

Structure of 2-(4-Chlorobenzoyl)-1,2,8,8a-tetrahydro-7-methyl-(7bR)-cyclopropa[c]pyrrolo[3,2-e]indol-4(5H)-one: Absolute Configuration of CC-1065

BY W. WATT,* D. G. MARTIN, D. J. DUCHAMP, S. A. MIZSAK, J. W. NIELSEN AND M. D. PRAIRIE

Research Laboratories, The Upjohn Company, Kalamazoo, MI 49001, USA

(Received 4 November 1987; accepted 4 May 1988)

Abstract. $C_{19}H_{15}ClN_2O_2 \cdot 0.35C_3H_6O$, $M_r = 359.21$, monoclinic, $C2$, $a = 20.670$ (2), $b = 7.468$ (1), $c = 11.695$ (1) Å, $\beta = 96.53$ (1)°, $V = 1793.7$ (2) Å³, $Z = 4$, $D_x = 1.33$ g cm⁻³, $\lambda(\text{Cu } K\alpha) = 1.5418$ Å, $\mu = 19.4$ cm⁻¹, $F(000) = 748.8$, $T = 123$ K, $R = 0.105$ for 1518 unique reflections ($R = 0.066$ for 721 reflections $> 3\sigma$). The title compound is the acyl derivative of the chiral fragment from the powerful antitumor agent CC-1065. This X-ray diffraction study was performed in order to establish the absolute configuration of CC-1065. The chiral centers, C(18) and C(20), have *R* and *S* configurations, respectively.

Experimental. After many attempts to obtain crystals suitable for X-ray examination, a few relatively poor crystals were obtained by recrystallization from acetone. A clear thin plate of dimensions $0.13 \times 0.06 \times 0.16$ mm was used for intensity measurements on a Syntex $P2_1$ diffractometer controlled by a Harris computer. $\text{Cu } K\alpha$ radiation and a graphite monochromator were used for intensity measurement. The step-scan technique was used with a scan speed of 2° min^{-1} , a scan width of 3.4° , and a $2\theta_{\text{max}}$ of 138° . Ten reflections periodically monitored showed no loss in intensity during the data collection. Of the 1518 unique reflections measured, 721 had intensities $> 3\sigma$. Standard deviations in the intensities were approximated by the equation:

$$\sigma^2(I) = \sigma^2(I)_{\text{counting statistics}} + (0.020I)^2$$

where the coefficient of I was calculated from the variations in intensities of the monitored reflections. Unit-cell parameters were determined accurately by least-squares fit of $K\alpha_1 2\theta$ values [$\lambda(K\alpha_1) = 1.5402$ Å] for 25 high- 2θ reflections (Duchamp, 1977). Lorentz and polarization corrections appropriate for a monochromator with 50% perfect character were applied, but with no absorption correction.

A partial trial solution, 27 atoms, was obtained by direct methods using *MULTAN80* (Main, Fiske, Hull, Lessinger, Germain, Declercq & Woolfson, 1980). The remaining atoms in the molecule were found by successive Fourier syntheses. H-atom positions were

found in difference maps very close to positions generated using planar or tetrahedral geometry, so generated positions were used.

From a difference Fourier map, three large peaks (1.7 , 1.5 and $1.2 \text{ e } \text{Å}^{-3}$) which were unaccounted for, with density in between, were found near a crystallographic twofold axis. Since they were not within bonding distance to atoms of the molecule, and since the compound was crystallized from acetone, a disordered acetone with half occupied atom positions (100% site occupancy) was used to fit this density. A general plane difference Fourier through the three peaks was calculated, and an initial acetone model was developed. Further Fourier analysis led us to revise the model. The temperature factor of one solvent atom refined to an unreasonably large value. A peak ($1.2 \text{ e } \text{Å}^{-3}$) was found 1.8 Å above the plane of the original acetone, and one of the methyl carbons was assigned to this peak. The positions of the remaining three solvent atoms were shifted to correspond to an acetone tilted approximately 76° to the twofold axis. All solvent atom positions are greater than 3.15 Å from any other non-hydrogen atom in the structure. After the revision, the temperature factors of the new model atoms refined to reasonable values. The electron density in the disordered region appears to be modeled adequately by this disordered acetone.

All reflections with $(\sin\theta)/\lambda < 0.2 \text{ Å}^{-1}$ (ca 5% of the original data) were excluded from the refinement since they were most significantly influenced by the disordered solvent. The structure was refined by least squares; parameters varied were coordinates of all non-hydrogen atoms, anisotropic thermal parameters for non-hydrogen atoms, isotropic thermal parameters for solvent atoms and a site occupancy factor for the solvent. Hydrogen parameters and solvent coordinates were included in the calculations but were not refined.

The enantiomer determination, using the method of Bijvoet (1955), was performed by calculating structure factors for both enantiomers and performing a computer search to find the reflections most significantly affected by anomalous dispersion. 34 of these reflections were scanned very accurately ($0.1^\circ \text{ min}^{-1}$) over each of its four positions; of these, 23 showed a consistent preference for an enantiomer. 22 of the 23

* To whom correspondence should be addressed.

Table 1. Fractional coordinates ($\times 10^4$) and B_{eq} (\AA^2) with e.s.d.'s in parentheses

$$B_{eq} = \frac{1}{3}(a^2B_{11} + b^2B_{22} + c^2B_{33} + abc\cos\gamma B_{12} + accos\beta B_{13} + bccos\alpha B_{23})$$

	x	y	z	B_{eq}
Cl(1)	-5295 (1)	-3163	-3601 (3)	10.5 (2)
C(1)	-5655 (4)	-5142 (11)	-4117 (8)	6.3 (4)
C(2)	-5522 (4)	-6718 (12)	-3478 (8)	5.8 (3)
C(3)	-5842 (3)	-8246 (11)	-3856 (7)	4.3 (3)
C(4)	-6281 (3)	-8271 (11)	-4838 (6)	3.8 (3)
C(5)	-6393 (4)	-6726 (10)	-5500 (7)	4.5 (3)
C(6)	-6084 (4)	-5153 (12)	-5128 (8)	6.2 (3)
C(7)	-6693 (3)	-9894 (12)	-5073 (5)	3.6 (3)
O(7)	-6915 (2)	-10702 (7)	-4295 (4)	4.7 (2)
N(8)	-6876 (2)	-10348 (8)	-6193 (4)	3.7 (2)
C(9)	-6575 (3)	-9969 (10)	-7166 (5)	3.6 (3)
C(10)	-5927 (3)	-9863 (12)	-7232 (5)	4.3 (3)
O(11)	-5078 (2)	-9670 (10)	-8418 (4)	6.4 (3)
C(11)	-5669 (3)	-9775 (12)	-8336 (6)	4.8 (3)
C(12)	-6160 (3)	-9876 (13)	-9325 (6)	4.6 (3)
N(13)	-6028 (3)	-9842 (10)	-10472 (5)	4.4 (2)
C(14)	-6612 (3)	-9974 (12)	-11146 (6)	4.6 (3)
C(15)	-7120 (3)	-10038 (12)	-10460 (5)	4.2 (3)
C(16)	-7820 (4)	-10149 (12)	-10901 (6)	5.1 (3)
C(17)	-6823 (3)	-10027 (11)	-9302 (5)	3.8 (3)
C(18)	-7072 (3)	-9988 (11)	-8185 (5)	3.5 (3)
C(19)	-7699 (4)	-9001 (12)	-7969 (7)	4.6 (3)
C(20)	-7650 (4)	-10949 (12)	-7782 (6)	4.4 (3)
C(21)	-7452 (3)	-11478 (11)	-6532 (7)	4.9 (3)
C(S1)	-5583	-4715	-10745	8.9
C(S2)	-4832	-4588	-10403	13.5
O(S2)	-4498	-4380	-9580	15.4
C(S3)	-4581	-5051	-11406	8.4

Table 2. Bond lengths (\AA) and bond angles ($^\circ$)

Cl(1)—C(1)	1.732 (8)	C(11)—C(12)	1.450 (9)
C(1)—C(2)	1.404 (13)	C(12)—N(13)	1.399 (8)
C(1)—C(6)	1.395 (12)	C(12)—C(17)	1.378 (8)
C(2)—C(3)	1.368 (12)	N(13)—C(14)	1.368 (8)
C(3)—C(4)	1.380 (10)	C(14)—C(15)	1.393 (9)
C(4)—C(5)	1.394 (11)	C(15)—C(16)	1.482 (9)
C(4)—C(7)	1.490 (11)	C(15)—C(17)	1.423 (9)
C(5)—C(6)	1.384 (11)	C(17)—C(18)	1.458 (8)
C(7)—O(7)	1.223 (8)	C(18)—C(19)	1.537 (10)
C(7)—N(8)	1.364 (8)	C(18)—C(20)	1.514 (10)
N(8)—C(9)	1.386 (8)	C(19)—C(20)	1.473 (12)
N(8)—C(21)	1.477 (9)	C(20)—C(21)	1.525 (11)
C(9)—C(10)	1.353 (8)	C(S1)—C(S2)	1.56
C(9)—C(18)	1.482 (8)	C(S2)—O(S2)	1.13
C(10)—C(11)	1.454 (9)	C(S2)—C(S3)	1.38
O(11)—C(11)	1.239 (7)		
Cl(1)—C(1)—C(2)	118.6 (7)	C(11)—C(12)—C(17)	126.6 (6)
Cl(1)—C(1)—C(6)	120.4 (7)	N(13)—C(12)—C(17)	108.8 (5)
C(2)—C(1)—C(6)	120.9 (8)	C(12)—N(13)—C(14)	107.3 (5)
C(1)—C(2)—C(3)	118.0 (8)	N(13)—C(14)—C(15)	110.1 (6)
C(2)—C(3)—C(4)	121.9 (8)	C(14)—C(15)—C(16)	124.9 (6)
C(3)—C(4)—C(5)	120.2 (7)	C(14)—C(15)—C(17)	106.0 (5)
C(3)—C(4)—C(7)	118.2 (7)	C(16)—C(15)—C(17)	129.1 (6)
C(5)—C(4)—C(7)	121.0 (6)	C(12)—C(17)—C(15)	107.7 (5)
C(4)—C(5)—C(6)	119.1 (7)	C(12)—C(17)—C(18)	118.0 (5)
C(1)—C(6)—C(5)	119.8 (8)	C(15)—C(17)—C(18)	134.0 (5)
C(4)—C(7)—O(7)	121.3 (6)	C(9)—C(18)—C(17)	116.0 (5)
C(4)—C(7)—N(8)	117.9 (6)	C(9)—C(18)—C(19)	112.5 (6)
O(7)—C(7)—N(8)	120.4 (7)	C(9)—C(18)—C(20)	104.7 (5)
C(7)—N(8)—C(9)	129.6 (5)	C(17)—C(18)—C(19)	123.2 (6)
C(7)—N(8)—C(21)	121.8 (5)	C(17)—C(18)—C(20)	129.9 (6)
C(9)—N(8)—C(21)	108.6 (5)	C(19)—C(18)—C(20)	57.7 (5)
N(8)—C(9)—C(10)	126.7 (6)	C(18)—C(19)—C(20)	60.4 (5)
N(8)—C(9)—C(18)	108.9 (5)	C(18)—C(20)—C(19)	61.9 (5)
C(10)—C(9)—C(18)	123.7 (5)	C(18)—C(20)—C(21)	106.6 (5)
C(9)—C(10)—C(11)	121.3 (6)	C(19)—C(20)—C(21)	113.9 (7)
C(10)—C(11)—O(11)	122.4 (6)	N(8)—C(21)—C(20)	103.3 (6)
C(10)—C(11)—C(12)	114.3 (5)	C(S1)—C(S2)—O(S2)	136.
O(11)—C(11)—C(12)	123.2 (6)	C(S1)—C(S2)—C(S3)	103.
C(11)—C(12)—N(13)	124.7 (5)	O(S2)—C(S2)—C(S3)	120.

reflections favored the chosen enantiomer over its mirror image. A listing of the Bijvoet data can be found in Table 6S.*

Using the parameters of Cromer & Liberman (1970), anomalous components were included in the final refinement cycle. The function minimized in the refinement was $\sum w(F_o^2 - F_c^2)^2$, where weights w were $1/\sigma^2(F_o^2)$. Atomic form factors were from Doyle & Turner (1968), and, for H, from Stewart, Davidson & Simpson (1965). In the final refinement cycle, all shifts were $< 0.15\sigma$. For those reflections used in the refinement, $R = 0.106$, $S = 1.73$ (1447 reflections) and $R = 0.058$ (654 reflections $> 3\sigma$). For all 1518 reflections, $R = 0.105$, and $R = 0.066$ (721 reflections $> 3\sigma$). The final site occupancy on the solvent was 70%. The final difference map showed no peaks $> 0.72 \text{ e \AA}^{-3}$ in the region of the disordered solvent and no peaks $> 0.36 \text{ e \AA}^{-3}$ outside the region of the solvent. The CRYM system of computer programs was used (Duchamp, 1984). A table of the final coordinates can be found in Table 1.

* Lists of structure factors, anisotropic thermal parameters, H-atom coordinates, torsion angles, close contacts and Bijvoet reflection data have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 51003 (15 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

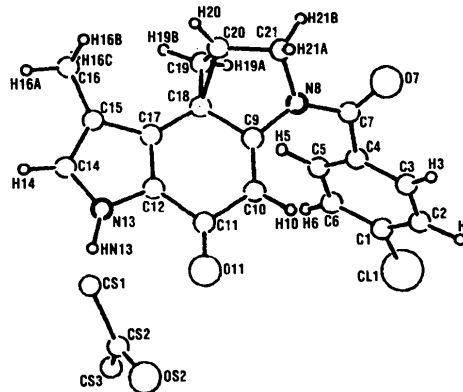


Fig. 1. Structure of title compound with atom numbering.

All of the bond distances and angles are within the expected ranges (Table 2). The amide linkage is twisted about 20° from planar. An intermolecular hydrogen bond, $N(13)\cdots O(11)$ $2.757(7) \text{ \AA}$, was found. A ball-and-stick drawing with numbering is shown in Fig. 1. The absolute configurations of C(18) and C(20) are *R* and *S*, respectively.

Related literature. CC-1065 is a powerful antitumor agent (Martin, Chidester, Duchamp & Mizsak, 1980; Chidester, Krueger, Mizsak, Duchamp & Martin, 1981), and the derivatized chiral fragment of CC-1065 is described (Martin, Kelly, Watt, Wicnienski, Mizsak, Nielsen & Prairie, 1988).

The authors thank the referees for their helpful suggestions on the disordered solvent model.

References

- BIJVOET, J. M. (1955). *Endeavour*, **14**, 71.
 CHIDESTER, C. G., KRUEGER, W. C., MIZSAK, S. A., DUCHAMP, D. J. & MARTIN, D. G. (1981). *J. Am. Chem. Soc.* **103**, 7629.
 CROMER, D. T. & LIBERMAN, D. (1970). *J. Chem. Phys.* **53**, 1891–1898.
 DOYLE, P. A. & TURNER, P. S. (1968). *Acta Cryst.* **A24**, 390–397.
 DUCHAMP, D. J. (1977). *ACS Symp. Ser.* **46**, 98–121.
 DUCHAMP, D. J. (1984). *CRYM. A System of Crystallographic Programs*. The Upjohn Company, Kalamazoo, MI, USA.
 MAIN, P., FISKE, S. J., HULL, S. E., LESSINGER, L., GERMAIN, G., DECLERCQ, J.-P. & WOOLFSON, M. M. (1980). *MULTAN80. A System of Computer Programs for the Automatic Solution of Crystal Structures from X-ray Diffraction Data*. Univs. of York, England, and Louvain, Belgium.
 MARTIN, D. G., CHIDESTER, C. G., DUCHAMP, D. J. & MIZSAK, S. A. (1980). *J. Antibiotics*, **33**, 902–903.
 MARTIN, D. G., KELLY, R. C., WATT, W., WICNIENSKI, N., MIZSAK, S. A., NIELSEN, J. W. & PRAIRIE, M. D. (1988). *J. Org. Chem.* In the press.
 STEWART, R. F., DAVIDSON, E. R. & SIMPSON, W. T. (1965). *J. Chem. Phys.* **42**, 3175–3187.

Acta Cryst. (1988). **C44**, 1677–1679

Structure of the Steroid Molecule 17 β -Hydroxy-1 α -methyl-5 α -androstan-3-one (Mesterolone)

BY SÜHEYLA DANACI AND ENGIN KENDI

Physics Department, Hacettep University, Ankara, Turkey

AND F. G. MOERS, H. BEHM AND PAUL T. BEURSKENS

Crystallography Laboratory, University of Nijmegen, Toernooiveld, 6525 ED Nijmegen, The Netherlands

(Received 1 March 1988; accepted 23 May 1988)

Abstract. $C_{20}H_{32}O_2$, $M_r = 304.5$, orthorhombic, $P2_12_12_1$, $a = 11.123$ (3), $b = 16.938$ (4), $c = 18.561$ (3) Å, $V = 3497$ (1) Å³, $Z = 8$, $D_x = 1.157$ g cm⁻³, $Cu K\alpha$, $\lambda = 1.54178$ Å, $\mu = 5.24$ cm⁻¹, $F(000) = 1344$, $T = 293$ K, final $R = 0.042$, $wR = 0.053$, for 4105 observed reflections and 416 variables. The hexane rings of the two independent molecules in the asymmetric unit have chair conformations, and the D rings are intermediate between 13 β -envelope and 13 β ,14 α -half-chair conformations.

Experimental. A crystal approximately $0.29 \times 0.09 \times 0.1$ mm was used for the measurements. Throughout the experiment $Cu K\alpha$ radiation was used with a graphite-crystal monochromator on a Nonius CAD-4 single-crystal diffractometer ($\lambda = 1.54178$ Å). The unit-cell dimensions were determined from the angular settings of 25 reflections with $10 < \theta < 28^\circ$. The space group was determined from systematic extinctions and the structure determination. The intensity data of 13 671 reflections were measured (half a sphere up to $\theta = 70^\circ$; $h - 13 \rightarrow 0$, $k - 20 \rightarrow 20$, $l - 22 \rightarrow 22$) using the $\omega - 2\theta$ scan technique, with a scan angle of 1.5° and a variable scan rate with a maximum scan time of 20 s per reflec-

tion. The intensity of the primary beam was checked throughout the data collection by monitoring three standard reflections every 30 min. The final drift correction factors were between 0.94 and 1.03. A profile analysis (Lehmann & Larsen, 1974; Grant & Gabe, 1978) was performed on all reflections. Lorentz and polarization corrections were applied and the data were reduced to $|F_o|$ values. Symmetry equivalent reflections were averaged, $R_{int} = 0.056$ for all reflections and 0.022 for the observed reflections only, resulting in 6636 unique reflections of which 4105 were observed with $F > 6\sigma(F)$.

A misplaced fragment of nine atoms was found with *MULTAN80* (Main, Fiske, Hull, Lessinger, Germain, Declercq & Woolfson, 1980) and this fragment was input to reciprocal translation functions (Beurskens, Gould, Bruins Slot & Bosman, 1987) and automatically expanded by *DIRDIF* (Beurskens, Bosman, Doesburg, van den Hark, Prick, Noordik, Beurskens, Gould & Parthasarathi, 1983) for the location of atoms of the two independent molecules.

Isotropic least-squares refinement, using *SHELX76* (Sheldrick, 1976), converged to $R = 0.10$. At this stage an additional empirical absorption correction was