distances correspond to normal van der Waals interactions.

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Structure of Racemic *cis*-4-Phenylcyclophosphamide*

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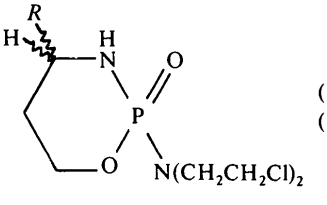
Abstract. $C_{13}H_{19}Cl_2N_2O_2P$, $M_r = 337{\cdot}2$, monoclinic, $P2_1/c$, $a = 8{\cdot}000\,(1)$, $b = 10{\cdot}279\,(2)$, $c = 20{\cdot}003\,(4)$ Å, $\beta = 102{\cdot}12\,(1)°$, $Z = 4$, $D_m = 1{\cdot}39\,(2)$ (flotation), $D_x = 1{\cdot}393$ Mg m^{-3}, μ(Mo $K\alpha$) $= 0{\cdot}507$ mm^{-1}. The final R value after full-matrix least-squares refinement was 0·037 for 1206 observed reflections. The molecule was found to exist in a chair conformation with the phenyl substituent and the phosphoryl O atom in equatorial positions. The crystal structure consists of centrosymmetric dimers linked by hydrogen bonds between N—H and O=P.

Introduction. Cyclophosphamide (1) is a well-known drug which exhibits antineoplastic activity against a broad spectrum of human cancers. Consequently, the metabolism, mechanism of action, and the influence of structural modification upon the therapeutic activity of (1) are of considerable interest. The relationship between biological activity and molecular configuration and conformation has prompted X-ray structure analyses of (1) as well as of numerous metabolites and analogs of (1). Recently, the synthesis, anti-cancer screening, NMR data and other chemical information for 4-phenylcyclophosphamide (2) were reported by Boyd, Zon, Himes, Stalick, Mighell & Secor (1980). Two racemic geometrical isomers of (2) were synthesized and chromatographically separated into the faster and slower-eluting racemates. We report here the single-crystal X-ray diffraction analysis of the faster-eluting racemate of (2) which was recrystallized from a mixture of chloroform and diethyl ether.



(1), R = H
(2), R = Ph

Data were collected on a clear, hexagonally shaped crystal of dimensions 0·10 × 0·13 × 0·15 mm using an automated four-circle diffractometer with graphite-monochromated Mo $K\alpha$ radiation, $\lambda = 0{\cdot}71069$ Å. Cell dimensions were determined by a least-squares refinement of the setting angles of 15 reflections with 2θ

* (2*RS*,4*SR*)-2-[Bis(2-chloroethyl)amino]-4-phenyl-2*H*-1,3,2-oxazaphosphorinane 2-oxide.

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values ranging between 20 and 27°. Systematic extinctions observed on the diffractometer established the space group as $P2_1/c$. Integrated diffraction intensities were measured in the bisecting mode with $2\theta_{max} = 40°$. The peaks were scanned over a range of $2\theta(K\alpha_1) - 1{\cdot}0°$ to $2\theta(K\alpha_2) + 1{\cdot}4°$ using variable scan rates of 2·0 to 29·3° min^{-1} depending on the intensity of the preliminary count. Background counts were taken at each end of the scan with a ratio of total background time to scan time of 0·5. Four standard reflections which were measured periodically showed no apparent decrease in intensity during data collection. The e.s.d. in intensity, $\sigma(I)$, was calculated from $\sigma^2(I) = TC + 0{\cdot}000288TC^2$ where TC is the total observed counts and the constant was derived from a statistical analysis of the intensity distributions of the four standard reflections. The data were corrected for Lorentz and polarization effects. In view of the crystal size and linear absorption coefficient, no absorption correction was made. Of the 1517 unique reflections measured, 1206 had $I \geq 3\sigma(I)$ and were subsequently used for structure determination and refinement.

The structure was solved by direct methods using *MULTAN* (Germain, Main & Woolfson, 1971) and was refined by full-matrix least-squares calculations. All H atoms were located in a difference Fourier map calculated at an intermediate stage of refinement. In subsequent cycles of refinement, each H atom was assigned a fixed thermal parameter. The positional parameters of the H atom bonded to the ring N atom were allowed to shift; all other H atoms were placed in calculated positions with C—H = 1·00 Å. Anisotropic refinement of the model resulted in a final R $(=\sum ||F_o| - |F_c||/\sum |F_o|)$ of 0·037 and R_w $(=\sum w^{1/2}||F_o| - |F_c||/\sum w^{1/2}|F_o|)$ of 0·030. The function minimized was $\sum w(|F_o| - |F_c|)^2$ where $w = [\sigma(F_o)]^{-2}$. The average shift divided by error was 0·051, while the maximum, 0·794, occurred in a position for H(N3). With the exception of one peak (≃0·5 e Å^{-3}) located 1·4 Å from both N(7) and C(8) and 1·2 Å from C(9), an analysis of the final difference map revealed no peak greater than 0·3 e Å^{-3}. The scattering factors used were those of Cromer & Mann (1968) for C, N, O, P, Cl and that of Stewart, Davidson & Simpson (1965) for H. Dispersion corrections for P and Cl were taken from *International Tables for X-ray Crystallography* (1974). All calculations (except *MULTAN*) were performed with the XRAY system (Stewart, Machin, Dickinson, Ammon, Heck & Flack, 1976). Table 1* lists the final atomic parameters.

Table 1. *Positional parameters and isotropic thermal parameters* (Å^2) *with e.s.d.'s in parentheses*

Equivalent isotropic temperature factors for the non-H atoms were calculated from $U_{eq} = \frac{1}{3}(U_{11} + U_{22} + U_{33})$.

	x	y	z	U
Cl(1)	0·6662 (2)	0·36785 (12)	1·06061 (7)	0·0684 (9)
Cl(2)	−0·1539 (2)	0·44201 (14)	0·89423 (7)	0·0788 (10)
P(2)	0·21342 (13)	0·03486 (10)	0·95790 (6)	0·0352 (7)
O(1)	0·3622 (3)	−0·0206 (2)	0·92592 (13)	0·040 (2)
O(2)	0·2252 (3)	−0·0228 (3)	1·02604 (13)	0·042 (2)
N(3)	0·0425 (4)	0·0003 (3)	0·9015 (2)	0·039 (2)
N(7)	0·2335 (4)	0·1935 (3)	0·9613 (2)	0·044 (2)
C(4)	0·0302 (5)	−0·0076 (4)	0·8275 (2)	0·041 (3)
C(5)	0·1926 (6)	−0·0715 (5)	0·8134 (2)	0·057 (3)
C(6)	0·3517 (5)	−0·0055 (4)	0·8535 (2)	0·060 (3)
C(8)	0·3654 (6)	0·2544 (5)	1·0190 (3)	0·061 (3)
C(9)	0·5161 (7)	0·2880 (4)	0·9923 (3)	0·068 (4)
C(10)	0·1221 (6)	0·2875 (4)	0·9179 (2)	0·056 (3)
C(11)	−0·0246 (6)	0·3221 (5)	0·9483 (3)	0·066 (4)
C(1′)	−0·1318 (5)	−0·0769 (4)	0·7942 (2)	0·041 (3)
C(2′)	−0·2423 (6)	−0·0237 (5)	0·7396 (2)	0·054 (3)
C(3′)	−0·3929 (7)	−0·0861 (6)	0·7094 (2)	0·060 (4)
C(4′)	−0·4327 (6)	−0·2032 (6)	0·7341 (3)	0·066 (4)
C(5′)	−0·3224 (8)	−0·2585 (5)	0·7886 (3)	0·069 (4)
C(6′)	−0·1743 (6)	−0·1944 (5)	0·8187 (2)	0·056 (4)
H(N3)	−0·040 (4)	0·007 (4)	0·913 (2)	0·039
H(4)	0·019	0·082	0·808	0·046
H(51)	0·195	−0·165	0·827	0·063
H(52)	0·192	−0·065	0·764	0·063
H(61)	0·455	−0·046	0·841	0·066
H(62)	0·348	0·089	0·842	0·066
H(81)	0·316	0·335	1·036	0·068
H(82)	0·396	0·191	1·058	0·068
H(91)	0·569	0·207	0·978	0·075
H(92)	0·484	0·348	0·952	0·075
H(101)	0·189	0·368	0·913	0·062
H(102)	0·079	0·249	0·872	0·062
H(111)	−0·094	0·243	0·951	0·072
H(112)	0·018	0·359	0·995	0·072
H(2′)	−0·213	0·062	0·721	0·060
H(3′)	−0·473	−0·045	0·670	0·066
H(4′)	−0·541	−0·248	0·713	0·073
H(5′)	−0·349	−0·345	0·806	0·076
H(6′)	−0·097	−0·234	0·859	0·062

Discussion. The molecular conformation of (2) and atom labeling are shown in Fig. 1. There are two asymmetric centers in (2), one at P(2) and the other at

* Lists of structure factors and anisotropic thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 36465 (20 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

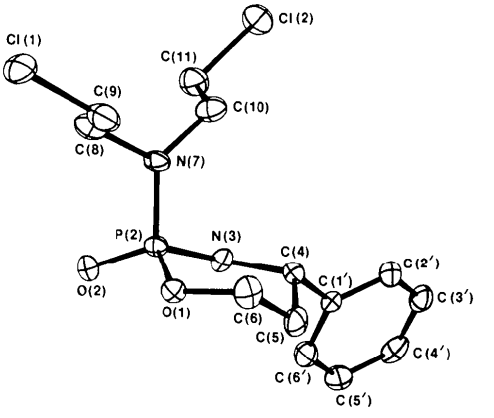

Fig. 1. Conformation of racemic *cis*-4-phenylcyclophosphamide. Thermal ellipsoids are drawn at a 25% probability level (*ORTEP*, Johnson, 1965).

C(4); the molecule in Fig. 1 is in the 2*R*,4*S* conformation. Bond distances and angles are given in Table 2 and dihedral angles in Table 3.

The structure analysis reveals that (2) has a chair conformation with a *cis* relationship between the equatorial phenyl substituent and the phosphoryl moiety. The phosphorus end of the chair is somewhat flattened as P(2) and C(5) are 0·485 (2) and 0·678 (4) Å respectively from the basal plane through O(1), N(3), C(4), C(6) (average deviation = 0·059 Å). The plane of the phenyl substituent forms an angle of 62·2° with the basal plane.

A least-squares plane calculated through P(2), N(7), C(8) and C(10) [deviations = 0·014 (2), −0·041 (5), 0·013 (4) and 0·015 (4) Å respectively] reveals the nearly planar geometry about N(7). This plane makes an angle of 89·7° with the basal plane, and is oriented in the direction of the P(2)—N(3) bond [dihedral angles N(3)—P(2)—N(7)—C(10) = −3·4 (4) and N(3)—P(2)—N(7)—C(8) = 169·1 (3)°]. The two chloroethyl groups are *anti* to one another as C(9) and C(11) are on opposite sides of the P(2), N(7), C(8), C(10) plane.

Although the P=O moiety is equatorial in (2) and axial in a series of related compounds, the corresponding bond lengths in the phosphamide groups [*e.g.* P(2)—O(1), P(2)—O(2), P(2)—N(3) and P(2)—N(7)] are remarkably similar [*R*(+)-cyclophosphamide (Karle, Karle, Egan, Zon & Brandt, 1977); *S*(−)-cyclophosphamide (Adamiak, Saenger, Kinas & Stec, 1977); cyclophosphamide hydrate (García-Blanco & Perales, 1972; Clardy, Mosbo & Verkade, 1974); (−)-(2*S*,4*R*)-4-methylcyclophosphamide (Gałdecki & Główka, 1981); 4-ketocyclophosphamide (Camerman & Camerman, 1973); trofosfamide (Perales & García-Blanco, 1977*b*; Smith, Camerman & Camerman, 1981); ifosfamide (Perales & García-Blanco, 1977*a*)]. In contrast, a comparison of the $-NCH_2CH_2Cl$ moieties within the same series of materials shows considerable diversity among the lengths of comparable bonds. Unusual distances in this group are often observed and various reasons have been cited to account for them. In the case of (2), the relatively long N(7)—C(8) and short C(8)—C(9) bond distances and the presence of a peak (≃0·5 e Å^{-3}) in the vicinity of C(8) in the difference map indicate a small amount of disorder within the chloroethyl chain. The two C—Cl bond distances are slightly longer than expected for paraffinic C—Cl bonds (1·77 Å), which suggests partial polarization of the C—Cl bonds in the bis(2-chloroethyl)amino moiety of (2).

In the crystal structure, molecules of (2) form centrosymmetric dimers (Fig. 2) with N(3)—H(N3) and N(3)···O(2) distances of 0·75 (4) and 2·837 (4) Å respectively, and an N(3)—H(N3)···O(2) angle of 164 (4)°. The N···O distance compares closely with that found in rhombohedral (+)-cyclophosphamide in which three symmetry-related molecules form a hydrogen-bonded trimer with the N···O distance equal to 2·84 Å.

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

Cl(1)—C(9)	1·815 (5)	C(4)—C(1′)	1·507 (6)
Cl(2)—C(11)	1·814 (5)	C(5)—C(6)	1·515 (6)
P(2)—O(1)	1·572 (3)	C(8)—C(9)	1·459 (8)
P(2)—O(2)	1·471 (3)	C(10)—C(11)	1·474 (8)
P(2)—N(3)	1·620 (3)	C(1′)—C(2′)	1·366 (6)
P(2)—N(7)	1·638 (3)	C(1′)—C(6′)	1·373 (7)
O(1)—C(6)	1·443 (6)	C(2′)—C(3′)	1·386 (7)
N(3)—C(4)	1·465 (5)	C(3′)—C(4′)	1·363 (9)
N(7)—C(8)	1·525 (6)	C(4′)—C(5′)	1·375 (8)
N(7)—C(10)	1·469 (5)	C(5′)—C(6′)	1·379 (7)
C(4)—C(5)	1·533 (7)		
O(1)—P(2)—O(2)	108·91 (15)	C(4)—C(5)—C(6)	111·2 (4)
O(1)—P(2)—N(3)	103·7 (2)	O(1)—C(6)—C(5)	110·4 (4)
O(1)—P(2)—N(7)	107·5 (2)	N(7)—C(8)—C(9)	108·3 (4)
O(2)—P(2)—N(3)	116·0 (2)	Cl(1)—C(9)—C(8)	107·3 (4)
O(2)—P(2)—N(7)	112·1 (2)	N(7)—C(10)—C(11)	110·6 (4)
N(3)—P(2)—N(7)	107·9 (2)	Cl(2)—C(11)—C(10)	108·8 (4)
P(2)—O(1)—C(6)	118·7 (2)	C(4)—C(1′)—C(2′)	121·0 (4)
P(2)—N(3)—C(4)	125·7 (3)	C(4)—C(1′)—C(6′)	120·9 (4)
P(2)—N(7)—C(8)	119·1 (3)	C(2′)—C(1′)—C(6′)	118·1 (4)
P(2)—N(7)—C(10)	126·1 (3)	C(1′)—C(2′)—C(3′)	121·3 (5)
C(8)—N(7)—C(10)	114·5 (3)	C(2′)—C(3′)—C(4′)	119·9 (4)
N(3)—C(4)—C(5)	109·2 (3)	C(3′)—C(4′)—C(5′)	119·5 (5)
N(3)—C(4)—C(1′)	109·9 (4)	C(4′)—C(5′)—C(6′)	119·9 (5)
C(5)—C(4)—C(1′)	113·6 (4)	C(1′)—C(6′)—C(5′)	121·2 (4)

Table 3. *Dihedral angles* (°) *with e.s.d.'s in parentheses*

O(2)—P(2)—O(1)—C(6)	164·0 (3)	C(8)—N(7)—C(10)—C(11)	−85·1 (5)
N(3)—P(2)—O(1)—C(6)	39·9 (3)	N(3)—C(4)—C(5)—C(6)	−51·5 (5)
N(7)—P(2)—O(1)—C(6)	−74·3 (3)	C(1′)—C(4)—C(5)—C(6)	−174·6 (4)
O(1)—P(2)—N(3)—C(4)	−31·2 (4)	N(3)—C(4)—C(1′)—C(2′)	128·8 (5)
O(2)—P(2)—N(3)—C(4)	−150·6 (3)	N(3)—C(4)—C(1′)—C(6′)	−50·0 (6)
N(7)—P(2)—N(3)—C(4)	82·7 (4)	C(5)—C(4)—C(1′)—C(2′)	−108·5 (5)
O(1)—P(2)—N(7)—C(8)	−79·5 (4)	C(5)—C(4)—C(1′)—C(6′)	72·7 (6)
O(1)—P(2)—N(7)—C(10)	108·0 (4)	C(4)—C(5)—C(6)—O(1)	63·4 (4)
O(2)—P(2)—N(7)—C(8)	40·2 (4)	N(7)—C(8)—C(9)—Cl(1)	177·1 (3)
O(2)—P(2)—N(7)—C(10)	−132·3 (4)	N(7)—C(10)—C(11)—Cl(2)	178·2 (3)
N(3)—P(2)—N(7)—C(8)	169·1 (3)	C(4)—C(1′)—C(2′)—C(3′)	−179·0 (5)
N(3)—P(2)—N(7)—C(10)	−3·4 (4)	C(6′)—C(1′)—C(2′)—C(3′)	−0·2 (6)
P(2)—O(1)—C(6)—C(5)	−59·8 (4)	C(4)—C(1′)—C(6′)—C(5′)	180·0 (5)
P(2)—N(3)—C(4)—C(5)	39·2 (5)	C(2′)—C(1′)—C(6′)—C(5′)	1·2 (8)
P(2)—N(3)—C(4)—C(1′)	164·4 (3)	C(1′)—C(2′)—C(3′)—C(4′)	−0·3 (8)
P(2)—N(7)—C(8)—C(9)	100·4 (4)	C(2′)—C(3′)—C(4′)—C(5′)	−0·2 (8)
C(10)—N(7)—C(8)—C(9)	−86·3 (5)	C(3′)—C(4′)—C(5′)—C(6′)	1·2 (9)
P(2)—N(7)—C(10)—C(11)	87·7 (5)	C(4′)—C(5′)—C(6′)—C(1′)	−1·7 (9)

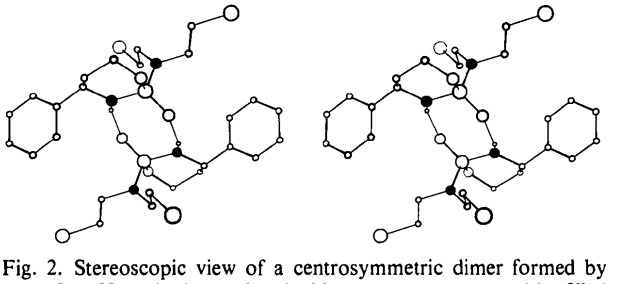

Fig. 2. Stereoscopic view of a centrosymmetric dimer formed by P=O···H—N hydrogen bonds. N atoms are represented by filled circles.

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2,3-Dimethoxybenzoic Acid. A Redetermination

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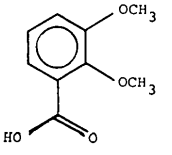
Abstract. $C_9H_{10}O_4$, monoclinic, $P2_1/n$, $a = 15{\cdot}538$ (5), $b = 6{\cdot}922$ (3), $c = 8{\cdot}196$ (3) Å, $\beta = 97{\cdot}96$ (2)° ($\lambda = 1{\cdot}5418$ Å), $U = 873{\cdot}0$ Å^3, $M_r = 182{\cdot}17$, $Z = 4$, $D_x = 1{\cdot}386$, $D_m = 1{\cdot}387$ (4) g cm^{-3} (flotation in aqueous KI), $F(000) = 384$, μ(Cu $K\alpha$) = 9·4 cm^{-1}. The structure was solved, independently of earlier work, by the multisolution tangent-formula method. Refinement by least squares gave $R = 0{\cdot}030$ for 1034 independent significant reflections. The molecules are present in the crystal as non-planar centrosymmetric hydrogen-bonded dimers [O—H···O 2·631 (2) Å]. The plane of the carboxy group is inclined at 36·3° to that of the phenyl ring. The plane of the 3-methoxy group makes an angle of 2·3° with that of the phenyl ring, but the plane of the 2-methoxy group is inclined to the phenyl plane at an angle of 74·2°, with O(1) on the same side of the ring as C(8).

Introduction. Swaminathan, Sarangapani & Lessinger (1977) (SSL) have reported the structure of the title compound (I) as determined from visually estimated photographic intensity data. We are interested in accurate information on packing modes of alkoxy-substituted benzoic acids (Bryan & Hartley, 1980) and felt it worthwhile to redetermine this structure using more accurate diffractometer intensity data.



(I)

A suitable crystal was obtained by recrystallization of a commercial sample of the acid (Aldrich Chemical Co.) from 95% ethanol. The unit-cell dimensions were derived from a least-squares fit to the observed diffractometer values of $\pm 2\theta$ for 24 strong general reflections. Systematic absences in $h0l$ with $h + l$ odd, and in $0k0$ with k odd uniquely define the space group as $P2_1/n$, a non-standard setting of $P2_1/c$, the space group identified by SSL. The cell given by SSL is

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