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Structure of (2*R*)-2-(1-Aziridinyl)-3-(2-chloroethyl)-2-oxo-1,3,2λ^5-oxazaphosphorinane

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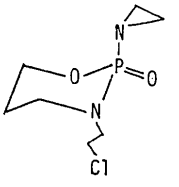
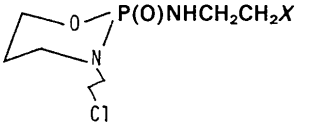
Abstract. $C_7H_{14}ClN_2O_2P$, $M_r = 224{\cdot}63$, orthorhombic, $P2_12_12_1$, $a = 20{\cdot}110\ (8)$, $b = 8{\cdot}098\ (5)$, $c = 6{\cdot}550\ (5)$ Å, $V = 1066{\cdot}7\ (11)$ Å^3, $Z = 4$, $D_x = 1{\cdot}399\ (1)$ g cm^{-3}, $\lambda(\text{Cu } K\alpha) = 1{\cdot}54178$ Å, $\mu = 42{\cdot}29$ cm^{-1}, $F(000) = 472$, room temperature, $R = 0{\cdot}064$ for 813 reflections with $I > 3\sigma(I)$. The oxazaphosphorinane ring is in a chair conformation, with the phosphoryl oxygen in an equatorial position, the aziridinyl group oriented axially, and the endocyclic 2-chloroethyl group extended away from the ring. The molecules are held together only by van der Waals forces.

Introduction. Both 1,3,2-dioxaphosphorinanyl and 1,3,2-oxazaphosphorinanyl ring systems are of basic interest relative to the question of the influence on the conformational properties of cyclohexane of replacing ring C atoms by various heteroatoms (Maryanoff, Hutchins & Maryanoff, 1979). Moreover, these are important in studies of the electronic *vs* steric factors governing the spatial location of exocyclic substituents attached to C, P and N atoms (Maryanoff *et al.*, 1979; Carpenter, Powell, Jacobson & Verkade, 1982; Shih, Wang & Liu, 1984; Bentrude, Day, Holmes, Quin Setzer, Sopchik & Holmes, 1984; Holmes, Day, Setzer, Sopchik & Bentrude, 1984). Another source of interest comes from the applicability of dioxaphosphorinanes and oxazaphosphorinanes bearing endo- and exocyclic chiral auxiliaries for stereoselective synthesis of P-chiral phosphine oxides (Segi, Nakamura, Nakajima & Suga, 1983), cyclic *O*-alkyl-*N*,*N*′-dialkyl phosphordiamidates (Stec, 1982) and cyclic *O*-alkyl-*N*-alkyl phosphoramidofluoridates (Misiura, Silverton & Stec, 1985). In the course of our studies on the structure–biological activity relationship within the family of cyclophosphamide and its congeners, all bearing a stereogenic phosphorus centre, (+)-(2*R*)-2-(1-aziridinyl)-3-(2-chloroethyl)-2-oxo-1,3,2λ^5-oxazaphosphorinane was synthesized (Pankiewicz, Kinas, Stec, Foster, Jarman & Van Maanen, 1979) [(+)-(*R*)-(1)], one of the key intermediates in the preparation of optically active forms of 2-haloethyl derivatives, (2), exerting interesting properties against L1210 lymphoid leukemia in mice (Misiura, Kinas, Stec, Kusnierczyk & Radzikowski, 1988).



(*R*)-(1)



(2)

In this report we present our results on the crystal and molecular structure of (+)-(*R*)-(1). To the best of our knowledge this is the first example of the structure of a 1,3,2-oxazaphosphorinanyl-type compound bearing an exocyclic aziridinyl substituent. Our results are complementary to those of other research establishments studying conformational properties of 1,3,2-oxazaphosphorinanes (Setzer, Sopchik & Bentrude, 1985).

Experimental. (+)-(*R*)-(1) was obtained according to the procedure presented in detail in Pankiewicz *et al.* (1979); yield 76%, $[\alpha]_D^{20{\cdot}0°C} = +25{\cdot}5°$[MeOH, 3·0 g dm^{-3}], m.p. 337–338 K. Crystals of racemic (1) obtained *via* treatment of racemic (2) with sodium hydride were unsuitable for X-ray analysis.

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Colourless crystals of (+)-(*R*)-(1) (0·5 × 0·5 × 0·8 mm), suitable for X-ray analysis, were obtained from ether:pentane (3:2). Space group and approximate lattice parameters were derived from oscillation and Weissenberg photographs. Cell parameters and intensity data were measured on a Hilger & Watts Y290 diffractometer. Accurate lattice parameters were determined by a least-squares refinement of 17 reflections (h: 4→20, k: −7→6, l: 1→3). Intensities were collected with $\omega/2\theta$ scan (30 steps: 24 steps for peak, 3 steps on each side for background), to a θ limit of 59° [$(\sin\theta)/\lambda = 0{\cdot}56$ Å^{-1}]. 1022 reflections were measured (h: 0→21, k: 0→8, l: 0→7), 925 unique, 813 with $I > 3\sigma(I)$. No significant loss of standard intensities (723, $\bar{7}23$) during data collection was observed.

Structure was solved by direct methods using *MULTAN*80 (Main, Fiske, Hull, Lessinger, Germain, Declercq & Woolfson, 1980), and refined by full-matrix least squares (based on F) using *SHELX*76 (Sheldrick, 1976). Positions of some H atoms were calculated geometrically with d(C—H) = 1·08 Å. H atoms were allowed to ride on their parent atoms with a common isotropic temperature factor. Final $R = 0{\cdot}064$ for 813 observed reflections, unit weights. Atomic scattering factors were from *International Tables for X-ray Crystallography* (1974). Maximum $\Delta/\sigma = 0{\cdot}1$, $S = 0{\cdot}998$, max. and min. heights in final difference Fourier map were 0·286 and −0·307 e Å^{-3} respectively. Calculations were performed on DEC 10 and RIAD 32 computers. Torsion angles were calculated using our own *GEOM* program, figures were drawn using *PLUTO* (Motherwell, 1978). The final atomic coordinates for the non-H atoms are listed in Table 1;* interatomic distances, angles and selected torsional angles are in Table 2.

After complete refinement of the structure, 35 reflections with the highest predicted Bijvoet differences were selected and corresponding intensities were carefully measured on the diffractometer. All intensity differences agreed qualitatively with values of predicted $F_c^2 = F_c^2(hkl) - F_c^2(\bar{h}\bar{k}\bar{l})$, and confirmed the configuration for P(1).

Table 1. *Final atomic coordinates* (× 10^4) *and equivalent isotropic thermal parameters* (× 10^4)

$U_{eq} = (U_{11} + U_{22} + U_{33})/3$.

	x	y	z	U_{eq}(Å^2)
P1	8452 (1)	2149 (3)	2303 (3)	560 (11)
O2	7742 (2)	2924 (7)	2782 (8)	655 (33)
C3	7385 (4)	3726 (12)	1111 (16)	727 (60)
C4	7288 (4)	2527 (12)	−639 (14)	704 (58)
C5	7949 (5)	1945 (13)	−1471 (14)	865 (67)
N6	8349 (4)	1141 (9)	157 (10)	661 (43)
O7	8715 (3)	1136 (8)	3962 (9)	751 (39)
N8	8881 (3)	3808 (10)	1740 (12)	702 (46)
C9	9210 (5)	4767 (17)	3387 (24)	873 (81)
C10	9617 (5)	3800 (18)	1977 (22)	925 (83)
C11	8618 (5)	−544 (14)	−153 (16)	836 (67)
C12	9166 (5)	−387 (14)	−1510 (19)	979 (78)
Cl13	9463 (1)	−2532 (4)	−1989 (5)	1125 (22)

Table 2. *Interatomic distances* (Å), *bond angles* (°), *and torsion angles* (°)

P1—O2	1·589 (5)	P1—N8	1·640 (8)
O2—C3	1·462 (10)	N8—C9	1·484 (14)
C3—C4	1·515 (12)	N8—C10	1·488 (12)
C4—C5	1·513 (11)	C9—C10	1·462 (17)
C5—N6	1·486 (10)	N6—C11	1·481 (13)
N6—P1	1·639 (6)	C11—C12	1·423 (13)
P1—O7	1·461 (6)	C12—C113	1·863 (12)
N6—P1—O2	104·7 (3)	N8—P1—N6	106·3 (4)
P1—O2—C3	118·0 (5)	P1—N8—C9	120·0 (8)
O2—C3—C4	110·2 (7)	P1—N8—C10	119·8 (8)
C3—C4—C5	111·0 (7)	C9—N8—C10	58·9 (7)
C4—N5—N6	110·7 (7)	N8—C9—C10	60·4 (7)
C5—N6—P1	117·7 (6)	N8—C10—C9	60·7 (7)
O7—P1—O2	113·6 (4)	C11—N6—P1	122·1 (6)
O7—P1—N6	113·8 (3)	C11—N6—C5	120·2 (7)
O7—P1—N8	115·9 (4)	N6—C11—C12	106·6 (9)
N8—P1—O2	101·2 (3)	C11—C12—C113	105·7 (8)
N6—P1—O2—C3	−45·3 (6)	O7—P1—N8—C9	−36·4 (9)
O7—P1—O2—C3	−170·0 (6)	O7—P1—N8—C10	32·7 (9)
N8—P1—O2—C3	65·1 (6)	P1—O2—O3—C4	57·3 (8)
O2—P1—N6—C5	42·2 (7)	O2—C3—C4—C5	−61·0 (9)
O2—P1—N6—C11	−135·4 (7)	C3—C4—C5—N6	58·3 (10)
O7—P1—N6—C5	166·7 (6)	C4—C5—N6—P1	−51·2 (9)
O7—P1—N6—C11	−10·9 (8)	C4—C5—N6—C11	126·4 (9)
N8—P1—N6—C5	−64·4 (7)	P1—N6—C11—C12	−107·3 (9)
N8—P1—N6—C11	118·0 (7)	C5—N6—C11—C12	75·2 (11)
O2—P1—N8—C9	86·9 (8)	P1—N8—C9—C10	108·7 (9)
O2—P1—N8—C10	155·9 (7)	P1—N8—C10—C9	−109·1 (9)
N6—P1—N8—C9	−164·1 (8)	N6—C11—C12—Cl13	−176·8 (6)
N6—P1—N8—C10	−95·8 (8)		

Discussion. Crystal and molecular structures of racemic 2-(2-chloroethyl)-3-(2-chloroethylamino)-2-oxo-1,3,2-oxazaphosphorinane (2, X = Cl) and its (−)-(*S*)-enantiomer were reported earlier (Perales & García-Blanco, 1977; Adamiak, Gdaniec, Pankiewicz & Stec, 1980). It has been demonstrated that the 1,3,2-oxazaphoshorinanyl ring exists in both forms of (2) in a chair conformation. The most striking difference between the structures of racemic (2) (X = Cl) and that of (−)-(*S*)-(2) (X = Cl) was the orientation of the exocyclic substituents at the P atom. The 2-chloroethylamino group in racemic (2) is equatorial, whereas in (−)-(*S*)-(1) this group is in an axial position. Since the title compound (+)-(*R*)-(1) has been obtained from (+)-(*R*)-(2) (X = Cl), it was of interest to study the spatial orientation of the aziridinyl substituent with respect to the 1,3,2-oxazaphosphorinanyl ring system. As shown in Fig. 1, this molecule exists in the solid state in a chair

* Lists of structure factors, anisotropic thermal parameters, H-atom coordinates and bond lengths and angles involving H atoms have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 52229 (8 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

conformation. The phosphoryl O atom O7 (notation as indicated in Fig. 1) occupies an equatorial position and the aziridinyl group is axially oriented. The torsion angle P1—N8—C9—C10 = 108·7 (9)° indicates sp^3 hybridization of N8, in contrast to the endocyclic N6 atom which is nearly sp^2 hybridized. Aziridinyl C atoms C9 and C10 are directed outwards from the oxazaphosphorinanyl ring and it can be safely assumed that the N8 lone pair dissects the angle O2—P1—N6 and is directed towards atom C5. The endocyclic 2-chloroethyl group is directed outwards from the ring.

The molecular packing in the crystal is presented in Fig. 2. The interactions between neighbouring molecules are of the van der Waals type.

An axial orientation of the aziridinyl group resembles that of the dimethylamino substituent in 2-dimethylamino-2-oxo-1,3,2-oxazaphosphorinane (Holmes *et al.*, 1984) and may be accounted for by the decrease in 1,3-*syn*-axial repulsions. The origin of the axial orientation of the aziridinyl group is, however, obscure and comparison of structural parameters of (+)-(*R*)-(1) with those of 2-alkyl(aryl)-amino-2-oxo-1,3,2-dioxaphosphorinanes seems to be premature, because the factors which govern the spatial orientations of alkyl(aryl)amino groups in the latter systems are also not well understood (Setzer *et al.*, 1985, and references cited therein). For example, the 2-phenylamino group in 5,5-dimethyl-2-phenylamino-2-seleno-1,3,2-dioxaphosphorinane (3) is axial, while the ethylamino function in 2-ethylamino-5,5-dimethyl-2-seleno-1,3,2-dioxaphosphorinane (4), both assigned in the solid state, is equatorial (Bartczak, Gałdecki, Trzezwinska & Wolf, 1983; Bartczak, Gałdecki, Wolf, Lesiak & Stec, 1986).

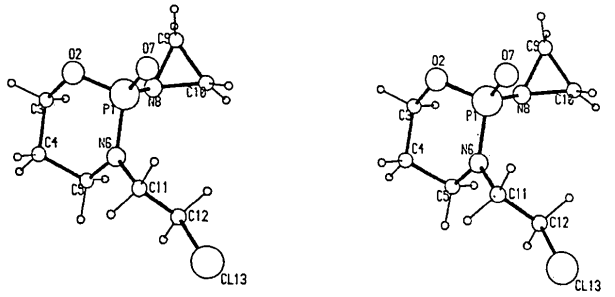


Fig. 1. A stereoview of the molecular structure of the title compound (1), with the atomic numbering scheme.

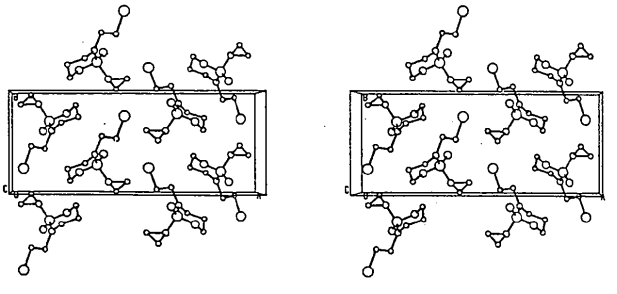
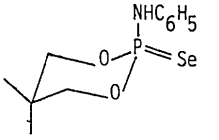
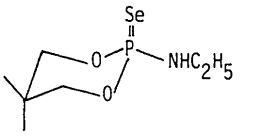


Fig. 2. A stereoview of the molecular packing of (1) in the unit cell.



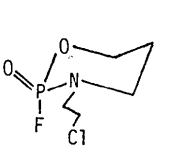
(3)



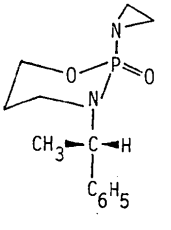
(4)

The absolute configuration at phosphorus in (+)-(1) was assigned to be *R*, which is consistent with stereochemical correlations established in earlier work (Pankiewicz *et al.*, 1979).

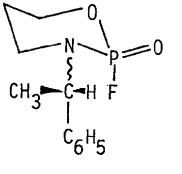
As mentioned above, compound (1) in reaction with hydrogen halides (HCl, HBr) gives 3-(2-chloroethyl)-2-haloethylamino-2-oxo-1,3,2-oxazaphosphorinanes (2). However, treatment of (1) with a poly(hydrogen fluoride)–pyridine complex leads exclusively to the cleavage of the P1—N8 bond and the formation of 3-(2-chloroethyl)-2-fluoro-2-oxo-1,3,2-oxazaphosphorinane (5) [treatment of (1) with HF–pyridine gives (5) with 72% yield (consistent IR, ^1H NMR, ^{31}P NMR and mass spectra)]. By analogy with (6), of which the crystal and molecular structures were assigned (Misiura *et al.*, 1985) indicating axial orientation of the F atom, we may assume that (5) also bears its F atom in an axial position. Because phosphorus–exocyclic nitrogen bond cleavage (7→6) occurs with inversion of configuration (Misiura *et al.*, 1985), it may be concluded that the (1)→(5) conversion occurs with inversion of configuration at the P atom which is accompanied by ring inversion. Most probably, both inversions are synchronous and occur within the process of nucleophilic substitution at P *via* a pentacovalent intermediate, where the oxazaphosphorinane ring occupies basal positions:



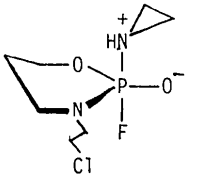
(5)



(*sc,sp*)-(7)



(*sc,sp*)-(6)



and both P—N and P—F bonds are collinear and located in apical positions.

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A New Description of the Structure of $(-)^{CD}_{500}$-*mer*-[Co(Ethylenediamine-*N*-acetate)(3-azapentane-1,5-diamine)]$Br_2.\frac{2}{3}CH_3OH.\frac{2}{3}H_2O$*

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Abstract. The crystal structure of $(-)^{CD}_{500}$-*mer*-[Co(edma)(dien)]$Br_2.\frac{2}{3}CH_3OH.\frac{2}{3}H_2O$ has recently been reported [Kawaguchi, Fukaki, Ama, Yasui, Okamoto & Hidaka (1988). *Bull. Chem. Soc. Jpn*, **61**, 2359–2364] in space group $P1$ [a = 13·824 (8), b = 13·814 (8), c = 8·055 (3) Å, α = 101·18 (6), β = 101·17 (6), γ = 116·32 (5)°, V = 1282·3 Å^3, Z = 3) and refined to R_F = 0·047 (wR = 0·056). The structure has now been refined in space group $R3$ (hexagonal axes, a = 23·495, c = 8·055 Å, Z = 9) to R_F = 0·034, based on the transformed original data. The increase in Laue symmetry – from $\bar{1}$ to $\bar{3}$ – has caused no significant changes in the geometry of the cation but the e.s.d.'s of the bonds and angles are typically half of those previously reported. A stereoview of the overall structure is presented and the possible hydrogen bonds are discussed.

Introduction. The crystal structure of $(-)^{CD}_{500}$-*mer*-[Co(edma)(dien)]$Br_2.\frac{2}{3}CH_3OH.\frac{2}{3}H_2O$ (edma and dien denote ethylenediaminemonoacetato and diethylenetriamine) has recently been described (Kawaguchi, Fukaki, Ama, Yasui, Okamoto & Hidaka, 1988) (hereafter KFAYOH). A preliminary communication on the crystal structure has also been reported (Okamoto, Yasui & Hidaka, 1987). The complex was prepared and resolved according to methods described in a previous paper (Yasui, Shikiji, Koine, Ama & Kawaguchi, 1987). The structure was reported and refined by KFAYOH in space

* Alternative nomenclature: $(-)^{CD}_{500}$-*mer*-(diethylenetriamine)-(ethylenediaminemonoacetato)cobalt dibromide–methanol–water (3/2/2).

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