	114.9 (4)	O(29)—C(16)—C(15)	124.2 (4)
C(5)—C(6)—C(7)	121.3 (4)	O(29)—C(16)—C(17)	116.2 (3)
C(5)—C(6)—C(9)	112.1 (4)	C(15)—C(16)—C(17)	119.6 (4)
C(7)—C(6)—C(9)	103.2 (4)	O(28)—C(17)—C(16)	119.8 (4)
O(24)—C(7)—O(25)	121.1 (5)	O(28)—C(17)—C(18)	120.5 (4)
O(24)—C(7)—C(6)	109.8 (4)	C(16)—C(17)—C(18)	119.7 (4)
O(25)—C(7)—C(6)	129.1 (4)	O(27)—C(18)—C(17)	114.7 (3)
O(24)—C(8)—C(9)	104.7 (4)	O(27)—C(18)—C(19)	124.4 (4)
C(6)—C(9)—C(8)	101.1 (4)	C(17)—C(18)—C(19)	120.8 (4)
C(6)—C(9)—C(10)	110.3 (4)	C(14)—C(19)—C(18)	120.2 (4)

The final cycle of full-matrix least-squares refinement was based on 1333 observed reflections and 262 variable parameters and converged with unweighted and weighted agreement factors of  $R = 0.040$  and  $wR = 0.050$  ( $R$  and  $wR$  for all 1621 observations = 0.055 and 0.054, respectively). The maximum shift/*e.s.d.* in the final cycle was 0.01. The standard deviation,  $S$ , of an observation of unit weight was 1.76. In the weighting scheme a  $p$  factor of 0.03 was used. Maximum and minimum peaks of 0.18 and  $-0.25 \text{ e \AA}^{-3}$ , respectively, were observed on the final difference Fourier map. Anomalous-dispersion effects were included in  $F_c$  (Ibers & Hamilton, 1964); the values for  $f'$  and  $f''$  were those of Cromer (1974). All calculations were performed using *TEXSAN* (Molecular Structure Corporation, 1985).

Table 1 lists positional parameters and equivalent isotropic temperature factors. Table 2 lists bond distances and angles for non-H atoms. Fig. 1 displays the title compound using an *ORTEPII* (Johnson, 1976) representation. Fig. 2 displays the

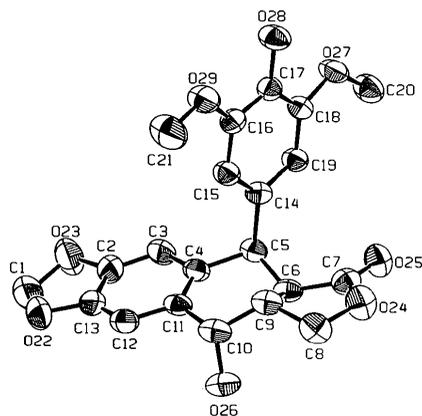


Fig. 1. *ORTEPII* (Johnson, 1976) plot of the molecular structure of 4'-demethylepipodophyllotoxin with coordinate atom labelling.

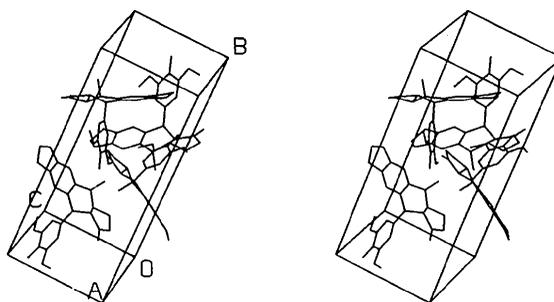


Fig. 2. *PLUTO* (Motherwell & Clegg, 1978) stereo plot of packing diagram; unit-cell axes and origin are labelled.

crystal packing arrangement in stereo form using *PLUTO* (Motherwell & Clegg, 1978).\*

**Related literature.** The title compound belongs to the class of natural products known as lignans which contain the 2,3-dibenzylbutane skeleton. These compounds show strong antimetabolic activity and many semi-synthetic derivatives of them have proven useful as anticancer drugs (Gupta & Ross, 1989). The synthesis of this compound serves as an initial step in the attempted design of more specific and potent compounds. Recently the crystal structure of a thymidine derivative of DMEP exhibiting POD-like antimetabolic activity was reported by Sicheri, Derry, Gupta & Yang (1991).

Structure-activity studies of podophyllotoxin and its derivatives, including 4'-demethylepipodophyllotoxin, on *in vitro* microtubule assembly have been investigated by Lokie, Brewer, Sternlicht, Gensler & Horwitz (1978).

\* Lists of structure factors, anisotropic thermal parameters, torsion angles and H-atom parameters have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 54648 (19 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

This research was supported in part by Chedoke-McMaster Hospital Foundation and Medical Research Council of Canada (DS-CY and RSG).

#### References

- CROMER, D. T. (1974). *International Tables for X-ray Crystallography*, Vol. IV, Table 2.3.1. Birmingham: Kynoch Press. (Present distributor Kluwer Academic Publishers, Dordrecht.)
- GILMORE, C. J. (1984). *J. Appl. Cryst.* **17**, 42-46.
- GUPTA, R. S. & ROSS, W. E. (1989). *Drug Resistance in Mammary Cells*, Vol. II, edited by R. S. GUPTA, pp. 89-107. Florida: CRC Press.
- IBERS, J. A. & HAMILTON, W. C. (1964). *Acta Cryst.* **17**, 781-782.
- JOHNSON, C. K. (1976). *ORTEPII*. Report ORNL-5138. Oak Ridge National Laboratory, Tennessee, USA.
- KUHN, M., KELLER-JUSLEN, C. & VON WARTBURG, A. (1969). *Helv. Chim. Acta*, **52**, 945-947.
- LOKIE, J. D., BREWER, C. T., STERNLICHT, H., GENSLER, W. J. & HORWITZ, S. B. (1978). *Cancer Res.* **38**, 2688-2693.
- Molecular Structure Corporation (1985). *TEXSAN. TEXRAY Structure Analysis Package*. MSC, 3200A Research Forest Drive, The Woodlands, TX 77381, USA.
- MOTHERWELL, W. D. S. & CLEGG, W. (1978). *PLUTO*. Program for plotting molecular and crystal structures. Univ. of Cambridge, England.
- NORTH, A. C. T., PHILLIPS, D. C. & MATHEWS, F. S. (1968). *Acta Cryst.* **A24**, 351-359.
- SICHERI, F. V., DERRY, W. B., GUPTA, R. S. & YANG, D. S.-C. (1991). *Acta Cryst.* **C47**, 2479-2482.

*Acta Cryst.* (1992). **C48**, 749-751

## Structure of 2-Methoxy-4-nitroaniline

BY SAFIA MEHDI

*X-ray Section, Indian Institute of Chemical Technology, Hyderabad-500 007, India*

(Received 24 June 1991; accepted 10 September 1991)

**Abstract.**  $C_7H_8N_2O_3$ ,  $M_r = 168.2$ , monoclinic,  $P2_1/a$ ,  $a = 7.086$  (1),  $b = 15.030$  (2),  $c = 7.214$  (1) Å,  $\beta = 91.75$  (1)°,  $V = 768.08$  (2) Å<sup>3</sup>,  $Z = 4$ ,  $D_m = 1.42$  (by flotation),  $D_x = 1.454$  g cm<sup>-3</sup>,  $\lambda(\text{Mo } K\alpha) = 0.71069$  Å,  $\mu = 1.082$  cm<sup>-1</sup>,  $F(000) = 352$ ,  $T = 295$  K,  $R = 0.0362$ ,  $wR = 0.0390$  for 675 reflections. The structure consists of planar molecules with intermolecular hydrogen bonding. The molecular geometry suggests the contribution of a quinonoid resonance form to the structure due to conjugation effects, as found in other *p*-nitroaniline derivatives [Ploug-Sørensen & Krogh Andersen (1982). *Acta Cryst.* **B38**, 671-673].

**Experimental.** A crystal of the title compound measuring  $0.15 \times 0.10 \times 0.5$  mm was used for inten-

sity data collection on a Siemens *R3m* diffractometer with graphite-monochromated Mo  $K\alpha$  radiation,  $\omega/2\theta$ -scan mode, scan speed  $1^\circ \text{ min}^{-1}$ ,  $\theta \leq 23.5^\circ$ . Cell constants obtained from the least-squares fit of  $2\theta$  values for 22 reflections ( $12 \leq 2\theta \leq 35^\circ$ ). Intensities were corrected for Lorentz and polarization effects, no correction for absorption. Total reflections 1115, unique 1039 ( $R_{\text{int}} = 0.0209$ ) and index range of  $h = -10$  to  $10$ ,  $k = 0$  to  $22$ ,  $l = 0$  to  $10$  ( $2\theta < 48^\circ$ ). Three standard reflections ( $\bar{1}71$ ,  $022$ ,  $152$ ) measured periodically displayed intensity variation  $< 3\%$ . Structure solved using the *SHELXTL* program (Sheldrick, 1983); 675 reflections at  $4\sigma$  level were used for refinement.  $w(|F_o| - |F_c|)^2$  minimized where  $w = 1.000[\sigma^2(F) + 0.002352(F^2)]$ . Final stage of refinement performed with 111 variables including