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Structure of 2-Chloro-6-(*p*-chlorophenyl)-3-(*p*-tolyl)-3,4-dihydro-1,3,2-oxazaphosphorine 2-Oxide, C₁₆H₁₄Cl₂NO₂P*

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Abstract. $M_r = 354.2$, monoclinic, $P2_1/a$, $a = 10.141$ (3), $b = 15.113$ (3), $c = 10.891$ (3) Å, $\beta = 93.22$ (2)°, $V = 1666.4$ Å³, $Z = 4$, D_m (floatation) = 1.41, $D_x = 1.42$ g cm⁻³, $\lambda(\text{Mo } K\alpha) = 0.7107$ Å, $\mu(\text{Mo } K\alpha) = 1.51$ cm⁻¹, $F(000) = 728.0$, $T = 293$ K. $R = 0.067$ for 1334 reflections. The 1,3,2-oxazaphosphorine ring takes a half-chair conformation. The exocyclic chlorine and oxygen connected to phosphorus are in axial and equatorial positions respectively. The P–O distance of 1.468 (6) Å agrees with values found in other cyclophosphamide, isophosphamide and trophosphamide compounds.

Introduction. The perhydro-1,3,2-oxazaphosphorine cyclophosphamide and its analogues isophosphamide and trophosphamide are clinically useful anticancer drugs. Several recent studies have shown that the perhydro-1,3,2-oxazaphosphorine ring undergoes conformational changes due to steric and electronic influences of the substituents on phosphorus (Bajwa, Bentrude, Pantaleo, Newton & Hargis, 1979; Gorenstein & Rowell, 1979; Gorenstein, Rowell & Findlay,

1980; Maryanoff, Hutchins & Maryanoff, 1979) and of the substituents on the ring nitrogen (Chandrasekharan & Bentrude, 1980; Bajwa, Chandrasekharan, Hargis, Sopchik, Blatter & Bentrude, 1982). Carbon-substituted derivatives have also undergone extensive clinical and biological testing. We report here the influence of a ring constraint (3,4-dihydro) on the conformational flexibility of the oxazaphosphorine ring.

Experimental. The title compound was prepared following a general procedure (Sahasrabudhe, 1983). Orange, needle crystal from alcohol solution, approximate dimensions 0.45 × 0.40 × 0.55 mm; lattice parameters from 20 reflections ($12^\circ < 2\theta < 35^\circ$); intensity data collected on an Enraf-Nonius CAD-4F-11M single-crystal X-ray diffractometer, graphite-monochromated Mo $K\alpha$ radiation, $\omega/2\theta$ scan mode, scan speed 1° min^{-1} , $\theta \leq 24^\circ$; of 2914 reflections collected 1334 were judged significant ($|F_o| > 3\sigma|F_o|$); intensities not corrected for absorption; structure solution by direct methods [*MULTAN*78 (Main, Hull, Lessinger, Germain, Declercq & Woolfson, 1978)]; full-matrix refinement of scale factor, positional and anisotropic thermal parameters (isotropic thermal parameters for H atoms,

* NCL communication No. 3333.

Table 1. Positional parameters ($\times 10^4$) and B_{eq} values (\AA^2)
$$B_{eq} = \frac{4}{3} \sum_i \sum_j \beta_{ij} a_i \cdot a_j$$

	x	y	z	B_{eq}
P	2399 (2)	4250 (1)	6123 (2)	3.8 (1)
Cl(1)	-2422 (3)	2162 (2)	623 (3)	5.4 (2)
Cl(2)	1162 (3)	3928 (2)	7431 (3)	4.5 (2)
O(1)	1641 (6)	3878 (4)	4944 (5)	4.2 (3)
O(2)	2615 (7)	5209 (4)	6083 (7)	4.5 (3)
N(3)	3694 (7)	3648 (4)	6316 (7)	3.7 (2)
C(1)'	675 (8)	2788 (5)	3622 (7)	3.5 (2)
C(2)'	-154 (9)	3441 (6)	3151 (8)	3.9 (3)
C(3)'	-1093 (9)	3258 (6)	2248 (9)	3.8 (2)
C(4)'	-1207 (9)	2385 (7)	1787 (8)	3.8 (2)
C(5)'	-407 (9)	1738 (5)	2252 (9)	3.6 (2)
C(6)'	546 (9)	1930 (5)	3149 (8)	3.3 (2)
C(1)''	4823 (8)	3938 (5)	7079 (8)	2.8 (1)
C(2)''	4867 (8)	3826 (5)	8334 (8)	4.7 (3)
C(3)''	6005 (8)	4089 (4)	9038 (9)	4.8 (2)
C(4)''	7074 (8)	4461 (5)	8517 (8)	4.6 (2)
C(5)''	6979 (8)	4567 (5)	7258 (7)	4.4 (2)
C(6)''	5853 (8)	4314 (5)	6537 (7)	4.2 (2)
C(4)	3547 (9)	2659 (5)	6177 (8)	4.2 (2)
C(5)	2557 (8)	2443 (5)	5200 (7)	3.8 (2)
C(6)	1661 (8)	2966 (4)	4595 (7)	3.7 (2)
C(7)	8289 (9)	4720 (6)	9241 (7)	4.8 (2)

Table 2. Bond lengths (\AA) and angles ($^\circ$) with e.s.d.'s in parentheses

P—Cl(2)	2.010 (4)	P—O(1)	1.564 (6)
P—O(2)	1.468 (6)	P—N(3)	1.602 (7)
Cl(1)—C(4)'	1.750 (9)	O(1)—C(6)	1.429 (9)
N(3)—C(4)	1.51 (1)	N(3)—C(1)''	1.44 (1)
C(4)''—C(5)	1.35 (1)	C(4)''—C(3)''	1.41 (1)
C(5)''—C(6)''	1.37 (1)	C(6)''—C(1)''	1.40 (1)
C(1)''—C(2)''	1.38 (1)	C(1)''—C(6)	1.44 (1)
C(2)''—C(3)''	1.36 (1)	C(6)—C(5)	1.35 (1)
C(4)—C(5)	1.46 (1)	C(1)''—C(2)''	1.37 (1)
C(1)''—C(6)''	1.35 (1)	C(2)''—C(3)''	1.45 (1)
C(3)''—C(4)''	1.37 (1)	C(4)''—C(5)''	1.38 (1)
C(4)''—C(7)	1.48 (1)	C(5)''—C(6)''	1.40 (1)
O(1)—P—O(1)	113.4 (4)	O(1)—P—N(3)	105.4 (3)
O(2)—P—N(3)	116.3 (4)	P—O(1)—C(6)	123.4 (5)
P—N(3)—C(4)	118.3 (6)	P—N(3)—C(1)''	121.4 (5)
C(4)—N(3)—C(1)''	115.4 (6)	Cl(1)—C(4)''—C(5)'	121.0 (8)
Cl(1)—C(4)''—C(3)''	118.5 (7)	C(5)''—C(4)''—C(3)''	120.5 (9)
C(4)''—C(5)''—C(6)''	120.0 (9)	C(5)''—C(6)''—C(1)''	120.5 (8)
C(6)''—C(1)''—C(2)''	119.0 (7)	C(6)''—C(1)''—C(6)	119.4 (7)
C(2)''—C(1)''—C(6)	121.6 (7)	C(1)''—C(2)''—C(3)''	120.8 (8)
C(4)''—C(3)''—C(2)''	119.1 (8)	O(1)—C(6)—C(1)''	110.8 (6)
O(1)—C(6)—C(5)	117.0 (7)	C(1)''—C(6)—C(5)	132.1 (7)
N(3)—C(4)—C(5)	110.8 (7)	C(6)—C(5)—C(4)	130.0 (8)
N(3)—C(1)''—C(2)''	121.0 (7)	N(3)—C(1)''—C(6)''	118.9 (7)
C(2)''—C(1)''—C(6)''	120.2 (7)	C(1)''—C(2)''—C(3)''	119.1 (7)
C(2)''—C(3)''—C(4)''	122.2 (7)	C(3)''—C(4)''—C(5)''	116.4 (7)
C(3)''—C(4)''—C(7)	122.8 (7)	C(5)''—C(4)''—C(7)	120.7 (7)
C(4)''—C(5)''—C(6)''	122.4 (7)	C(1)''—C(6)''—C(5)''	119.6 (7)

Table 3. Some important torsion angles ($^\circ$)

N(3)—P—O(1)—C(6)	32.0 (7) $^\circ$
P—O(1)—C(6)—C(5)	-11.7 (9)
O(1)—C(6)—C(5)—C(4)	0 (1)
C(6)—C(5)—C(4)—N(3)	-12 (1)
C(5)—C(4)—N(3)—P	36.4 (9)
C(4)—N(3)—P—O(1)	-44.5 (7)
O(2)—P—N(3)—C(4)	-171.1 (6)
C(6)—O(1)—P—Cl(2)	-80.6 (6)
C(6)—O(1)—P—O(2)	160.2 (6)
C(4)—N(3)—P—Cl(2)	63.2 (6)

located from a difference map) converged to an R of 0.067 and $R_w = 0.062$; $\sum w(|F_o| - |F_c|)^2$ minimized, where $w = [3.5 + 1.0|F_o| + 0.025|F_o|^2]^{-1}$; $(\Delta/\sigma)_{\max} = 0.1$, final $|\Delta\rho|$ peaks $\leq 0.3 \text{ e \AA}^{-3}$; atomic scattering factors from *International Tables for X-ray Crystallography* (1974); *LALS* (Gantzel, Sparks & Trueblood, 1961) was used for refinement.

Discussion. The atomic parameters with their standard deviations and equivalent isotropic thermal parameters for non-H atoms are given in Table 1.* Bond lengths and bond angles involving the non-H atoms are given in Table 2. Table 3 gives some important torsion angles. Fig. 1 gives a perspective view of the molecule along with the numbering of atoms. The bond lengths and bond angles are normal. P—O(2) of 1.468 (6) \AA agrees with values found in other cyclophosphamide, isophosphamide and trophosphamide compounds (Mikołajczyk, Omelanczuk, Abdulkharov, Miller, Wieczorek & Wojciechowska, 1982). The 1,3,2-oxazirane ring takes a half-chair conformation as in cyclohexene (Eliel & Allinger, 1974). The exocyclic chlorine and oxygen connected to phosphorus are in axial and equatorial positions respectively (Fig. 2). The torsion

* 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 39269 (17 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

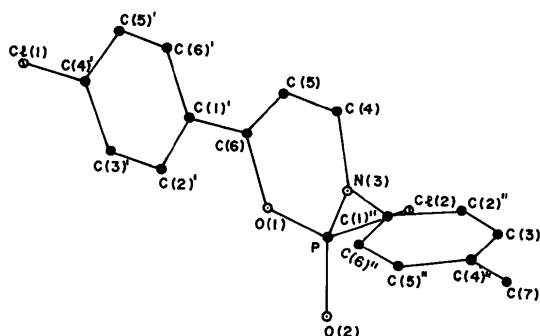


Fig. 1. A perspective view of the molecule down a.

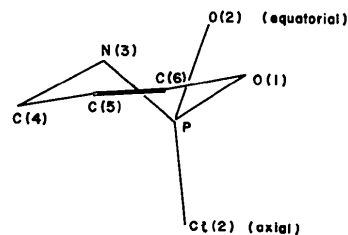


Fig. 2. Conformation of the oxazaphosphorine ring.

angle P–N(3)–C(1)′–C(6)′ [–97.7 (8)°] indicates that the phenyl substituent on N(3) rotates by about 90° (angle between oxaza ring and phenyl ring is 83.3°). Since the conformation of the oxaza ring is forced to be a half chair, the above rotation occurs so as to avoid interactions with the axial oxygen. The angle between the oxaza ring and the phenyl substituent on the C atom is 3.3° which shows the extent of π delocalization in the molecule due to the presence of the double bond in the oxaza ring. The angle between the two phenyl rings is 80.5°. The packing of the molecules in the unit cell essentially involves van der Waals contacts.

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Structure of (–)-7 α -Acetyl-4,5 α -epoxy-3-methoxy-N-methyl-6,14-ethenomorphinan, C₂₂H₂₅NO₃

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Abstract. $M_r = 351.45$, trigonal, $P3_2$, $a = 10.899$ (2), $c = 13.422$ (5) Å, $V = 1380.4$ Å³, $Z = 3$, $D_x = 1.27$ Mg m⁻³, $\lambda(\text{Mo } K\alpha) = 0.71069$ Å, $\mu = 0.091$ mm⁻¹, $F(000) = 564$, $T = 293$ K, final $R = 0.039$ for 2022 unique observed reflections. The acetyl substituent is in the 7 α position of the 6,14-ethenomorphinan skeleton. This means that the Diels–Alder reaction of methyl vinyl ketone with (–)-6-demethoxythebaine affords one isomer. There are no unusual bond lengths or angles.

Introduction. The title compound (2) was prepared by Diels–Alder reaction of (–)-6-demethoxythebaine (1) with methyl vinyl ketone (Hutchins, Cooper, Pürro &

