

Crystal and molecular structure of 6-*t*-butyl-3-cyclohexyl-3, 4-dihydro-2-(2-chlorophenoxy)-2H-1, 3, 2-benzoxazaphosphorine-2-oxide

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Abstract. The structure of the title compound was determined by the Patterson method and refined to an R of 0.10 for 8065 observed reflections. The crystals are triclinic $P\bar{1}$, $a = 12.408(2)$, $b = 13.157(2)$, $c = 14.479(8)\text{Å}$, $\alpha = 74.706(8)$, $\beta = 88.728(9)$, $\gamma = 88.660(13)^\circ$ with $Z = 4$. The intensity data were collected on an Enraf-Nonius CAD-4 single crystal X-ray diffractometer. The benzoxazaphosphorine ring adopts a conformation intermediate between a half-chair and a sofa with the phosphoryl oxygen O(2) in an axial and the 2-chlorophenyl and *t*-butyl groups which are *trans* to each other in equatorial positions. The cyclohexyl ring adopts a chair conformation with the nitrogen atom N(5) in an equatorial position. In one conformation of the molecule (I) the *t*-butyl group atoms and one of the carbon atoms, C(24) in the cyclohexyl ring are disordered. In the other conformation (molecule II) the 2-chlorophenyl ring adopts a conformation midway between a half-chair and a sofa. The molecular packing involves mainly van der Waals contacts.

Keywords. Benzoxazaphosphorine; structure; conformation.

1. Introduction

The 1, 3, 2-oxazaphosphorine cyclophosphamide and its analogues, isophosphamide and trophosphamide, are clinically useful anti-cancer drugs. Studies have shown that the perhydro-1, 3, 2-oxazaphosphorine ring undergoes conformational changes due to steric and electronic interactions between various substituents on the phosphorus atom (Bajwa *et al* 1979; Gorenstein and Rowell 1979; Gorenstein *et al* 1980; Maryanoff 1979) and the substituents on the ring nitrogen atom (Chandrasekharan and Bentrude 1980; Bajwa *et al* 1982). We report here the X-ray structure and conformation of the 1, 3, 2-benzoxazaphosphorine ring in the title compound. The molecular diagram and numbering of atoms are shown in figure 1.

2. Experimental

Transparent, colourless needle-shaped crystals were grown from methanol. The cell parameters are $a = 12.408(2)$, $b = 13.157(2)$, $c = 14.479(8)\text{Å}$, $\alpha = 74.706(8)$, $\beta = 88.728(9)$, $\gamma = 88.660(13)^\circ$, $V = 2279\text{Å}^3$. Space group $P\bar{1}$ with $Z = 4$, $C_{23}H_{29}O_3NPCl$. $M_r = 433.9$

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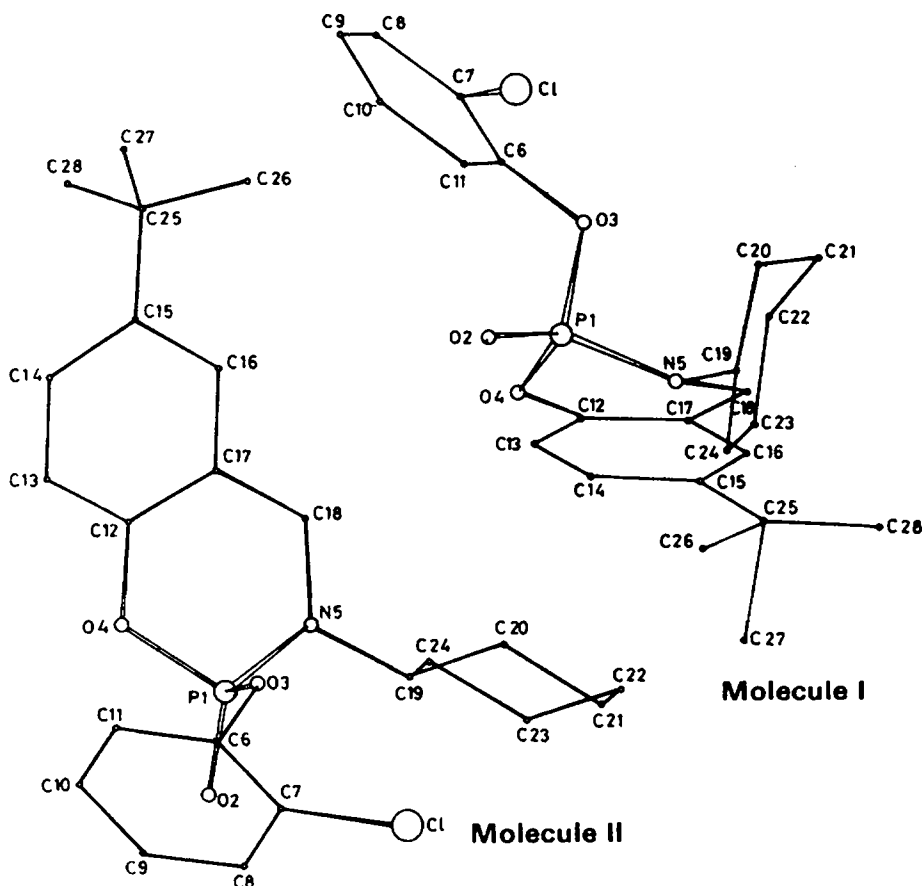


Figure 1. The molecular diagram and numbering of atoms.

$F(000) = 920$, $D_c = 1.26 \text{ gm/cm}^3$, $D_m = 1.27 \text{ gm/cm}^3$, $\lambda(\text{CuK}\alpha) = 1.5418 \text{ \AA}$, $\mu = 23.5 \text{ cm}^{-1}$. A crystal of size $0.33 \times 0.44 \times 0.55 \text{ mm}^3$ was used for data collection. Lattice parameters and their e.s.d.'s derived from a least-squares refinement of 25 reflections ($30 < \theta < 45^\circ$). Intensity data were collected on an Enraf-Nonius CAD-4 single crystal X-ray diffractometer, graphite monochromated $\text{CuK}\alpha$ radiation. 9383 independent reflections with $4 < 2\theta < 160^\circ$ ($h0 \rightarrow 14$, $k - 16 \rightarrow 16$, $l - 17 \rightarrow 18$) of which 8065 were considered as observed [$I > 3\sigma(I)$, where (I) was determined from counting statistics]. Lorentz, polarization and approximate absorption (w -scans $T_{\text{max}} = 85.64\%$, $T_{\text{min}} = 8.9\%$) corrections were applied.

The structure was determined by the Patterson method with SHELXS86 (Sheldrick 1986) and refined by the full-matrix least-squares method using SHELX-76 (Sheldrick 1976). The disordered *t*-butyl group atoms and one of the ring atoms, C(24) in molecule I (figure 1) were assigned an occupancy factor of 0.5 and were refined. The site occupancy and thermal parameters were refined alternately, until the *t*-butyl group geometry and ring atom geometry in molecule I were satisfactory. The hydrogen atoms (except those attached to the disordered atoms) located from a difference Fourier map, were not refined. The final R is 0.10 ($R_w = 0.12$) for 8065 reflections

Table 1. Fractional co-ordinates and equivalent isotropic thermal parameters for non-hydrogen atoms with e.s.d.'s in parentheses.

$$B_{\text{eq}} = (8/3)\pi^2 \sum_i \sum_j U_{ij} a_i^* a_j^* a_i a_j$$

Atom	x	y	z	$B_{\text{eq}}(\text{\AA}^2)$
<i>Molecule I</i>				
Cl	-0.1274(2)	0.2502(2)	0.2227(2)	10.1(1)
P(1)	0.1360(1)	0.2937(1)	0.0976(1)	3.8
O(2)	0.1401(3)	0.2197(3)	0.1912(2)	5.3(1)
O(3)	0.0167(2)	0.3173(2)	0.0550(2)	4.3(1)
O(4)	0.1988(2)	0.2483(2)	0.0206(2)	3.9(1)
N(5)	0.1851(3)	0.4095(3)	0.0847(2)	4.1(1)
C(6)	-0.0486(3)	0.2337(4)	0.0514(3)	4.6(1)
C(7)	-0.0467(5)	0.1957(6)	-0.0255(4)	6.9(2)
C(8)	-0.1130(7)	0.1121(7)	-0.0268(6)	8.9(3)
C(9)	-0.1831(5)	0.0727(5)	0.0527(6)	7.7(2)
C(10)	-0.1830(4)	0.1095(5)	0.1279(6)	6.9(2)
C(11)	-0.1175(4)	0.1936(4)	0.1291(4)	5.5(1)
C(12)	0.2260(3)	0.3117(3)	-0.0704(3)	3.4(1)
C(13)	0.2554(3)	0.2631(3)	-0.1395(3)	4.2(1)
C(14)	0.2893(4)	0.3209(4)	-0.2283(3)	4.5(1)
C(15)	0.2938(3)	0.4312(4)	-0.2500(3)	4.3(1)
C(16)	0.2625(3)	0.4783(3)	-0.1785(3)	4.0(1)
C(17)	0.2271(3)	0.4209(3)	-0.0872(3)	3.4(1)
C(18)	0.1960(3)	0.4798(3)	-0.0136(3)	4.0(1)
C(19)	0.1729(4)	0.4692(4)	0.1595(3)	5.2(1)
C(20)	0.0591(5)	0.4931(5)	0.1801(4)	6.2(2)
C(21)	0.0502(6)	0.5528(7)	0.2563(6)	8.6(3)
C(22)	0.1144(8)	0.5033(7)	0.3441(6)	9.9(3)
C(23)	0.2296(8)	0.4861(7)	0.3182(6)	9.9(3)
C(24)	0.2599(13)	0.4583(14)	0.2184(2)	6.1(2)
C(24)D	0.2370(7)	0.4149(8)	0.2494(7)	
C(25)	0.3348(5)	0.4955(5)	-0.3465(4)	
C(26)	0.3655(13)	0.4336(12)	-0.4194(11)	
C(27)	0.4622(13)	0.4740(12)	-0.3495(11)	
C(28)	0.3397(12)	0.6108(11)	-0.3590(10)	
C(26)D	0.4243(10)	0.5650(9)	-0.3403(9)	
C(27)D	0.2844(15)	0.4712(14)	-0.4267(13)	
C(28)D	0.2341(9)	0.5640(9)	-0.3949(8)	
<i>Molecule II</i>				
Cl	0.6724(2)	0.1295(1)	0.3863(1)	8.9(1)
P(1)	0.5303(1)	-0.0514(1)	0.2464(1)	3.4
O(2)	0.6409(2)	-0.0697(2)	0.2190(2)	4.4(1)
O(3)	0.5211(2)	-0.0171(2)	0.3445(2)	4.2(1)
O(4)	0.4607(2)	-0.1549(2)	0.2664(2)	3.9(1)
N(5)	0.4585(2)	0.0365(2)	0.1716(2)	3.7(1)
C(6)	0.5837(3)	-0.0607(4)	0.4235(3)	4.3(1)
C(7)	0.5712(5)	-0.1626(5)	0.4781(4)	6.3(2)
C(8)	0.3678(6)	0.2014(5)	-0.5597(5)	7.9(2)
C(9)	0.7056(5)	-0.1368(6)	0.5863(4)	7.0(2)
C(10)	0.7180(4)	-0.0354(6)	0.5344(4)	6.2(2)
C(11)	0.6545(4)	0.0037(4)	0.4512(3)	4.8(1)
C(12)	0.3498(3)	-0.1468(3)	0.2854(3)	3.7(1)

(continued)

Table 1. (continued)

Atom	x	y	z	$B_{eq}(\text{\AA}^2)$
C(13)	0.3038(4)	-0.2300(3)	0.3501(4)	5.2(1)
C(14)	0.1941(4)	-0.2244(4)	0.3727(4)	5.4(1)
C(15)	0.1319(3)	-0.1357(3)	0.3307(3)	4.3(1)
C(16)	0.1829(3)	-0.0522(3)	0.2654(3)	4.2(1)
C(17)	0.2921(3)	-0.0573(3)	0.2415(3)	3.7(1)
C(18)	0.3422(4)	0.0329(4)	0.1690(4)	6.2(1)
C(19)	0.5128(3)	0.1358(3)	0.1184(3)	4.0(1)
C(20)	0.4768(5)	0.2309(4)	0.1529(4)	5.8(1)
C(21)	0.5403(5)	0.3283(4)	0.0955(5)	7.2(2)
C(22)	0.5236(5)	0.3490(4)	-0.0094(5)	6.7(2)
C(23)	0.5571(6)	0.2532(5)	-0.0432(4)	7.4(2)
C(24)	0.4965(5)	0.1559(4)	0.0115(4)	5.9(1)
C(25)	0.0115(4)	-0.1279(4)	0.3572(4)	5.5(1)
C(26)	-0.0193(5)	-0.0195(6)	0.3620(5)	7.7(2)
C(27)	-0.0522(5)	-0.1450(9)	0.2752(8)	11.7(4)
C(28)	0.0157(7)	0.2036(9)	-0.4480(8)	14.5(4)

D is disordered atom

($\Delta/\sigma = 0.1$). A final difference density map was featureless ($\Delta\rho = \pm 0.1 \text{ e\AA}^{-3}$), $w = 2.142/[\sigma^2|F0| + 0.00171|F0|^2]$. The atomic scattering factors are from the SHELX-76 program. Computer program: PARST (Nardelli 1983) was used for geometrical calculations. The final positional and thermal parameters are listed in table 1.

3. Discussion

Bond lengths and angles are given in tables 2a and 2b respectively. Selected torsion angles are given in table 3. The molecules are arranged in anti-parallel pairs about the centre of symmetry. The bond lengths of the P(1)=O(2) bond which are equal to 1.45(3)Å in both molecules I and II agree with those in a related 1,3,2-benzoxazaphosphorine structure (Subramanian *et al* 1989). The C-Cl bond distances of 1.71(7) and 1.69(5) Å, and Cl-C-C bond angles of 120.3(5) and 119.8(5)°, respectively, in molecules I and II compare well with a related oxazaphosphorine compound (Acharya *et al* 1984). In molecule II the 2-chlorophenyl ring has a conformation midway between a half-chair and a sofa. The dihedral angle between the planes C(7)-C(6)-C(11) and C(7)-C(8)-C(10)-C(11) is 21.3° and between C(7)-C(8)-C(10)-C(11) and C(8)-C(9)-C(10) is 162.9°. The puckering parameters for the 2-chlorophenyl ring are $q_2 = 1.8262$, $q_3 = 1.2752$, $Q = 2.2274$, $\phi_2 = 120.0$ and $\theta_2 = 55.1$. The oxazaphosphorine ring adopts a conformation intermediate between a half-chair and a sofa. The dihedral angle and puckering parameters for the phosphorine ring are given in table 4. The substituent at N(5) is rotated (-58.0° in I; 37.7° in II) with the O(2)-C(19) = 3.46(6) in I; 3.13(4)Å in II indicating conformational change as suggested by Chandrasekharan and Bentrude (1980). The phosphoryl oxygen O(2) occupies an axial position. The cyclohexyl ring adopts a chair conformation with the nitrogen N(5) occupying an equatorial position. The least-squares plane of the 2-chlorophenyl ring is inclined at an angle of 34(2)° to the phosphorine ring in molecule I, and 58.2(2)° in molecule II.

Table 2a. Bond distances (Å) involving non-hydrogen atoms.

Bond distance	Molecule I	Molecule II
P(1)–O(2)	1.446(3)	1.452(3)
Cl–C(11)	1.711(7)	1.691(5)
P(1)–O(3)	1.608(3)	1.601(4)
P(1)–O(4)	1.580(3)	1.587(3)
P(1)–N(5)	1.617(4)	1.624(3)
O(3)–C(6)	1.394(6)	1.383(5)
O(4)–C(12)	1.400(5)	1.404(5)
N(5)–C(18)	1.484(5)	1.447(6)
N(5)–C(19)	1.500(7)	1.497(4)
C(6)–C(7)	1.393(6)	1.375(7)
C(6)–C(11)	1.335(9)	1.371(7)
C(7)–C(8)	1.392(8)	1.426(7)
C(8)–C(9)	1.303(12)	1.358(9)
C(9)–C(10)	1.418(11)	1.391(8)
C(10)–C(11)	1.393(12)	1.392(7)
C(12)–C(13)	1.361(7)	1.366(5)
C(12)–C(17)	1.393(5)	1.374(5)
C(13)–C(14)	1.372(6)	1.398(7)
C(14)–C(15)	1.404(7)	1.390(6)
C(15)–C(16)	1.384(7)	1.400(5)
C(16)–C(17)	1.405(5)	1.395(5)
C(17)–C(18)	1.513(7)	1.498(6)
C(19)–C(20)	1.480(8)	1.519(7)
C(20)–C(21)	1.515(12)	1.552(7)
C(21)–C(22)	1.503(11)	1.489(10)
C(22)–C(23)	1.497(13)	1.514(9)
C(23)–C(24)	1.616(15)	1.522(8)
C(24)–C(19)	1.312(10)	1.517(7)
C(25)–C(15)	1.514(7)	1.542(6)
C(25)–C(26)	1.531(18)	1.487(9)
C(25)–C(27)	1.600(17)	1.509(12)
C(25)–C(28)	1.482(16)	1.466(8)
C(23)–C(24)D	1.537(15)	
C(25)–C(26)D	1.481(14)	
C(25)–C(27)D	1.442(21)	
C(25)–C(28)D	1.587(12)	

D is disordered atom

Table 2b. Bond angles (degrees) involving non-hydrogen atoms.

Angle between atoms	Molecule I	Molecule II
Cl–C(7)–C(8)	119.7(5)	118.2(5)
Cl–C(7)–C(6)	121.0(5)	121.4(4)
O(4)–P(1)–N(5)	104.6(3)	104.0(2)
O(3)–P(1)–N(5)	104.0(3)	104.4(2)
O(2)–P(1)–N(5)	118.2(3)	118.0(3)
O(2)–P(1)–O(4)	110.8(2)	112.2(2)

(continued)

Table 2b. (continued)

Angle between atoms	Molecule I	Molecule II
O(2)–P(1)–O(3)	114·2(3)	113·0(3)
O(3)–P(1)–O(4)	103·5(3)	104·0(2)
P(1)–O(4)–C(12)	122·1(2)	118·4(3)
P(1)–N(5)–C(19)	123·0(4)	117·6(3)
P(1)–N(5)–C(18)	118·3(3)	122·7(3)
C(18)–N(5)–C(19)	112·7(4)	118·4(4)
O(3)–C(6)–C(11)	120·6(5)	118·7(4)
O(3)–C(6)–C(7)	117·9(5)	122·3(5)
C(7)–C(6)–C(11)	121·5(4)	119·8(5)
C(6)–C(7)–C(8)	119·2(6)	120·4(5)
C(7)–C(8)–C(9)	119·9(7)	118·7(6)
C(8)–C(9)–C(10)	121·6(7)	120·3(6)
C(9)–C(10)–C(11)	118·5(8)	118·7(6)
C(6)–C(11)–C(10)	119·2(6)	120·0(6)
O(4)–C(12)–C(17)	120·2(4)	120·5(4)
O(4)–C(12)–C(13)	118·0(4)	117·1(4)
C(13)–C(12)–C(17)	121·8(4)	122·4(5)
C(12)–C(13)–C(14)	120·6(4)	119·1(5)
C(13)–C(14)–C(15)	120·8(5)	121·0(5)
C(14)–C(15)–C(25)	121·3(5)	121·2(4)
C(14)–C(15)–C(16)	117·2(5)	117·8(5)
C(16)–C(15)–C(25)	121·5(5)	120·9(4)
C(15)–C(16)–C(17)	123·0(4)	121·7(4)
C(12)–C(17)–C(16)	116·6(4)	118·0(3)
C(16)–C(17)–C(18)	118·9(4)	119·7(4)
C(12)–C(17)–C(18)	124·5(4)	122·3(5)
N(5)–C(19)–C(24)	113·7(8)	110·4(4)
N(5)–C(18)–C(17)	112·9(4)	115·1(5)
N(5)–C(19)–C(20)	113·2(5)	113·0(4)
N(5)–C(19)–C(24)D	111·0(5)	
C(20)–C(19)–C(24)	113·8(6)	110·9(4)
C(20)–C(19)–C(24)D	113·7(6)	
C(19)–C(20)–C(21)	111·5(6)	108·7(5)
C(20)–C(21)–C(22)	113·5(7)	111·6(5)
C(21)–C(22)–C(23)	111·0(7)	110·3(6)
C(22)–C(23)–C(24)	110·4(8)	111·4(6)
C(22)–C(23)–C(24)D	110·5(8)	
C(19)–C(24)–C(23)	112·2(11)	110·6(5)
C(16)–C(25)–C(27)	112·6(6)	107·1(6)
C(15)–C(25)–C(26)	116·1(8)	111·3(5)
C(15)–C(25)–C(27)	106·8(7)	107·1(6)
C(15)–C(25)–C(28)	116·0(7)	109·2(5)
C(15)–C(25)–C(26)D	113·7(7)	
C(15)–C(25)–C(27)D	113·8(9)	
C(15)–C(25)–C(28)D	105·3(6)	
C(19)–C(24)D–C(23)	107·8(7)	

D is disordered atom

The *t*-butyl group and one of the ring atoms in the cyclohexyl ring in molecule I are highly disordered with an average distance of 1·511(5)Å and a C–C–C angle of 111·8(7)° in the unconstrained refinement. In the constrained refinement, the bond

Table 3. Selected torsion angles (degrees).

Torsion angle between the atoms	Molecule I	Molecule II
C(19)–C(20)–C(21)–C(22)	–45.3(9)	53.0(6)
C(20)–C(21)–C(22)–C(23)	48.8(9)	–48.8(6)
C(21)–C(22)–C(23)–C(24)	–30.2(9)	126.7(6)
C(22)–C(23)–C(24)–C(19)	8.5(9)	–129.0(6)
C(23)–C(24)–C(19)–C(20)	–5.2(9)	43.5(5)
C(24)–C(19)–C(20)–C(21)	23.6(10)	–52.1(6)
O(4)–P(1)–N(5)–C(18)	43.0(4)	26.0(4)
P(1)–N(5)–C(18)–C(17)	–33.0(5)	0.7(6)
N(5)–C(18)–C(17)–C(12)	10.6(6)	–18.2(7)
C(18)–C(17)–C(12)–O(4)	–2.3(7)	2.5(7)
C(17)–C(12)–O(4)–P(1)	17.1(5)	31.1(5)
C(12)–O(4)–P(1)–N(5)	–34.8(4)	–41.9(3)
O(2)–P(1)–O(3)–C(6)	–47.5(4)	–36.5(4)
C(18)–N(5)–P(1)–O(2)	156.1(3)	140.0(3)
O(2)–P(1)–N(5)–C(19)	–35.0(5)	–36.2(3)
O(4)–P(1)–O(3)–C(6)	62.6(3)	74.7(4)
C(14)–C(15)–C(25)–C(26)	2.5(10)	129.1(6)
C(14)–C(15)–C(25)–C(27)	–65.1(9)	–95.5(7)
C(14)–C(15)–C(25)–C(28)	–162.1(8)	–138.1(8)
C(16)–C(15)–C(25)–C(26)	–163.7(8)	–33.5(7)
C(16)–C(15)–C(25)–C(27)	97.3(8)	70.4(7)
C(16)–C(15)–C(25)–C(28)	0.3(9)	27.8(3)

Table 4. Dihedral angles (degrees) and puckering parameters for the phosphorine ring.

Dihedral angle between the planes	Molecule I	Molecule II
C(12)–C(17)–C(18) and O(4)–C(12)–C(18)–N(5)	173.0°	11.1°
O(4)–C(12)–C(18)–N(5) and O(4)–P(1)–N(5)	35.9°	147.4°
Puckering parameters for phosphorine ring	$q_2 = 0.294$	$q_2 = 0.408$
	$q_3 = 0.263$	$q_3 = 0.151$
	$Q = 0.394$	$Q = 0.435$
	$\varphi_2 = -37.4$	$\varphi_2 = -88.0$
	$\theta_2 = 48.1$	$\theta_2 = 69.7$

lengths and angles vary between 1.48(2) and 1.60(2) Å and 106.8(7)° and 116.0(7)°, respectively. The phenyl and *t*-butyl groups are *trans* to each other and are at equatorial positions on the phosphorine ring. Figure 2 shows the packing of the molecules in the unit cell viewed along the *c* axis. The packing of the molecules in the unit cell is stabilized by van der Waals contacts.

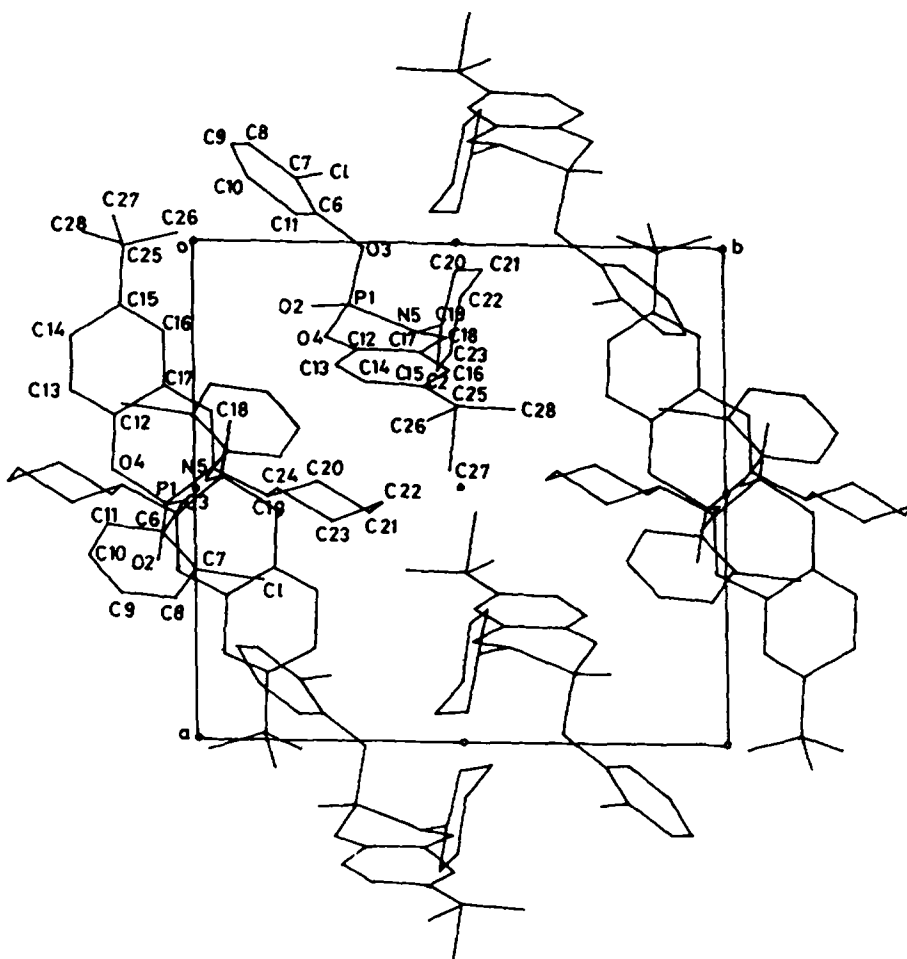


Figure 2. The packing of the molecules in the unit cell viewed along the *c* axis.

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