Acta Cryst. (1990). C46, 2182–2185

Structure and Conformation of 5-Methoxymethyl-N^4-methyl-2′-deoxycytidine

BY ZONGCHAO JIA,* GUY TOURIGNY,† ALLAN L. STUART,‡ LOUIS T. J. DELBAERE* AND SAGAR V. GUPTA‡

Departments of Biochemistry, Chemistry and Veterinary Physiological Sciences, University of Saskatchewan, Saskatoon, Canada S7N 0W0

(*Received* 5 *December* 1989; *accepted* 2 *February* 1990)

Abstract. $C_{12}H_{19}N_3O_5$, $M_r = 285{\cdot}25$, monoclinic, $P2_1$, $a = 7{\cdot}0180\ (6)$, $b = 8{\cdot}6946\ (11)$, $c = 10{\cdot}7715\ (10)$ Å, $\beta = 91{\cdot}055\ (7)°$, $V = 657{\cdot}15$ Å^3, $Z = 2$, $D_x = 1{\cdot}441$ g cm^{-3}, λ(Cu $K\alpha$) = 1·5418 Å, $\mu = 9{\cdot}63$ cm^{-1}, $F(000) = 304$, $T = 287$ K, $R = 0{\cdot}039$ for 1424 observed reflections. The furanose ring adopts the C(1′)-*exo* envelope conformation (E_1), with the glycosyl linkage *anti* ($\chi = 193{\cdot}8°$). The pseudorotational parameters are $P = 130{\cdot}9°$ and $\tau_m = 39{\cdot}4°$. In the deoxyribose ring, the side chain on C(5′) has the *t* conformation. In the pyrimidine ring the N^4-methyl takes a *cis* conformation to N(3) and the methoxymethyl side chain is on the same side of the cytidine plane as O(4′).

Introduction. Analogs of cytidine are useful therapeutic agents. Arabinofuranosylcytosine (ara-C) is extensively used for the treatment of neoplastic diseases in humans (Pallavicini, 1984). 5-Iodo-2′-deoxycytidine has been reported to inhibit replication of herpes viruses (Schildkraut, Cooper & Greer, 1975; Fox, Dobersen & Greer, 1983) and 5-fluoro-2′-deoxycytidine is active against Lewis lung carcinoma and mammary adenocarcinoma (Mekras, Bootham, Perez & Greer, 1984; Bootham, Briggle & Greer, 1987). (*E*)-5-(2-Bromovinyl)-2′-deoxycytidine is a potent and selective inhibitor of herpes simplex virus (HSV) (DeClercq, 1982; Aduma, Gupta & DeClercq, 1990). The compound 2′,3′-dideoxycytidine is active against human immunodeficiency virus, an etiological agent of AIDS (Mitsuya & Broder, 1986).

A major drawback for the therapeutic use of cytidine compounds is their tendency to undergo deamination in the presence of deaminating enzymes. These enzymes are usually present in blood and mammalian cells and catalyze the deamination of the cytidine compounds to the corresponding uridine analogs, which are either less active (Camiener & Smith, 1965) or do not display selectivity towards infected cells (Fox *et al.*, 1983). The problem of deamination can be overcome by modification of the molecule to induce resistance to deaminases (Fox, Miller & Wempen, 1966; Dollinger, Burchenal, Kreis & Fox, 1967; Wang, Sharma & Bloch, 1973; Mancini & Lin, 1983).

Of considerable interest are the findings that alkyl derivatives of 5-iododeoxycytidine (N^4-methyl, -ethyl and -isopropyl) were incorporated into viral DNA without deamination (Fox *et al.*, 1983). 5-Methoxymethyl-2′-deoxycytidine has potent activity against HSV-1 when co-administered with a deaminase inhibitor (Aduma, Gupta, Stuart & Tourigny, 1990; Gupta, Tourigny, Aduma & Stuart, 1989). 5-Methoxymethyl-N^4-methyl-2′-deoxycytidine (N^4-methyl-MMdCyd) was prepared to make the molecule resistant to the action of deaminases. However, N^4-methyl-MMdCyd was found to be devoid of antiherpes activity (Gupta *et al.*, 1989). Since phosphorylation is an essential step for the antiherpes activity of the pyrimidine nucleoside analogs (DeClercq, 1982; Gupta, Tourigny, Stuart, DeClercq, Quail, Ekiel, El-Kabbani & Delbaere, 1987), it was felt that one possible reason for the loss of bioactivity of N^4-methyl-MMdCyd may be that the conformation of the molecule has been altered. This hypothesis is based on studies which have shown that the conformation of the deoxyribofuranose moiety is important in determining substrate specificity towards the viral enzyme (El-Kabbani, Ekiel, Delbaere, Tourigny, Stuart & Gupta, 1986; Quail, Ekiel, El-Kabbani, Tourigny, Delbaere, Stuart & Gupta, 1986; Quail, Tourigny, Delbaere, El-Kabbani, Stuart & Gupta, 1988; Gupta *et al.*, 1987; Tourigny, Stuart, Ekiel, Aduma & Gupta, 1989; Jia, Tourigny, Stuart, Delbaere & Gupta, 1990). The crystal structure of N^4-methyl-MMdCyd was determined by X-ray diffraction analysis. To our knowledge, this is the first X-ray analysis of an N^4-alkyl-substituted deoxycytidine derivative.

Experimental. *Synthesis of 5-methoxymethyl-N^4-methyl-2′-deoxycytidine (N^4-methyl-MMdCyd).* 1,2,4-Triazole (5·6 g, 81 mmol), $POCl_3$ (1·7 mL, 18 mmol) and triethylamine (11 mL, 78 mmol) were added with stirring to 24 mL of dry acetonitrile at 277 K. Then,

* Department of Biochemistry.
† Department of Chemistry.
‡ Department of Veterinary Physiological Sciences.

0108-2701/90/112182-04$03.00

5-methoxymethyl-2′-deoxy-3′,5′-diacetyluridine [1·07 g, 3·0 mmol (Jia *et al.*, 1990)], dissolved in 12 mL of actonitrile, was added to the suspension and the reaction mixture was stirred at 293 K for 1·5 h. The solvent was removed and the residue was dissolved in $CHCl_3$, washed with a saturated $NaHCO_3$ solution and water. After drying over $MgSO_4$ and evaporation of the solvent 3′,5′-diacetyl-4-triazolyl-5-methoxymethyl-2′-deoxy-1-β-D-ribofuranosylpyrimidin-2-one was obtained as an oil. UV (MeOH) $\lambda 250/\lambda 322 = 1{\cdot}45$. The oil was dissolved in 40 mL of dried peroxide-free 1,4-dioxane, cooled in an ice-bath and saturated with methylamine. The solution was allowed to stand at room temperature for 18 h in a Wheaton pressure bottle. The solvent was removed and recrystallization from methanol–ethyl ether gave 5-methoxymethyl-N^4-methyl-2′-deoxycytidine (590 mg, yield 69%), m.p. 432–433 K; UV (0·1 *M* HCl), λ_{max} 283 nm (ε 13800), λ_{min} 244 nm (ε 2100), UV (0·1 *M* NaOH), λ_{max} 273 nm (ε 10600), λ_{min} 251 nm (ε 7400). ^{1}H NMR (Me_2SO-d_6), δ 7·78 (*s*, 1, 6-H), 7·05 (*q*, 1, 4-NH), 6·14 (*m*, 1, 1′-H), 4·11, 4·08 (pair *d*, 2, 5-CH_2O), 3·75 (*m*, 1, 4′-H), 3·56 (*m*, 2, 5′5″-H), 3·20 (*s*, 3, 5-OCH_3), 2·78 (*d*, 3, 4-NCH_3), 1·9–2·1 (*m*, 2, 2′2″-H). Analysis: calculated for $C_{12}H_{19}N_3O_5$: C, 50·52; H, 6·71; N, 14·73%; found: C, 50·62; H, 6·52; N, 14·76%.

X-ray analysis. Suitable crystals of N^4-methyl-MMdCyd were obtained from a solution of 50% ethyl ether and 50% methanol (*v*/*v*). The colorless crystal was 0·60 × 0·28 × 0·10 mm in size; the density was not determined (calculated density = 1·441 g cm^{-3}). Quantitative intensity data were collected on an Enraf–Nonius CAD-4F diffractometer with an $\omega/2\theta$ scan and Ni-filtered copper radiation (λ = 1·5418 Å). The cell parameters were determined by least squares using 25 reflections with $28{\cdot}69 < \theta < 46{\cdot}29°$. Three standard reflections were checked every 10000 s for intensity variations and every 200 reflections for orientation. There was no significant decay of the crystal over the entire data collection. A total of 1636 reflections was collected to $\theta = 75°$, $-8 \le h \le 8$, $0 \le k < 10$, $-13 \le l \le 0$; of 1436 unique reflections, 1424 had net $I > 3\sigma(I)$. No absorption or extinction corrections were applied. Merging *R* based on intensities was 1·47% for 164 replicate reflections. All non-hydrogen atoms were found on an *E* map and refined anisotropically. Hydrogen atoms were located by using difference Fourier maps and refined isotropically. $R = 0{\cdot}039$, $wR = 0{\cdot}043$ [$w = 1/\sigma^2(F)$], $S = 3{\cdot}816$ for 1424 observed reflections. A total of 256 parameters were refined and *F* magnitudes were used in least-squares refinement. Final $(\Delta/\sigma)_{ave} = 0{\cdot}060$, $(\Delta/\sigma)_{max} = 0{\cdot}82$. $\Delta\rho$ in final difference map were +0·18 and −0·18 e Å^{-3}. X-ray data were processed and the structure was solved by direct methods using *XTAL*2.4 (Hall & Stewart, 1988). Atomic scattering factors were taken from *International Tables for X-ray Crystallography* (1974). The atomic parameters are summarized in Table 1. Bond distances, angles and torsion angles are listed in Table 2.* Fig. 1 is an *ORTEP* drawing (Johnson, 1976) of N^4-methyl-MMdCyd. All calculations were performed on a VAX 8650 computer at the University of Saskatchewan.

Table 1. *Fractional coordinates and average thermal parameters, with e.s.d.'s in parentheses*

$U_{eq} = (U_{11} + U_{22}\sin^2\beta + U_{33} + 2U_{13}\cos\beta)/3\sin^2\beta$.

	x	*y*	*z*	U_{eq}(Å^2 × 10^3)
N(1)	0·4746 (2)	0·3695 (3)	0·2547 (2)	31·9
C(2)	0·6258 (3)	0·4635 (4)	0·2936 (2)	32·0
O(2)	0·6459 (2)	0·4924 (3)	0·4053 (1)	40·3
N(3)	0·7469 (2)	0·5183 (3)	0·2083 (2)	32·8
C(4)	0·7161 (3)	0·49020	0·0884 (2)	29·1
N(4,1)	0·8439 (3)	0·5418 (3)	0·0072 (2)	36·2
C(4,2)	1·0147 (4)	0·6232 (5)	0·0472 (3)	47
C(5)	0·5492 (3)	0·4078 (4)	0·0430 (2)	31·7
C(5,1)	0·4985 (3)	0·3952 (4)	−0·0917 (2)	35·9
O(5,2)	0·6427 (3)	0·3151 (4)	−0·1544 (1)	45·8
C(5,3)	0·6090 (5)	0·3144 (5)	−0·2848 (2)	50
C(6)	0·4369 (3)	0·3482 (4)	0·1309 (2)	32·2
C(1′)	0·3569 (3)	0·2992 (4)	0·3509 (2)	33·5
C(2′)	0·2125 (4)	0·4048 (4)	0·4100 (3)	46
C(3′)	0·0675 (3)	0·2915 (4)	0·4588 (2)	31·0
O(3′)	0·0954 (3)	0·2543 (3)	0·5868 (1)	45·1
C(4′)	0·0885 (3)	0·1508 (3)	0·3740 (2)	29·8
O(4′)	0·2462 (2)	0·1835 (3)	0·2941 (2)	39·9
C(5′)	−0·0851 (3)	0·1162 (4)	0·2935 (2)	36·2
O(5′)	−0·0632 (3)	−0·0204 (3)	0·2238 (2)	42·9

Discussion. The glycosidic bond has the *anti* conformation with a torsion angle O(4′)—C(1′)—N(1)—C(2) of 193·8 (2)° and the 5′-CH_2OH side chain exhibits the *t* conformation. The deoxyribose ring adopts an envelope conformation with C(1′)-*exo* (E_1) and C(1′) is 0·049 Å from the mean plane through O(4′), C(2′), C(3′) and C(4′). A pseudorotational analysis of the furanose-ring torsional angles in terms of the two degrees of freedom for ring puckering (Altona & Sundaralingam, 1972) gives a phase angle $P = 130{\cdot}9°$ and a puckering amplitude $\tau_m = 39{\cdot}4°$, which correspond to an *S*-type conformation. The C(5) side chain is on the same side of the cytidine plane as is O(4′) of the furanose ring. The pyrimidine ring is slightly non-planar; the atoms with the largest deviations from this mean plane are C(2) [Δ = 0·043 (4) Å] and C(5) [Δ = 0·043 (4) Å]. The N^4-methyl group has a *cis* relationship to N(3) with a torsion angle N(3)—C(4)—N(4,1)—C(4,2) of 1·4°.

* Lists of structure amplitudes, anisotropic thermal parameters and H-atom coordinates have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 53023 (9 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 2. *Bond distances* (Å), *angles* (°) *and torsion angles* (°), *with e.s.d.'s in parentheses*

N(1)—C(2)	1·398 (3)	C(5,1)—O(5,2)	1·411 (3)
N(1)—C(6)	1·367 (2)	O(5,2)—C(5,3)	1·420 (3)
N(1)—C(1′)	1·470 (3)	C(1′)—C(2′)	1·517 (4)
C(2)—O(2)	1·235 (2)	C(1′)—O(4′)	1·404 (3)
C(2)—N(3)	1·349 (3)	C(2′)—C(3′)	1·517 (4)
N(3)—C(4)	1·329 (2)	C(3′)—O(3′)	1·426 (2)
C(4)—N(4,1)	1·342 (2)	C(3′)—C(4′)	1·536 (3)
C(4)—C(5)	1·450 (2)	C(4′)—O(4′)	1·443 (2)
N(4,1)—C(4,2)	1·451 (3)	C(4′)—C(5′)	1·512 (3)
C(5)—C(5,1)	1·492 (3)	C(5′)—O(5′)	1·416 (4)
C(5)—C(6)	1·347 (3)		

C(2)—N(1)—C(6)	120·3 (2)	C(5,1)—O(5,2)—C(5,3)	111·6 (2)
C(2)—N(1)—C(1′)	117·7 (1)	N(1)—C(6)—C(5)	121·9 (2)
C(6)—N(1)—C(1′)	122·0 (2)	N(1)—C(1′)—C(2′)	115·7 (2)
N(1)—C(2)—O(2)	118·9 (2)	N(1)—C(1′)—O(4′)	107·7 (1)
N(1)—C(2)—N(3)	119·1 (1)	C(2′)—C(1′)—O(4′)	104·4 (2)
O(2)—C(2)—N(3)	122·0 (2)	C(1′)—C(2′)—C(3′)	102·1 (2)
C(2)—N(3)—C(4)	120·3 (1)	C(2′)—C(3′)—O(3′)	113·6 (2)
N(3)—C(4)—N(4,1)	118·3 (1)	C(2′)—C(3′)—C(4′)	103·8 (1)
N(3)—C(4)—C(5)	122·3 (1)	O(3′)—C(3′)—C(4′)	112·4 (2)
N(4,1)—C(4)—C(5)	119·4 (1)	C(3′)—C(4′)—O(4′)	106·3 (2)
C(4)—N(4,1)—C(4,2)	121·9 (2)	C(3′)—C(4′)—C(5′)	114·5 (1)
C(4)—C(5)—C(5,1)	122·8 (2)	O(4′)—C(4′)—C(5′)	108·4 (1)
C(4)—C(5)—C(6)	115·7 (1)	C(1′)—O(4′)—C(4′)	107·8 (1)
C(5,1)—C(5)—C(6)	121·5 (2)	C(4′)—C(5′)—O(5′)	112·1 (2)
C(5)—C(5,1)—O(5,2)	110·0 (1)		

C(6)—N(1)—C(2)—O(2)	173·3 (2)	C(4)—C(5)—C(5,1)—O(5,2)	62·7 (3)
C(6)—N(1)—C(2)—N(3)	−7·7 (4)	C(6)—C(5)—C(5,1)—O(5,2)	−120·2 (3)
C(1′)—N(1)—C(2)—O(2)	−5·1 (4)	C(4)—C(5)—C(6)—N(1)	2·4 (4)
C(1′)—N(1)—C(2)—N(3)	174·0 (2)	C(5,1)—C(5)—C(6)—N(1)	−174·9 (2)
C(2)—N(1)—C(6)—C(5)	4·3 (4)	C(5)—C(5,1)—O(5,2)—C(5,3)	−174·0 (2)
C(1′)—N(1)—C(6)—C(5)	−177·4 (2)	N(1)—C(1′)—C(2′)—C(3′)	157·2 (1)
C(2)—N(1)—C(1′)—C(2′)	77·5 (2)	O(4′)—C(1′)—C(2′)—C(3′)	39·0 (2)
C(2)—N(1)—C(1′)—O(4′)	−166·2 (2)	N(1)—C(1′)—O(4′)—C(4′)	−160·8 (2)
C(6)—N(1)—C(1′)—C(2′)	−100·8 (3)	C(2′)—C(1′)—O(4′)—C(4′)	−37·4 (2)
C(6)—N(1)—C(1′)—O(4′)	15·5 (3)	C(1′)—C(2′)—C(3′)—O(3′)	96·6 (2)
N(1)—C(2)—N(3)—C(4)	3·8 (3)	C(1′)—C(2′)—C(3′)—C(4′)	−25·8 (2)
O(2)—C(2)—N(3)—C(4)	−177·1 (2)	C(2′)—C(3′)—C(4′)—O(4′)	4·9 (2)
C(2)—N(3)—C(4)—N(4,1)	−177·5 (2)	C(2′)—C(3′)—C(4′)—C(5′)	−114·8 (2)
C(2)—N(3)—C(4)—C(5)	3·2 (3)	O(3′)—C(3′)—C(4′)—O(4′)	−118·3 (2)
N(3)—C(4)—N(4,1)—C(4,2)	1·4 (3)	O(3′)—C(3′)—C(4′)—C(5′)	122·0 (2)
C(5)—C(4)—N(4,1)—C(4,2)	−179·2 (3)	C(3′)—C(4′)—O(4′)—C(1′)	20·3 (2)
N(3)—C(4)—C(5)—C(5,1)	170·9 (2)	C(5′)—C(4′)—O(4′)—C(1′)	143·8 (2)
N(3)—C(4)—C(5)—C(6)	−6·3 (3)	C(3′)—C(4′)—C(5′)—O(5′)	−175·9 (1)
N(4,1)—C(4)—C(5)—C(5,1)	−8·4 (3)	O(4′)—C(4′)—C(5′)—O(5′)	65·6 (2)
N(4,1)—C(4)—C(5)—C(6)	174·3 (2)		

There are two intermolecular hydrogen bonds per unit cell. The first is O(2)···H—O(3′)($1-x$, $\frac{1}{2}+y$, $1-z$); the distances from O(2) to O(3′) and H are 2·913 (4) and 2·04 (5) Å, respectively. The second is O(3′)···H—O(5′)($-x$, $\frac{1}{2}+y$, $1-z$); the distances from O(3′) to O(5′) and H are 2·841 (3) and 2·04 (5) Å, respectively. Birnbaum, Deslauriers, Lin, Shiau & Prusoff (1980) reported an intramolecular short contact C(6)—H···O(4′) in 5-hydroxymethyl-2′-deoxyuridine with distances between O(4′) and C(6) and H of 2·786 and 2·27 Å, which was suggested to stabilize the conformation of the sugar ring. A similar short contact was also detected in N^4-methyl-MMdCyd, with distances between O(4′) and C(6) and H of 2·649 (3) and 2·29 (3) Å, respectively. Intramolecular hydrogen bonding O(5,1)···H—N(4,1) was not observed in MMdCyd (Jia *et al.*, 1990).

MMdCyd is a selective antiherpes agent (Aduma, Gupta, Stuart & Tourigney, 1990; Gupta *et al.*, 1989). However, N^4-methylation results in a complete loss of activity (Gupta *et al.*, 1989). Differences in activity can be rationalized on the basis of altered conformations of the N^4-substituent and/or the 5′-CH_2OH side chain. Since phosphorylation of the C(5′)OH group is required for metabolic activation of the nucleoside, it appears that the molecule is not readily phosphorylated by HSV-induced dCyd/dThd kinase when the group does not have the g^+ conformation (Gupta *et al.*, 1987). Furthermore the *cis* relationship between the N^4-substituent and N(3) may interfere with enzymatic interaction.

N^4-Aminocytidine hemihydrate, a potent mutagen (Takahashi, Nishizawa, Negishi, Hanaoka, Yamada & Hayatsu, 1988), is the only N^4-substituted cytidine derivative for which the structure has been reported (Kashino, Negishi & Hayatse, 1988). Both N^4-

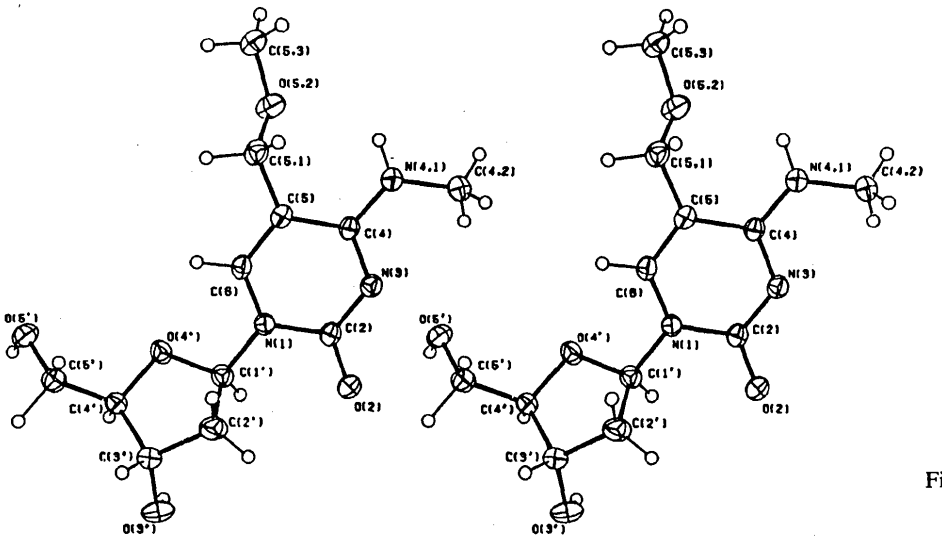

Fig. 1. Stereoscopic *ORTEP* view (Johnson, 1976) of the title compound, with atomic numbering.

methyl-MMdCyd and N^4-amino-dCyd have a *cis* relationship between the N^4-substituent and N(3).

This research was funded by grants from the Medical Research Council of Canada to SVG, GT and LTJD. ZJ is the recipient of a University of Saskatchewan Graduate Scholarship. We thank Mr Ted Mazurek, Plant Biotechnology Institute, for the NMR spectrum, Mr Ken Toms, Department of Chemistry, for the CHN analysis and Dr L. Prasad, Department of Biochemistry, for valuable suggestions.

References

ADUMA, P. J., GUPTA, V. S. & DECLERCQ, E. (1990). *Antiviral Res.* **13**, 111–126.

ADUMA, P. J., GUPTA, V. S., STUART, A. L. & TOURIGNY, G. (1990). *Antiviral Chem. Chemother.* Submitted.

ALTONA, C. & SUNDARALINGAM, M. (1972). *J. Am. Chem. Soc.* **94**, 8205–8212.

BIRNBAUM, G. I., DESLAURIERS, G. I., LIN, T.-S., SHIAU, G. T. & PRUSOFF, W. H. (1980). *J. Am. Chem. Soc.* **102**, 4236–4241.

BOOTHAM, D. A., BRIGGLE, T. A. & GREER, S. (1987). *Cancer Res.* **47**, 2344–2353.

CAMIENER, G. W. & SMITH, C. G. (1965). *Biochem. Pharmacol.* **14**, 1405–1416.

DECLERCQ, E. (1982). *Trends Pharmacol. Sci.* **3**, 492–501.

DOLLINGER, M. R., BURCHENAL, J. H., KREIS, W. & FOX, J. J. (1967). *Biochem. Pharmacol.* **16**, 689–706.

EL-KABBANI, O. A. L., EKIEL, I., DELBAERE, L. T. J., TOURIGNY, G., STUART, A. L. & GUPTA, V. S. (1986). *Nucleosides Nucleotides*, **5**, 95–112.

FOX, J. J., MILLER, N. & WEMPEN, I. (1966). *J. Med. Chem.* **9**, 101–105.

FOX, L., DOBERSEN, M. J. & GREER, S. (1983). *Antimicrob. Agents Chemother.* **23**, 465–476.

GUPTA, V. S., TOURIGNY, G., ADUMA, P. J. & STUART, A. L. (1989). US Patent Application No. 448,944; Candian Patent Application No. 615,352.

GUPTA, V. S., TOURIGNY, G., STUART, A. L., DECLERCQ, E., QUAIL, J. W., EKIEL, I., EL-KABBANI, O. A. L. & DELBAERE, L. T. J. (1987). *Antiviral Res.* **7**, 69–77.

HALL, S. R. & STEWART, J. M. (1988). Editors. *XTAL2.4. Users Manual.* Univs. of Western Australia, Australia, and Maryland, USA.

International Tables for X-ray Crystallography (1974). Vol. IV. Birmingham: Kynoch Press. (Present distributor Kluwer Academic Publishers, Dordrecht.)

JIA, Z., TOURIGNY, G., STUART, A. L., DELBAERE, L. T. J. & GUPTA, V. S. (1990). *Can. J. Chem.* **68**, 836–841.

JOHNSON, C. K. (1976). *ORTEP*II. Report ORNL-5138. Oak Ridge National Laboratory, Tennessee, USA.

KASHINO, S., NEGISHI, K. & HAYATSE, H. (1988). *Acta Cryst.* C**44**, 1454–1457.

MANCINI, W. R. & LIN, T. S. (1983). *Biochem. Pharmacol.* **32**, 2427–2432.

MEKRAS, J. A., BOOTHAM, D. A., PEREZ, L. M. & GREER, S. (1984). *Cancer Res.* **44**, 2551–2560.

MITSUYA, H. & BRODER, S. (1986). *Proc. Natl Acad. Sci. USA*, **83**, 1911–1915.

PALLAVICINI, M. G. (1984). *Pharmacol. Ther.* **25**, 207–235.

QUAIL, J. W., EKIEL, I., EL-KABBANI, O. A. L., TOURIGNY, G., DELBAERE, L. T. J., STUART, A. L. & GUPTA, V. S. (1986). *Can. J. Chem.* **64**, 1355–1359.

QUAIL, J. W., TOURIGNY, G., DELBAERE, L. T. J., EL-KABBANI, O. A. L., STUART, A. L. & GUPTA, V. S. (1988). *Acta Cryst.* C**44**, 150–154.

SCHILDKRAUT, I., COOPER, G. M. & GREER, S. (1975). *Mol. Pharmacol.* **11**, 153–158.

TAKAHASHI, M., NISHIZAWA, M., NEGISHI, K., HANAOKA, F., YAMADA, M. & HAYATSU, H. (1988). *Cell Mol. Biol.* **8**, 347–352.

TOURIGNY, G., STUART, A. L., EKIEL, I., ADUMA, P. J. & GUPTA, V. S. (1989). *Nucleosides Nucleotides*, **8**, 1189–1200.

WANG, M. C., SHARMA, R. A. & BLOCH, A. (1973). *Cancer Res.* 33, 1265–1271.

Acta Cryst. (1990). C**46**, 2185–2189

Structure of *N-tert*-Butoxycarbonyl-D-prolyl-L-prolyl-D-proline Methyl Ester, a Triproline Derivative with Alternating Configurations

BY FEDERICO GIORDANO*

Dipartimento di Chimica, Università di Napoli, Via Mezzocannone n. 4, 80134 *Napoli, Italy*

PASQUALE DE SANTIS

Dipartimento di Chimica, Università di Roma, 'La Sapienza', 00185 *Roma, Italy*

AND ABELARDO M. SILVA

Departamento de Fisica, Facultad de Ciencias Exactas, Universidad Nacional de la Plata, cc no. 67, 1900 *La Plata, Argentina*

(*Received* 9 *November* 1989; *accepted* 2 *February* 1990)

Abstract. $C_{21}H_{33}N_3O_6$, $M_r = 423{\cdot}5$, orthorhombic, $P2_12_12_1$, $a = 12{\cdot}610\ (1)$, $b = 15{\cdot}773\ (3)$, $c = 11{\cdot}670\ (1)$ Å, $V = 2321{\cdot}1\ (9)$ Å^3, $Z = 4$, $D_x = 1{\cdot}21$ g cm^{-3}, λ(Cu $K\alpha$) = 1·5418 Å, $\mu = 6{\cdot}97$ cm^{-1}, $F(000) = 912$, room temperature, final $R = 0{\cdot}050$ for 1770 independent reflections and 271 parameters.

* Author to whom correspondence should be addressed.

0108-2701/90/112185-05$03.00