*Acta Cryst.* (1979). B35, 1620–1622

# The Crystal and Molecular Structure of 3-Chloroethyl-2-(mesyloxyethylamino)tetrahydro-2*H*-1,3,2-oxazaphosphorine 2-Oxide: Suphosphamide ($C_8H_{18}ClN_2O_5PS$)

BY A. PERALES, J. FAYOS AND S. GARCÍA-BLANCO

*Departamento de Rayos X, Instituto de Química-Física 'Rocasolano', Serrano* 119, *Madrid* 6, *Spain*

(*Received* 19 *December* 1978; *accepted* 16 *March* 1979)

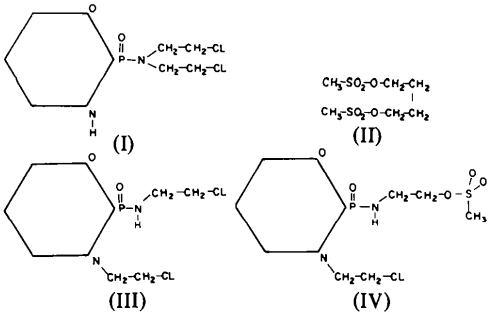
## Abstract

Suphosphamide is monoclinic, space group $P2_1/n$, with $a = 14{\cdot}822$ (2), $b = 9{\cdot}063$ (1), $c = 11{\cdot}227$ (1) Å, $\beta = 107{\cdot}36$ (2)°, $Z = 4$. The configuration at the P atom is axial for the phosphoryl O atom, and equatorial for the extracyclic N(2), as seems to be usual for cyclophosphamide derivatives. The ring is in the chair conformation. The molecules are linked by N—H···O hydrogen bonds.

## Introduction

Cyclophosphamide (I) (Fig. 1), an antitumour alkylating agent, is widely used in the treatment of many types of cancer. On the other hand, busulfan (II), as the main representative of the mesyloxyalkyl compounds, is used only for chronic myeloid leukaemia. Both compounds are leukotoxic but each has a characteristic leukotoxicity. The underlying causes of the differences in activity between the 2-chloroethyl and mesyloxyalkyl groups have not yet been elucidated.

The agents chemically derived from iphosphamide (III) are of particular interest because of their chemotherapeutic properties. The ASTA Werke Laboratories have developed a series of compounds with a range of molecular variations. Suphosphamide (IV) is characterized by the presence of the extracyclic alkylsulphonyloxyalkyl amino group. We have undertaken the present structural study to obtain a greater knowledge of the configuration of this drug.



(I) (II) (III) (IV)

Fig. 1. Schematic formulae of compounds which have antitumour activities. (I) Cyclophosphamide. (II) Busulfan. (III) Iphosphamide. (IV) Suphosphamide.

0567-7408/79/071620-03$01.00

## Experimental

A powder sample of suphosphamide was kindly provided by ASTA Werke Laboratories. Crystals were obtained from warm methylene chloride which, after cooling, was treated with ether, followed by slow cooling. Crystals grew as clear, colourless needles. Although they were of poor quality, a crystal $0{\cdot}2 \times 0{\cdot}4 \times 0{\cdot}15$ mm was used for data collection. Preliminary photographs indicated a monoclinic $P2_1/n$ lattice. Crystal data are given in Table 1. The intensities were collected on an automatic four-circle Philips PW 1100 diffractometer with graphite-monochromatized Mo $K\alpha$ radiation and the $\omega/2\theta$ scan mode to a limit of $2\theta = 25°$. 3341 independent reflections were measured; only 1618 with $I > 2\sigma(I)$ were used to refine the structure. The data were corrected for Lorentz and polarization effects but not for absorption. An overall temperature factor ($B = 3{\cdot}42$ Å$^2$) and scale factor were calculated from a Wilson plot and used to compute normalized structure factors (Karle & Hauptman, 1956).

## Structure determination and refinement

The structure was solved with *MULTAN* (Main, Woolfson, Lessinger, Germain & Declercq, 1977) from 300 reflections with $E > 1{\cdot}5$. An $E$ map calculated from the best set of phases showed a molecular

Table 1. *Crystal data*

| | |
|---|---|
| $C_8H_{18}ClN_2O_5PS$ | $M_r = 320{\cdot}73$ |
| $a = 14{\cdot}822$ (2) Å | Space group $P2_1/n$ |
| $b = 9{\cdot}063$ (1) | $Z = 4$ |
| $c = 11{\cdot}227$ (1) | $D_c = 1{\cdot}47$ Mg m$^{-3}$ |
| $\beta = 107{\cdot}36$ (2)° | $\mu = 0{\cdot}528$ mm$^{-1}$ |
| $V = 1439{\cdot}3$ (3) Å$^3$ | $\lambda$(Mo $K\alpha$) = 0·7107 Å |

fragment of twelve atoms. Subsequent Fourier maps led to the identification of the remaining atoms. The structure was refined by full-matrix least squares with anisotropic temperature factors for non-H atoms. The fixed H atoms were positioned from molecular geometry on the assumption that C—H = 1·1 Å and H—C—H = 104°. A difference synthesis confirmed the location of these H atoms. The H atom attached to N(2) which is involved in the hydrogen bond was found in the difference synthesis.

The isotropic thermal parameters assigned to the H atoms were those of the atoms to which they are bonded (Hamilton, 1959). A final refinement including all H atoms converged to $R = 0{\cdot}087$. In this calculation, the positional and isotropic thermal parameters for H atoms were fixed. During the refinement, unit weights were used for all observed reflections; this is because, after plotting $\langle \Delta^2 F \rangle$ *vs* $F_o$ or $\sin\theta/\lambda$, $\langle \Delta^2 F \rangle_{max} < 3\langle \Delta^2 F \rangle_{min}$. Anomalous-dispersion corrections were applied for Cl, S and P. The calculations were performed with XRAY 70. The numbering of the atoms is shown in Fig. 2. The coordinates for non-hydrogen atoms are in Table 2.*

Table 2. *Fractional atomic coordinates* ($\times 10^4$) *for non-hydrogen atoms*

E.s.d.'s are given in parentheses and refer to the last positions.

| | *x* | *y* | *z* |
|---|---|---|---|
| Cl | 1457 (3) | 2781 (4) | −3374 (3) |
| S | 2067 (2) | 6805 (4) | 4079 (2) |
| P | 415 (2) | 6900 (3) | −1076 (2) |
| O(1) | 329 (5) | 8628 (8) | −938 (6) |
| O(2) | −488 (5) | 6133 (9) | −1283 (7) |
| O(3) | 1654 (7) | 8216 (12) | 4060 (9) |
| O(4) | 1646 (7) | 5570 (13) | 4438 (8) |
| O(5) | 2168 (5) | 6478 (8) | 2751 (6) |
| N(1) | 900 (6) | 6801 (9) | −2221 (7) |
| N(2) | 1186 (5) | 6352 (9) | 196 (7) |
| C(1) | 472 (12) | 7690 (18) | −3344 (11) |
| C(2) | 389 (11) | 9255 (16) | −2992 (13) |
| C(3) | −113 (8) | 9495 (12) | −2040 (11) |
| C(4) | 1439 (10) | 5428 (19) | −2438 (11) |
| C(5) | 771 (11) | 4382 (18) | −3082 (15) |
| C(6) | 2138 (7) | 6922 (14) | 689 (9) |
| C(7) | 2297 (7) | 7635 (12) | 1950 (8) |
| C(8) | 3244 (8) | 6872 (16) | 4993 (10) |

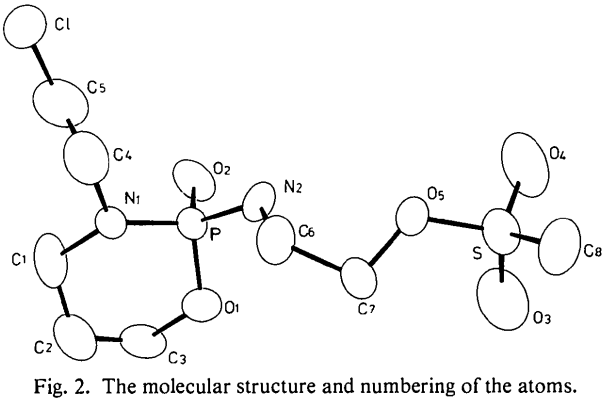



Fig. 2. The molecular structure and numbering of the atoms.

## Discussion

The conformation of the suphosphamide molecule is illustrated in Fig. 3. The ring assumes an almost perfect chair conformation (Table 4). The phosphoryl O atom is axial to the ring whereas the position of the other P substituent, N(2), is equatorial; this conformation is similar to that found in iphosphamide. The conformation of the two different chains is given by the torsion angles and is shown in Fig. 3; both are extended and directed away from each other.

The sum of the bond angles around the equatorial N(2) is 360°, showing a planar configuration, which differs from the pyramidal N(1) of the ring, whose bond angles sum to 354·6°. Other geometrical features are given in Tables 3 and 4. The planarity around the extracyclic N(2) is reflected in the distances around this atom, which are rather shorter than normal, especially for P—N(2), indicating that the N(2) lone-pair electrons contribute to a large degree to the $p\pi$–$d\pi$ P—N(2) bond and, to a lesser extent, to N(2)—C(6). The endocyclic N(1), on the other hand, deviates somewhat from a planar configuration and the degree of $p\pi$–$d\pi$ P—N(1) bonding is less appreciable. N(1)—C(1) is considerably shorter than N(1)—C(4) which, like C(5)—Cl, is too long; in consequence, C(4)—C(5) is short for C($sp^3$)—C($sp^3$) hydridization. The thermal motion for C(1), C(4) and C(5) is, however, large. A close parallel of these results has been observed in other cyclo-

* Lists of structure factors and anisotropic thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 34257 (15 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

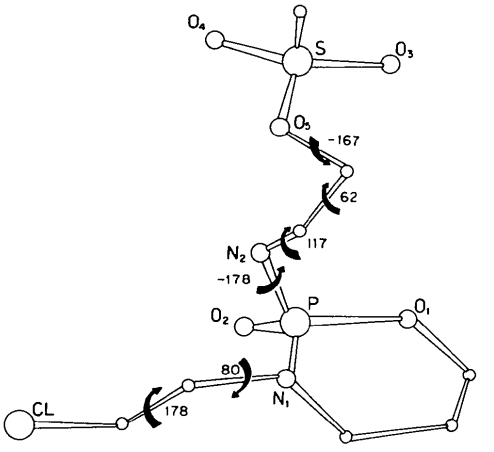



Fig. 3. The conformation of the suphosphamide molecule. The average e.s.d. for torsion angles is 1° (ranging from 0·6 to 1·2°).

phosphamide analogues and derivatives: (+)-cyclophosphamide (Karle, Karle, Egan, Zon & Brandt, 1977); 4-peroxycyclophosphamide (Sternglanz, Einspahr & Bugg, 1974); trophosphamide (Perales & García-Blanco, 1977*b*; and iphosphamide (Perales & García-Blanco, 1977*a*). In order to interpret these results it would be useful to know the process of rearrangement to form a new compound, since it is considered that the cytostatic effect takes place *via* biological oxidation at C(1).

Table 3. *Bond lengths* (Å) *and angles* (°)

| | | | |
|---|---|---|---|
| Cl–C(5) | 1·86 (2) | O(1)–C(3) | 1·45 (2) |
| S–O(3) | 1·42 (1) | O(5)–C(7) | 1·43 (1) |
| S–O(4) | 1·40 (1) | N(1)–C(1) | 1·47 (2) |
| S–O(5) | 1·57 (1) | N(1)–C(4) | 1·54 (2) |
| S–C(8) | 1·74 (2) | N(2)–C(6) | 1·45 (2) |
| P–O(1) | 1·58 (1) | C(1)–C(2) | 1·49 (2) |
| P–O(2) | 1·46 (1) | C(2)–C(3) | 1·49 (3) |
| P–N(1) | 1·65 (2) | C(4)–C(5) | 1·41 (2) |
| P–N(2) | 1·62 (2) | C(6)–C(7) | 1·51 (2) |

| | | | |
|---|---|---|---|
| O(3)–S–O(4) | 120·0 (7) | S–O(5)–C(7) | 121·8 (6) |
| O(3)–S–O(5) | 108·6 (5) | P–N(1)–C(1) | 117·4 (9) |
| O(3)–S–C(8) | 109·3 (6) | P–N(1)–C(4) | 122·4 (8) |
| O(4)–S–O(5) | 107·4 (5) | C(1)–N(1)–C(4) | 114·8 (9) |
| O(4)–S–C(8) | 108·3 (6) | P–N(2)–C(6) | 125·4 (7) |
| O(5)–S–C(8) | 101·7 (5) | P–N(2)–H(N2) | 117·3 |
| O(1)–P–O(2) | 112·9 (4) | C(6)–N(2)–H(N2) | 117·3 |
| O(1)–P–N(1) | 101·3 (4) | N(1)–C(1)–C(2) | 110·1 (9) |
| O(1)–P–N(2) | 105·9 (4) | C(1)–C(2)–C(3) | 115·4 (1·2) |
| O(2)–P–N(1) | 116·1 (4) | O(1)–C(3)–C(2) | 109·8 (9) |
| O(2)–P–N(2) | 111·5 (4) | N(1)–C(4)–C(5) | 108·0 (1·1) |
| N(1)–P–N(2) | 108·2 (4) | Cl–C(5)–C(4) | 106·2 (1·1) |
| P–O(1)–C(3) | 118·9 (9) | N(2)–C(6)–C(7) | 111·9 (9) |
| | | O(5)–C(7)–C(6) | 105·2 (8) |

Table 4. *Least-squares planes and deviations* (Å) *of the atoms from them*

The equations of the best planes (expressed in orthogonal space as $PI + QJ + RK = S$)

Plane I: $0{\cdot}9354I + 0{\cdot}0694J + 0{\cdot}3466K = 0{\cdot}9460$
Plane II: $0{\cdot}6998I + 0{\cdot}5816J + 0{\cdot}4147K = 3{\cdot}8420$
Plane III: $0{\cdot}5007I - 0{\cdot}6977J - 0{\cdot}5123K = -3{\cdot}2841$

| Plane I | | Plane II | | Plane III | |
|---|---|---|---|---|---|
| P | 0·001 (3) | P | 0·000 (3) | P | 0·000 (3) |
| O(1) | −0·001 (7) | C(1) | 0·000 (16) | C(6) | 0·000 (11) |
| C(1) | −0·001 (17) | C(4) | 0·000 (16) | H(N2) | 0·000 (0) |
| C(2) | 0·001 (17) | N(1)* | 0·210 (9) | N(2)* | 0·007 (8) |
| N(1)* | 0·601 (10) | | | | |
| C(3)* | −0·624 (12) | | | | |
| O(2)* | −1·310 (8) | | | | |
| N(2)* | 1·110 (8) | | | | |

* Not included in the calculation of the plane.

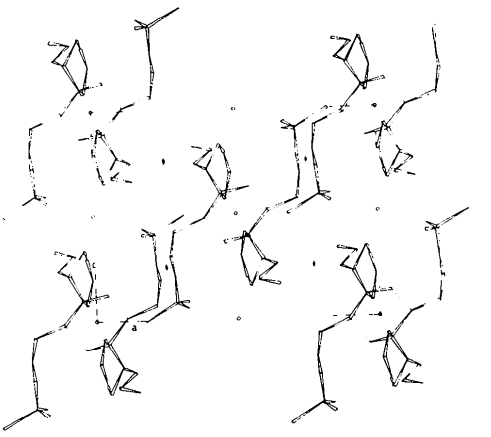


Fig. 4. The arrangement of the molecules viewed down **b**. Broken lines indicate hydrogen bonds.

Fig. 4 shows the molecular packing viewed down **b**. N(2)–H···O=P hydrogen bonds link molecules into dimers across a centre of symmetry. The O(2)···N(2) distance is 2·89 (2) Å, compared with N–H···O bonds of 2·95 Å for iphosphamide (Perales & García-Blanco, 1977*a*), 2·93 Å for endoxan (García-Blanco & Perales, 1972) and 2·84 Å for (+)-cyclophosphamide. The geometry of the present hydrogen bond is: N–H···O ($-x$, $-y+\frac{1}{2}$, $-z$): N–H 1·11 Å, O···H 1·80 Å, N···O 2·89 (2) Å; ∠N–H···O 167·35°.

## References


García-Blanco, S. & Perales, A. (1972). *Acta Cryst.* B**28**, 2647–2652.

Hamilton, W. C. (1959). *Acta Cryst.* **12**, 609–610.

Karle, I. L., Karle, J. M., Egan, W., Zon, G. & Brandt, J. A. (1977). *J. Am. Chem. Soc.* **99**, 4803–4807.

Karle, J. & Hauptman, H. (1956). *Acta Cryst.* **9**, 635–651.

Main, P., Woolfson, M. M., Lessinger, L., Germain, G. & Declercq, J. P. (1977). *MULTAN* 74. *A System of Computer Programs for the Automatic Solution of Crystal Structures from X-ray Diffraction Data.* Univs. of York, England, and Louvain, Belgium.

Perales, A. & García-Blanco, S. (1977*a*). *Acta Cryst.* B**33**, 1935–1939.

Perales, A. & García-Blanco, S. (1977*b*). *Acta Cryst.* B**33**, 1939–1943.

Sternglanz, H., Einspahr, H. M. & Bugg, C. E. (1974). *J. Am. Chem. Soc.* **96**, 4014–4015.