distances and angles have normal values. The thiocin ring has a boat conformation (Fig. 1). The length of the $C(sp^3)$–S bond, 1·833 (8) Å, is in agreement with corresponding values [1·836 (10), 1·819 (14), 1·803 (10) and 1·785 (10) Å] reported for *N*-methyl-1,4-dithiane-2,3-dicarboximide (Dobrowolska & Bukowska-Strzyżewska, 1980). The $C(sp^2)$–S bond, 1·779 (7) Å, is a typical single bond [$C(sp^2)$–S = 1·77 Å (Argay, Kálmán, Nahlovski & Ribár, 1975)]. The angle $C(sp^2)$–S–$C(sp^3)$, 103·6 (4)°, agrees well with the corresponding value of 103·0 (6)° reported by Argay, Kálmán, Kapor & Ribár (1980).

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X-ray Structure and Absolute Configuration of (–)-(2*S*,4*R*)-4-Methylcyclophosphamide {2-[Bis(2-chloroethyl)amino]-4-methyltetrahydro-2*H*-1,3,2-oxazaphosphorine 2-Oxide}

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Abstract. $C_8H_{17}Cl_2N_2O_2P$, M_r = 275·2, orthorhombic, $P2_12_12_1$, a = 8·084 (3), b = 9·021 (3), c = 18·024 (6) Å, V = 1314·4 Å^3, Z = 4, d_o = 1·40, d_c = 1·390 Mg m^{-3}, $[\alpha]_D^{25°C}$ = –8·3 (concentration = 3·0 g dm^{-3}, methanol), m.p. = 329–330 K. The structure has been solved by direct methods and refined by full-matrix least squares to R = 0·068 for 899 of the 1123 reflections collected. The 1,3,2-oxazaphosphorinane ring is in a conformation intermediate between sofa and half-chair with the P end flattened and with the 4-methyl and *N*,*N*-bis(2-chloroethyl) groups in equatorial positions. The molecules form chains along the [100] direction by means of $\geq$P=O···HN hydrogen bonds with an O···N distance of 2·860 (6) Å.

Introduction. Cyclophosphamide (CPA) is a widely used antitumour drug. The compound has virtually no cytotoxic activity against mammalian cell cultures (Arnold, Bourseaux & Brock, 1958) and only the products of its oxidation at C(4) are presumed to be responsible for the activation of CPA (Hill, Laster & Struck, 1972). 4-Methylcyclophosphamide is of interest since the methyl group prevents further oxidation, so the substitution must affect the biological activity. Besides, since biological systems normally exhibit a marked enantiomeric selectivity, it was expected, and found, that the optical isomers of CPA (Cox, Farmer, Jarman, Jones, Stec & Kinas, 1976) and 4-methyl-CPA (Kinas, Pankiewicz, Stec, Farmer, Foster & Jarman, 1977) have different therapeutic effects.

Up to the present time the crystal structures of racemic CPA monohydrate (García-Blanco & Perales, 1972; Clardy, Mosbo & Verkade, 1974), 4-hydroperoxy-CPA (Camerman, Smith & Camerman, 1977), 4-peroxy-CPA (Sternglanz, Einspahr & Bugg, 1974), 4-keto-CPA (Camerman & Camerman, 1973) and enantiomeric CPA (Karle, Karle, Egan, Zon & Brandt, 1977; Adamiak, Saenger, Kinas & Stec, 1977) have been determined. Preliminary communications concerning the crystal data for two (Gałdecki & Główka, 1979) and configurations proposed on the basis of chemical data for all four enantiomeric 4-methylcyclophosphamides (Kinas *et al.*, 1977) have been published. This study was undertaken to widen the experimental basis for discussing the relationship between structure (especially configuration) and biological activity of enantiomeric 4-methyl-CPA.

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Table 1. *Positional parameters* (×10⁴) *and isotropic temperature factors for non-hydrogen atoms*

$B_{iso} = \frac{8}{3}\pi^2 \sum_i \sum_j U_{ij} a_i^* a_j^* \mathbf{a}_i . \mathbf{a}_j$.

	x	*y*	*z*	B_{iso} (Å²)
Cl(1)	5728 (3)	−2400 (2)	1745 (1)	6·6 (1)
Cl(2)	25 (3)	−827 (2)	1028 (1)	5·8 (1)
P	5113 (2)	971 (2)	25 (1)	3·11 (7)
O(1)	6448 (5)	−119 (5)	−317 (3)	4·3 (2)
O(2)	5850 (5)	2202 (5)	446 (2)	3·9 (2)
N(1)	3972 (6)	−47 (6)	580 (3)	3·0 (2)
N(3)	3960 (6)	1369 (6)	−692 (3)	3·2 (2)
C(1)	4075 (9)	169 (8)	1387 (4)	3·7 (3)
C(2)	5634 (9)	−421 (8)	1722 (4)	5·0 (4)
C(3)	3246 (12)	1667 (11)	−1977 (4)	7·4 (5)
C(4)	4657 (9)	1653 (8)	−1434 (4)	4·3 (3)
C(5)	5962 (11)	450 (9)	−1603 (4)	5·7 (4)
C(6)	7215 (10)	318 (9)	−1015 (5)	5·6 (4)
C(7)	2969 (8)	−1235 (8)	275 (3)	3·3 (3)
C(8)	1171 (9)	−862 (8)	168 (4)	4·2 (3)

Colourless, transparent crystals of the compound were kindly furnished by Dr R. Kinas of the Centre of Molecular and Macromolecular Studies, Polish Academy of Sciences, Łódź. 1123 independent reflections were collected on a CAD-4 diffractometer from a spherical crystal; 899 reflections with $F_o \geq 3\sigma F_o$ were assumed to be observed. The phases of 200 $E \geq 1{\cdot}4$ were determined using *MULTAN* (Main, Lessinger, Woolfson, Germain & Declercq, 1978). The best solution gave the positions of 13 atoms and a further Fourier synthesis showed the whole molecule (R = 28%). The model structure was refined by full-matrix least squares using the *ORFLS* and *CRYLSQ* programs of XRAY 70 (Stewart, Kundell & Baldwin, 1970). Four cycles of refinement with isotropic and then two cycles with anisotropic thermal parameters resulted in an R of 0·098. The final agreement factors were 0·068 (R) and 0·080 (R_w) after four cycles of refinement with H atoms included (but not refined). The H atom positions were calculated geometrically with *XANADU*. The scattering factors for P, O and C were those from Doyle & Turner (1968) and those for H were from *International Tables for X-ray Crystallography* (1962). The calculations were performed on RIAD 32 and ODRA 1305 (*MULTAN* only) computers. Atomic parameters are given in Table 1.*

Discussion. The packing of molecules and numbering of atoms are shown in Fig. 1; Table 2 lists the bond lengths and angles. The vast majority of these data represent values very close to those commonly observed in similar structures and therefore do not need to be discussed in detail. The molecules are connected into chains along the [100] direction by intermolecular hydrogen bonds between the N(3) H atom and the phosphoryl O atom with an O(2)···N(3) distance of 2·860 (6) Å [the O(2)···H distance, 1·99 Å, is uncertain because of the geometric calculation of the H atom position with the assumption of planar character for the N(3) atom].

The ring exists in a conformation intermediate between sofa and half-chair characterized by asymmetry parameters (Duax & Norton, 1975): ΔC_S^3 = 4·7 (7), $\Delta C_2^{2,3}$ = 5·9 (7), $\Delta C_2^{1,2}$ = 18·5 (7), $\tilde{\varphi}$ = 53·1 (7)°. The ring is flattened at the P end with dihedral angles of 127·6 (7) and 143·2 (6)° between the plane defined by four central atoms and that defined by C(4), C(5), C(6) and O(1), P, N(3), respectively. The N(1) atom shows a trigonal-planar

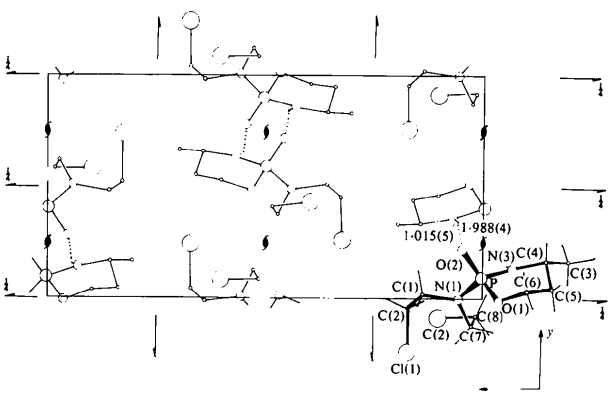

Fig. 1. Packing of molecules and the atom-numbering scheme, showing the hydrogen bonds (Å).

Table 2. *Bond lengths* (Å) *and angles* (°) *with their e.s.d.'s in parentheses*

Cl(1)–C(2)	1·787 (8)	O(1)–P–O(2)	113·1 (3)
Cl(2)–C(8)	1·807 (7)	O(1)–P–N(1)	105·8 (3)
P–O(1)	1·584 (5)	O(1)–P–N(3)	102·6 (3)
P–O(2)	1·472 (5)	O(2)–P–N(1)	109·6 (3)
P–N(1)	1·641 (5)	O(2)–P–N(3)	118·2 (3)
P–N(3)	1·632 (5)	N(1)–P–N(3)	106·5 (3)
O(1)–C(6)	1·458 (10)	P–O(1)–C(6)	117·3 (5)
N(1)–C(1)	1·471 (8)	P–N(1)–C(1)	119·8 (4)
N(1)–C(7)	1·451 (9)	P–N(1)–C(7)	119·8 (4)
N(3)–C(4)	1·474 (8)	C(1)–N(1)–C(7)	120·2 (5)
C(1)–C(2)	1·495 (10)	P–N(3)–C(4)	122·6 (4)
C(3)–C(4)	1·503 (11)	N(1)–C(1)–C(2)	113·6 (6)
C(4)–C(5)	1·544 (11)	Cl(1)–C(2)–C(1)	113·6 (5)
C(5)–C(6)	1·470 (12)	N(3)–C(4)–C(3)	107·6 (6)
C(7)–C(8)	1·504 (10)	N(3)–C(4)–C(5)	108·5 (6)
O(2)···N(3)	2·860 (6)	C(3)–C(4)–C(5)	113·3 (6)
O(2)···H[N(3)]	1·988 (2)	C(4)–C(5)–C(6)	112·7 (6)
		O(1)–C(6)–C(5)	110·5 (6)
		N(1)–C(7)–C(8)	115·1 (6)
		Cl(2)–C(8)–C(7)	112·9 (5)

* Lists of structure factors, anisotropic thermal parameters and H atom parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 35783 (10 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

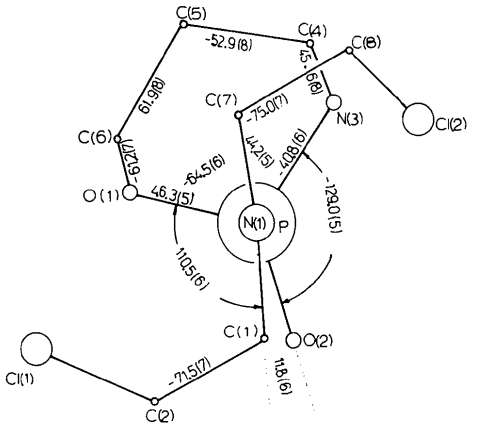

Fig. 2. Torsion angles (°).

character with the sum of its valency angles equal to 359·8°. Similar values have been reported for other cyclophosphamides, apart from (+)-CPA (Karle *et al.*, 1977) and 4-hydroperoxy-CPA (Camerman, Smith & Camerman, 1977) in which angles of 355 and 357° were found. The 2-chloroethyl chains are not significantly extended as the Cl(1)···Cl(2) distance is only 4·994 (5) Å, similar to those found in other 4-substituted cyclophosphamides, *e.g.* 5·10 Å for 4-keto-CPA (Camerman & Camerman, 1973) and 4·91 Å for 4-hydroperoxy-CPA (Camerman, Smith & Camerman, 1977), whereas distances of 6·75, 6·77 and 6·81 Å were observed in (+)-CPA, 3-(2-chloroethyl)-CPA and (±)-CPA respectively. The plane defined by N(1), C(1) and C(7) is nearly perpendicular to the 1,3,2-oxazaphosphorinane ring (Fig. 2) with the O(2)–P–N(1)–C(1) torsion angle at only 11·8 (6)°.

The absolute configuration of the molecule has been determined by refinement of the crystal structure parameters with regard to anomalous-dispersion corrections (Cromer & Liberman, 1970) for the Cl, P and O atoms. The final R and R_w values for molecules of opposite configuration were 0·079 and 0·086, respectively. The significance test on the R factor (Hamilton, 1965) shows the probability of error in the determination of the absolute configuration to be less than 0·5%:

$$\mathscr{R}_{1,987,0\cdot005} = 1\cdot004; \frac{R_1}{R_2} = 1\cdot162 \left(\frac{R_{w1}}{R_{w2}} = 1\cdot075\right).$$

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