O'CONNOR, J. E. & AMMA, E. L. (1969). *Inorg. Chem.* **8**, 2367.
ROBINSON, W. T., HOLT, S. L. JR, & CARPENTER, G. B. (1967). *Inorg. Chem.* **6**, 605.
SIRIGU, A. (1969). *J. Chem. Soc.* (*D*), p. 256.
SPOFFORD, W. A. III (1966). Program for calculating least-squares planes on the I.B.M. 1620.
SPOFFORD, W. A. III (1967). Least-squares Program for Cell Constants for the IBM 1620.
SPOFFORD, W. A. III, BOLDRINI, P. & AMMA, E. L. (1971). *Inorg. Chim. Acta*, **5**, 70.
SPOFFORD, W. A. III, BOLDRINI, P., AMMA, E. L., CARFAGNO P. & GENTILE, P. S. (1970). *Chem. Commun.* p. 40.
STEWART, R. F., DAVIDSON, E. R. & SIMPSON, W. T. (1965). *J. Chem. Phys.* **42**, 3175.
TRUTER, M. R. (1960). *J. Chem. Soc.* p. 997.
WEININGER, M. S., O'CONNOR, J. E. & AMMA, E. L. (1969). *Inorg. Chem.* **8**, 424.

Acta Cryst. (1972). B**28**, 2647

The Crystal Structure of *N*,*N*-Bis-2-chloroethyl-*N'*,*O*-propylene Phosphoric Ester Diamide Monohydrate (Endoxan)

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Crystals of endoxan were crystallized from an ether solution at −10 °C. The crystals are triclinic, with space group $P\bar{1}$ and cell dimensions: $a = 13{\cdot}402$, $b = 8{\cdot}669$, $c = 6{\cdot}003$ Å, $\alpha = 100{\cdot}3$, $\beta = 96{\cdot}4$ and $\gamma = 106{\cdot}8°$. The structure was solved by direct methods for phase determination, and successive Fourier syntheses. The structure was subsequently refined by the full-matrix least-squares method to an R value of 0·042 for 2255 reflexions collected on an automatic diffractometer with Mo $K\alpha$ radiation. All the hydrogen atoms were located in a difference Fourier synthesis. The molecules are held together in three dimensions by one N–H···O and two O–H···O hydrogen bonds.

Introduction

The study of the crystal structure of endoxan was carried out to collect new data for those interested in the use of citostatics for the chemotherapy of cancer tumours. Endoxan has partially solved some of the main problems caused by nitrogen mustard in the human organism (Arnold & Bourseaux, 1958). Mustards were used for a long time in the therapy of neoplastic diseases, since they can control the smaller metastases which are innaccessible by other techniques such as surgery and radiation.

The citostatic effect of the chloroalkyl-amine of the nitrogen mustard stems from the large lability of the chlorine atoms located in the β-position of the nitrogen atom. According to Ross (1945), the dissociation of these compounds results in a positively charged carbonium ion with biological activity. The amine groups of the mustard behave as alkylating agents in a biological medium reacting with active atoms of H. This is similar to the behaviour of SH groups in proteins or enzymes producing lessening of growth or even a destruction of the malignant cells.

Experimental

The crystals of endoxan were kindly supplied by ASTA-WERKE laboratories (Chemische fabrik, Westfalia, Germany). The samples were recrystallized from an ether solution prepared by means of ether extraction in a Soxhlet aparatus and subsequent cooling of the solution to a temperature of −10°. The crystals are prismatic with the longest dimension along the *c* axis. Preliminary cell dimensions were obtained from Weissenberg photographs taken from a crystal rotated about the *b* and *a* axes. Precise unit-cell constants were determined by the least-squares method from the angular settings of 24 independent reflexions measured on an AED Siemens diffractometer. The density was measured by flotation in a mixture of carbon tetrachloride and n-heptane.

Crystal data

$Cl_2PN_2O_2C_7H_{15}.H_2O$, M.W. 278·98, m.p. 40–41 °C, crystal size: $0{\cdot}15 \times 0{\cdot}26 \times 0{\cdot}33$ mm. Triclinic, $a = 13{\cdot}402\ (20)$, $b = 8{\cdot}669\ (10)$, $c = 6{\cdot}003\ (8)$ Å, $\alpha = 100{\cdot}3\ (5)$, $\beta = 96{\cdot}4\ (5)$, $\gamma = 106{\cdot}8\ (5)°$, $D_m = 1{\cdot}41$ g.cm^{-3}, $D_x = 1{\cdot}423$ g.cm^{-3}, $Z = 2$. Linear absorption coefficient for Mo $K\alpha$ radiation $\mu = 4{\cdot}31$ cm^{-1}.

The statistical averages suggest that the electron density distribution within the unit cell is centrosymmetric. Hence the space group $P\bar{1}$ was assumed for the study, and this was confirmed by the successful structure analysis.

The reflexion intensities were measured on an automatic diffractometer (four circle AED Siemens) using Zr-filtered Mo $K\alpha$ radiation. Intensities for 2552 reflexions were measured by scanning in the θ–2θ mode up to $2\theta=51°$. Of these, 1276 reflexions were considered to be unobserved, because their net intensities did not exceed twice the estimated standard deviation from counting statistics. The standard deviations in the intensities were calculated, in this case, from the formula $\sigma(I)=[I_+^2+(0{\cdot}02I_-)^2]^{1/2}$ where $I_+=i_p+i_{gr}$ and $I_-=i_p-i_{gr}$ (i_p is the peak intensity and i_{gr} is the background intensity, both of them are integrated). The intensities were corrected for the Lorentz and polarization factors. Absorption and extinction corrections were not applied.

Structure determination and refinement

The structure was solved by direct phasing methods, applying the Sayre relation (Sayre, 1952).

After the observed structure factors were scaled and normalized to $|E|$ values by means of a Wilson plot, 355 reflexions with $|E|$ values greater than 1·5 were obtained.

The whole process was performed using a Fortran IV computer program (Long, 1965), but only 260 reflexions with values of $|E|\geq 1{\cdot}6$ were introduced. The E map corresponding to the solution of highest consistency index ($c=0{\cdot}992$) revealed a set of peaks of which two were higher than the rest. It was assumed that they are associated with the chlorine or phosphorus atoms. The vectors Cl(1)–Cl(1), Cl(2)–Cl(2), Cl(1)–Cl(2), Cl(1)–P, Cl(2)–P and P–P were confirmed in a preliminary three-dimensional Patterson synthesis. In addition eleven other peaks were consistent with nitrogen, oxygen and carbon atoms of a stereochemically reasonable model of the endoxan molecule. A more complete Fourier synthesis revealed the conformation of the endoxan molecule. A structure-factor calculation based on the non-hydrogen atom coordinates and a uniform isotropic temperature factor of 4·5 Å^2 gave an R value of 0·286, which dropped to 0·132 in three cycles of isotropic least-squares refinement. The Oak Ridge National Laboratory least-squares program (Busing, Martin & Levy, 1962), modified by R. Shiono, was used in the refinement. At this stage, three anisotropic least-squares cycles on the non-hydrogen atoms reduced the R value to 0·067. A three-dimensional difference synthesis was computed including the contribution of non-hydrogen atoms. This synthesis revealed the 17 hydrogen atoms. Up to this stage, the refinement was performed with unit weights. In subsequent least-squares cycles an individual weighting scheme was employed.

The quantity minimized in the least-squares calculations was $\sum w(F_o-F_c)^2$ and the weights applied were: $w=1/\sigma^2(F)$ where $\sigma(F)=0{\cdot}5\,F_o\sigma(I)/I+0{\cdot}001$ and $\sigma(I)$ is defined above.

Three additional anisotropic least-squares cycles, refining the positional parameters and anisotropic temperature factors of the non-hydrogen atoms, and only the positional parameters of the hydrogen atoms gave an R value of 0·042 and a weighted $R=0{\cdot}031$. The hydrogen atoms were given the isotropic thermal parameter of the atom to which they were bonded, and these were not refined.

The atomic scattering factors for all heavy atoms were taken from Hanson, Herman, Lea & Skillman (1964); those for hydrogen atoms were taken from *International Tables for X-ray Crystallography* (1962). The anomalous dispersion corrections for chlorine and phosphorus atoms were also taken from *International Tables*.

The final fractional atomic coordinates and their standard deviations for heavy and hydrogen atoms are given in Tables 1 and 2. Table 3 shows the final anisotropic thermal parameters for non-hydrogen atoms. The thermal parameters U_{ij} as given here are defined by: $\exp[-2\pi^2(U_{11}a^{*2}h^2+U_{22}b^{*2}k^2+U_{33}c^{*2}l^2+2U_{12}a^*b^*hk+2U_{13}a^*c^*hl+2U_{23}b^*c^*kl]$.

Table 1. *Final fractional atomic coordinates and their standard deviations (in parentheses) for non-hydrogen atoms*

	x	y	z
Cl(1)	0·4004 (1)	0·7879 (1)	0·0214 (2)
Cl(2)	−0·1193 (1)	0·3191 (1)	0·7532 (2)
P	0·2086 (1)	0·2415 (1)	0·4619 (2)
O(1)	0·3054 (1)	0·3498 (2)	0·3704 (3)
O(2)	0·1156 (1)	0·1510 (2)	0·2831 (3)
O(*W*)	0·1091 (2)	0·9458 (3)	0·8447 (4)
N(1)	0·1794 (1)	0·3732 (3)	0·6522 (4)
N(2)	0·2629 (2)	0·1342 (3)	0·6025 (4)
C(1)	0·2969 (2)	0·6567 (5)	0·7950 (6)
C(2)	0·2600 (2)	0·4860 (4)	0·8418 (6)
C(3)	0·0738 (2)	0·3913 (4)	0·6346 (6)
C(4)	0·0056 (2)	0·2809 (4)	0·7640 (6)
C(5)	0·3447 (3)	0·0681 (5)	0·5191 (7)
C(6)	0·4266 (3)	0·1975 (5)	0·4455 (7)
C(7)	0·3778 (3)	0·2703 (5)	0·2723 (7)

Table 2. *Parameters of hydrogen atoms with their standard deviations (in parentheses)*

The B values are in Å^2.

	x	y	z	B
H(1)	0·330 (3)	0·657 (5)	0·655 (7)	3·85
H(2)	0·240 (3)	0·706 (5)	0·799 (7)	3·85
H(3)	0·316 (3)	0·446 (4)	0·851 (6)	2·95
H(4)	0·231 (3)	0·489 (4)	0·984 (6)	2·95
H(5)	0·039 (3)	0·355 (4)	0·473 (6)	2·61
H(6)	0·079 (3)	0·505 (4)	0·703 (6)	2·61
H(7)	0·031 (3)	0·296 (5)	0·912 (6)	3·04
H(8)	−0·007 (3)	0·177 (5)	0·699 (7)	3·04
H(9)	0·311 (3)	0·972 (5)	0·380 (7)	3·75
H(10)	0·378 (3)	0·036 (5)	0·640 (7)	3·75
H(11)	0·480 (3)	0·148 (4)	0·376 (6)	3·98
H(12)	0·470 (3)	0·280 (5)	0·571 (7)	3·98
H(13)	0·335 (3)	0·181 (6)	0·144 (7)	4·23
H(14)	0·426 (3)	0·357 (5)	0·230 (7)	4·23
H(15)	0·036 (3)	0·907 (5)	0·800 (6)	3·76
H(16)	0·116 (3)	1·003 (5)	0·967 (7)	3·76
H(17)	0·222 (3)	0·067 (4)	0·675 (6)	1·52

A table of final observed and calculated structure factors is available from the authors on request.

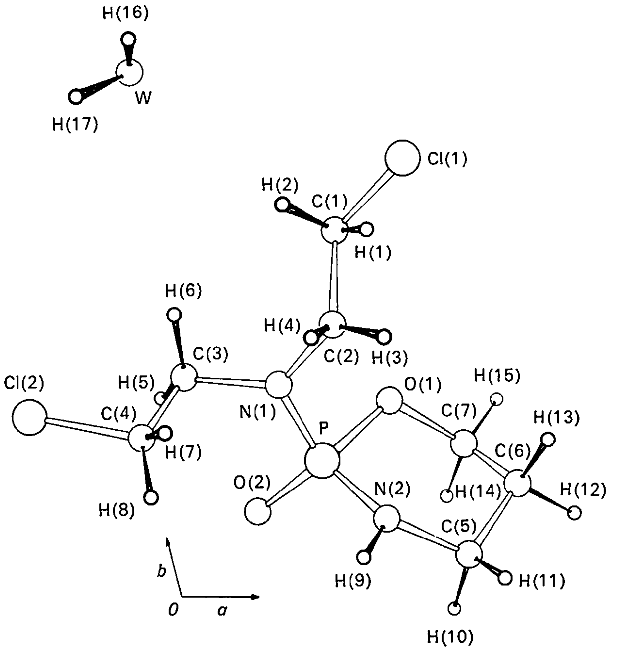

Fig. 1. The configuration of the molecule of endoxan.

Discussion of the structure

The molecular conformation

The configuration of the molecule of endoxan is illustrated in Fig. 1. This molecule consists of two parts: the bischloroethylamine (nitrogen mustard) or active group, and the phosphamidic ring or transport unit. In Table 4, various calculated least-squares planes of the molecule are collected. The maximum deviations of the atoms in planes I and II were considered somewhat higher in order to obtain a perfectly planar conformation.

The ethylene chloride chains present an extended conformation, which was derived from the calculation of torsion angles (Sundaralingam, 1969) through the bridges C(1)–C(2), C(2)–N(1), N(1)–C(3), C(3)–C(4) and P–N(1). In Table 5 the above-mentioned torsion angles are collected. The C(1)–C(2) torsion angle is higher than C(3)–C(4). This difference is, however, smaller than in the case of the bridges N(1)–C(2) and N(1)–C(3). Table 5 shows that the torsion of the bridge P–N(1) is the smallest (−1·92°).

The angle defined by the normals to the planes III and IV is 89·10°, *i.e.* the hetercyclic ring is practically normal to the ethylene chloride chains.

Table 3. *Final anisotropic thermal parameters for non-hydrogen atoms with standard deviations in parentheses*

U values in Å^2.

	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
Cl(1)	0·0610 (6)	0·0824 (8)	0·0867 (8)	−0·0026 (5)	0·0064 (6)	−0·0289 (6)
Cl(2)	0·0459 (5)	0·0707 (7)	0·0841 (7)	0·0205 (5)	0·0255 (5)	0·0146 (5)
P	0·0401 (5)	0·0449 (5)	0·0366 (5)	0·0154 (4)	0·0086 (4)	0·0052 (4)
O(1)	0·050 (1)	0·060 (2)	0·050 (2)	0·023 (1)	0·023 (1)	0·023 (1)
O(2)	0·049 (2)	0·062 (2)	0·047 (2)	0·016 (1)	−0·002 (1)	−0·009 (1)
O(*W*)	0·057 (2)	0·076 (2)	0·049 (2)	0·014 (2)	0·017 (2)	0·014 (2)
N(1)	0·032 (1)	0·042 (1)	0·039 (1)	0·016 (1)	0·004 (1)	0·003 (1)
N(2)	0·046 (2)	0·043 (2)	0·046 (2)	0·019 (2)	0·016 (1)	0·016 (2)
C(1)	0·053 (3)	0·052 (3)	0·061 (3)	0·000 (2)	−0·001 (2)	−0·001 (2)
C(2)	0·042 (2)	0·051 (2)	0·047 (2)	0·018 (2)	0·002 (2)	0·002 (2)
C(3)	0·039 (2)	0·041 (2)	0·049 (2)	0·016 (2)	0·013 (2)	0·012 (2)
C(4)	0·041 (2)	0·053 (2)	0·066 (3)	0·019 (2)	0·014 (2)	0·020 (2)
C(5)	0·052 (3)	0·053 (3)	0·086 (4)	0·028 (2)	0·025 (2)	0·016 (2)
C(6)	0·042 (3)	0·070 (3)	0·086 (3)	0·024 (2)	0·018 (2)	0·020 (3)
C(7)	0·060 (3)	0·093 (4)	0·068 (3)	0·031 (3)	0·034 (3)	0·017 (3)

Table 4. *Equations of least-squares planes in the endoxan molecule and distances of the atoms from these planes*

The equations of the planes are of the form $AX+BY+CZ=D$, where X, Y, Z are coordinates (in Å) referred to the orthogonal axes.

Plane	Atoms in plane	A	B	C	D
I	Cl(1)-C(1)-C(2)-N(1)	−0·7868	0·3861	0·5259	1·2755
II	Cl(2)-C(4)-C(3)-N(1)	0·2029	0·5100	0·8248	4·4478
III	P-N(1)-C(2)-C(3)	−0·3471	−0·7434	0·5684	0·1368
IV	P-N(2)-C(5)-C(6)-C(7)-O(1)	0·3646	0·4555	0·7913	3·5091

Plane I	
Cl(1)	−0·019
C(1)	0·019
C(2)	0·024
N(1)	−0·024

Plane II	
Cl(2)	0·024
C(4)	−0·023
C(3)	−0·030
N(1)	0·029

Plane III	
P	−0·007
N(1)	0·020
C(2)	−0·007
C(3)	−0·007

Plane IV	
P	−0·139
N(2)	0·147
C(5)	−0·203
C(6)	0·258
C(7)	−0·275
O(1)	−0·212

Table 5. *Conformation about the bis-β-chloroethylamine group*

N(1)–C(2)–C(1)–Cl(1)	183·15°
P–N(1)–C(2)–C(1)	−35·50
N(1)–C(3)–C(4)–Cl(2)	172·60
P–N(1)–C(3)–C(4)	−88·20
C(3)–N(1)–P–O(2)*	−1·92

* The torsion angle about P–N(1) was determined by O(2)–P–N(1) and P–N(1)–C(3)–C(2).

Plane IV indicates that the six-membered ring exhibits almost a chair conformation. The two atoms which are linked to this ring, O(2) and N(1), are displaced from this plane −1·468 and 1·042 Å respectively and their conformations are axial and equatorial respectively.

Bond lengths and bond angles

The bond lengths and bond angles with their estimated standard deviations are listed in Table 6. In this structure the exocyclic C–C single bonds have a value of 1·506 Å, *i.e.* a little shorter than the single C(sp^3)–C(sp^3) bond ($\simeq 4\sigma$). The C–C single bonds of the ring are 0·01 Å shorter than the exocyclic ones. One might suggest that the heterocyclic ring is under strain. The angle C(5)–C(6)–C(7) of 111·3° is slightly

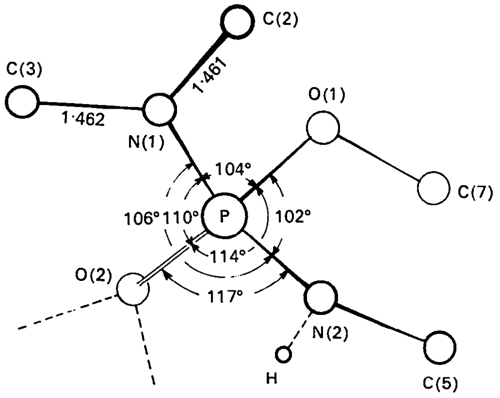

Fig. 2. Bond angles within the phosphamide group.

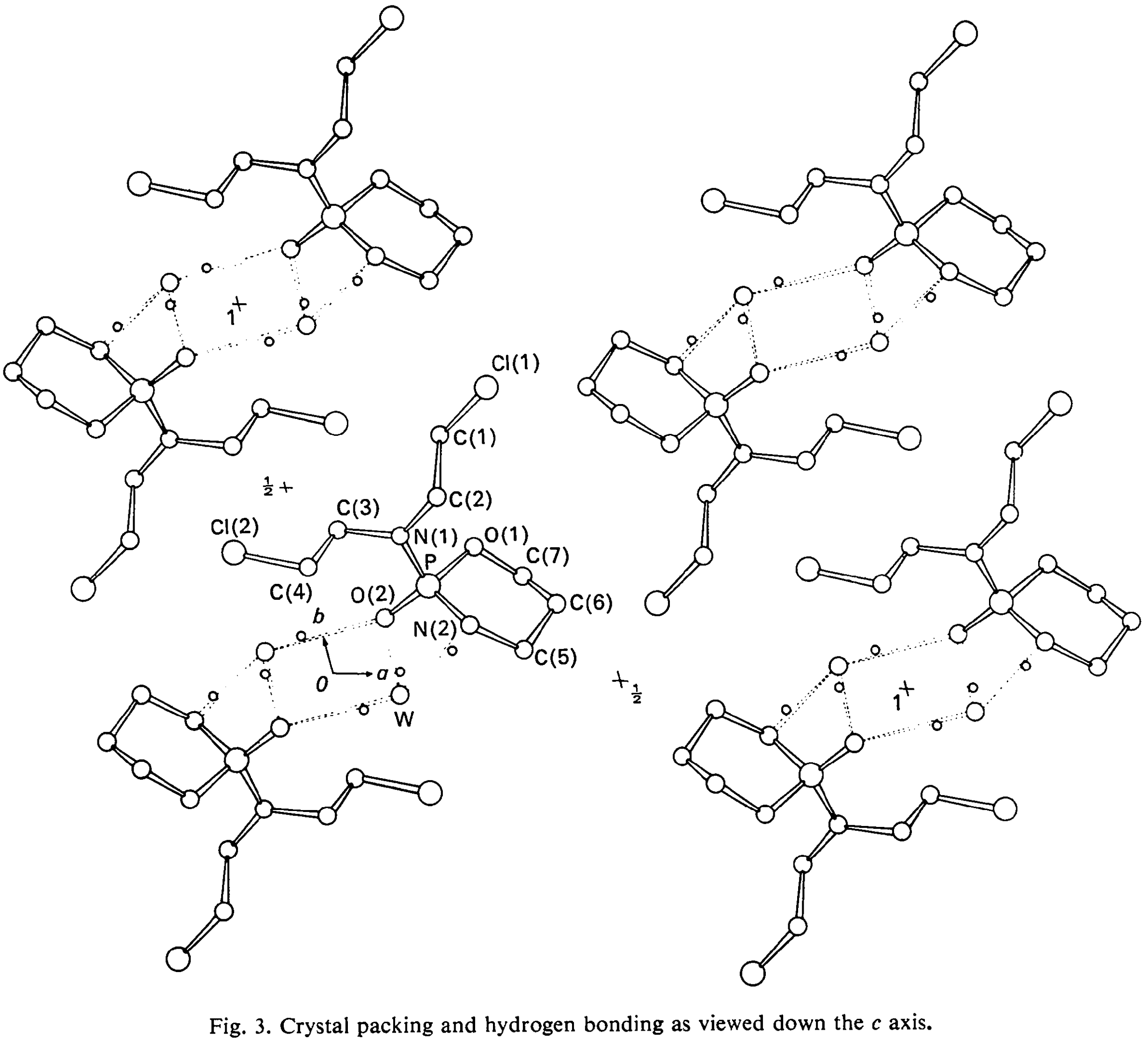

Fig. 3. Crystal packing and hydrogen bonding as viewed down the *c* axis.

greater than tetrahedral. The C–N average bond is 1·465 Å, in good agreement with the accepted value. Similarly the C–H average is 0·96 Å. The C–O bond, however, at 1·460 Å is greater than the C(sp^3)–O bond (1·43 Å). Furthermore, the C(1)–Cl(1) bond is 1·784 Å and the C(4)–Cl(2) 1·794 Å. Both of them nearly agree with the expected value for the paraffinic C–Cl bond (1·77 Å). Although the error is within 3σ, this result may indicate, particularly for the bond C(4)–Cl(2), a partial polarization, which is consistent with the fact that this compound is known to be an alkylating agent. It can also explain the shortening of the C–C bonds in chlorocthylated chains. Fig. 2 shows the phosphamide group; the two P–O bonds are different from each other. The P=O bond of 1·470 Å is very similar to the P=O bond in adenosine-3′-phosphate (Sundaralingam, 1966). On the other hand, the P–O of 1·582 Å is quite similar to the bonds such as P–OC in serine phosphate (McCallum, Robertson & Sim, 1959) and dibenzyl hydrogen phosphate (Dunitz & Rollet, 1956). The P–N bonds are 1·630 and 1·625 Å. These values are in agreement with those obtained by Ahmed & Pollard (1971) for the segments P–N–C. The O–P–O, O–P–N and N–P–N angles in the phosphamide group lie in the range 102 to 117°. The smallest angle involves the substituted atoms, while the largest involves the unsubstituted atom O(2).

Table 6. *Bonds lengths and angles and their standard deviations for non-hydrogen atoms*

	Distance (Å)		Angle (°)
Cl(1)–C(1)	1·784 (6)	Cl(1)–C(1)–C(2)	109·5 (3)
C(1)–C(2)	1·505 (7)	C(1)–C(2)–N(1)	110·7 (3)
C(2)–N(1)	1·462 (6)	C(2)–N(1)–C(3)	116·8 (3)
N(1)–C(3)	1·463 (6)	N(1)–C(3)–C(4)	110·8 (3)
C(3)–C(4)	1·507 (7)	C(3)–C(4)–Cl(2)	108·7 (3)
C(4)–Cl(2)	1·794 (6)	C(2)–N(1)–P	121·1 (2)
N(1)–P	1·630 (4)	C(3)–N(1)–P	121·9 (2)
P——N(2)	1·625 (5)	N(1)–P——N(2)	106·8 (2)
N(2)–C(5)	1·472 (7)	P——N(2)–C(5)	121·9 (3)
C(5)–C(6)	1·494 (8)	N(2)–C(5)–C(6)	110·7 (3)
C(6)–C(7)	1·493 (8)	C(5)–C(6)–C(7)	111·3 (4)
C(7)–O(1)	1·460 (7)	C(6)–C(7)–O(1)	110·3 (4)
O(1)–P	1·582 (4)	C(7)–O(1)–P	118·6 (2)
O(2)–P	1·470 (4)	O(1)–P——N(2)	102·4 (1)
		O(1)–P——O(2)	114·1 (1)
		O(2)–P——N(1)	110·0 (1)
		O(1)–P——N(1)	104·7 (1)

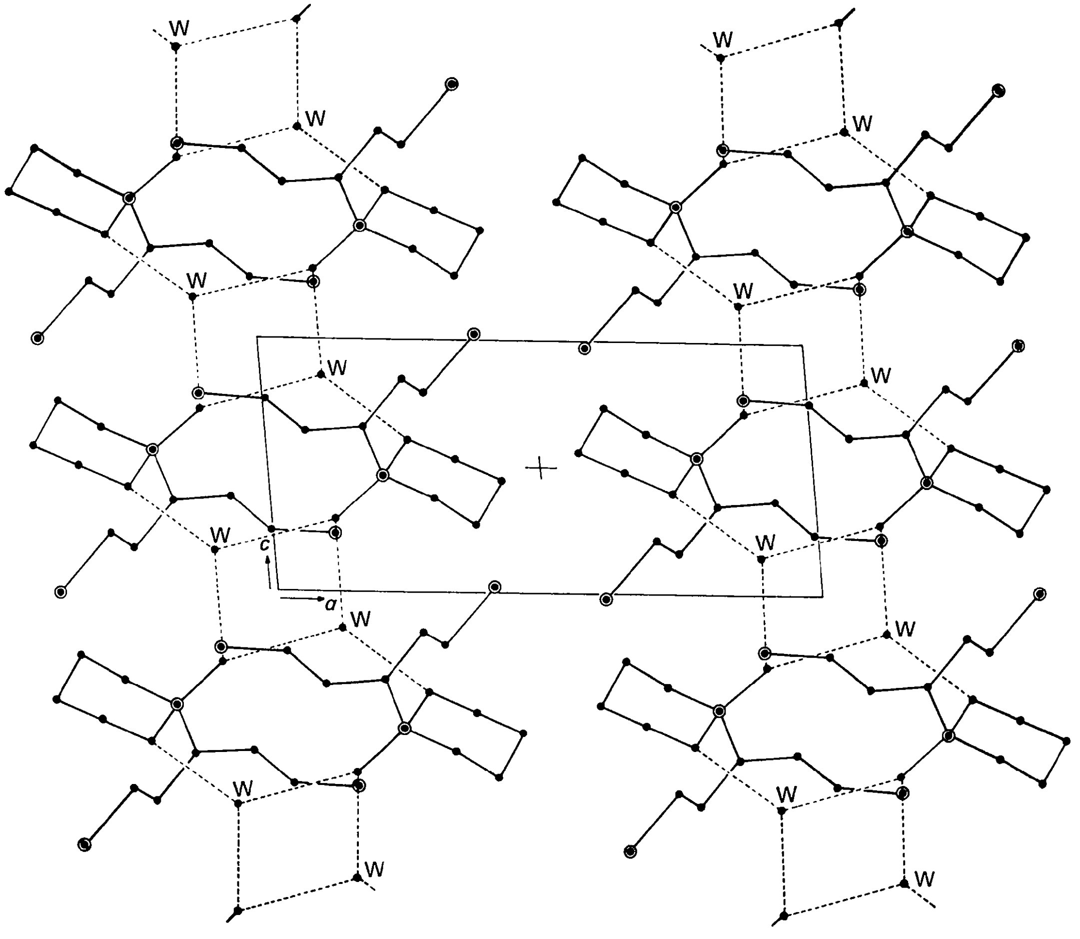

Fig. 4. Hydrogen bonding and molecular packing as viewed down the *b* axis.

Molecular packing

Figs. 3 and 4 show the molecular structure along the *c* and *b* axes. Each molecule possesses three intermolecular hydrogen bonds: O–H$\cdots$O of 2·87 and 2·85 Å respectively, and N–H$\cdots$O of 2·93 Å. The hydrogen bonding geometry around the water molecule is shown in Fig. 5.

The phosphamide group is involved in three hydrogen bonds; the N(2) atom is a hydrogen-bond donor, while the O(2) atom is an acceptor from the O(*W*) atom. The phosphate ester oxygen [O(1)] does not contribute to the intermolecular hydrogen bond, as already suggested by Sundaralingam (1970).

The molecules are arranged unidirectionally in the form of strings along the *c* axis by means of the intermolecular hydrogen bonds, related by symmetry centres, to form a stable three-dimensional intermolecular network. In addition to the water hydrogen bonds, there are intermolecular forces of the van der Waals type. In Table 7 the intermolecular distances less than 3·00 Å are given.

Table 7. *Intermolecular distances involving hydrogen atoms* ≤3·00 Å

	Symmetry code	Distance
Cl(2)—H(24)	$-x, y, 1-z$	2·94 Å
Cl(2)—H(19)	$-x, 1-y, 2-z$	2·92
O(1)—H(19)	$x, y, 1-z$	3·00
O(2)—H(23)	$x, -y, 1-z$	2·82
O(*W*)-H(20)	$-x, 1-y, 1-z$	2·96
H(16)-H(26)	$1-x, 1-y, 1-z$	2·67
H(20)-H(21)	$-x, 1-y, z$	2·50
H(20)-H(30)	$-x, 1-y, 1-z$	2·42
H(31)-H(32)	$x, 1+y, z$	2·42
H(22)-H(30)	$-x, 1-y, 2-z$	2·72

All computer calculations on this structure were performed on the 7090 IBM computer of the Centro de Calculo de la Universidad de Madrid, and on the Univac 1108 computer of the Ministerio de Educación y Ciencia de Madrid.

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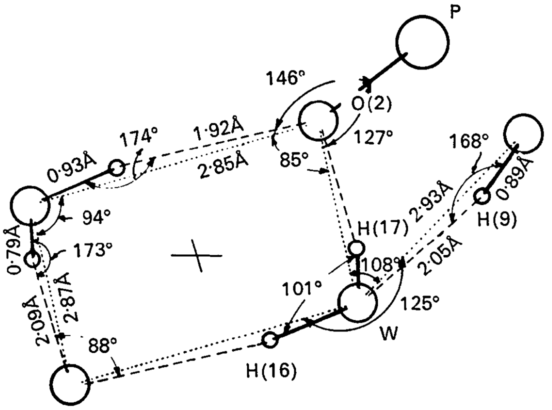

Fig. 5. Environment of the water molecule.

References

Arnold, H., Bourseaux, F. & Brock, N. (1958). *Naturwiss.* **45**, 64.

Ahmed, F. R. & Pollard, D. R. (1971). *Acta Cryst.* B**27**, 163.

Busing, W. R., Martin, K. O. & Levy, H. A. (1962). *ORFLS*. Report ORNL-TM-305, Oak Ridge National Laboratory, Oak Ridge, Tennessee.

Dunitz, J. D. & Rollett, J. S. (1956). *Acta Cryst.* **9**, 327.

Hanson, H. P., Herman, F., Lea, J. D. & Skillman, S. (1964). *Acta Cryst.* **17**, 1040.

International Tables for X-ray Crystallography (1962). Vol. III. Birmingham: Kynoch Press.

Long, R. E. (1965). Ph.D. Dissertation. Univ. of California at Los Angeles.

McCallum, G. H., Robertson, J. M. & Sim, G. A. (1959). *Nature, Lond.* **186**, 1863.

Ross, W. C. Y. (1945). *Advanc. Cancer Res.* p. 397.

Sayre, D. (1952). *Acta Cryst.* **5**, 60.

Sundaralingam, M. (1966). *Acta Cryst.* **21**, 495.

Sundaralingam, M. (1969). *Biopolymers*, **7**, 821.

Sundaralingam, M. & Putkey, E. F. (1970). *Acta Cryst.* B**26**, 790.