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Structure of the Radiation Protection Agent *S*-2-(3-Aminopropylamino)ethylphosphorothioic Acid (WR 2721)

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Abstract. $C_5H_{15}N_2O_3PS.3H_2O$, $M_r = 268{\cdot}3$, orthorhombic, $P2_12_12_1$, $a = 6{\cdot}762$ (1), $b = 8{\cdot}458$ (1), $c = 21{\cdot}564$ (3) Å, $V = 1233{\cdot}3$ Å^3, $Z = 4$, $D_x = 1{\cdot}445$ g cm^{-3}, Cu $K\alpha$, $\lambda = 1{\cdot}54178$ Å, $\mu = 36{\cdot}1$ cm^{-1}, $F(000) = 576$, room temperature, final $R = 3{\cdot}55\%$ for 1075 reflections with $|F_o| > 3\sigma$. The overall conformation of the molecule is folded with an intramolecular hydrogen bond between N(3) and O(1) of the SPO_3 group. The folded conformation of the molecule has a chiral twist. The molecule is a double zwitterion with the two phosphate hydrogens moved to the two nitrogen atoms, and the three P–O bonds are of equal length at 1·52 Å. The S–P bond is unusually long at 2·12 Å. Each H atom on each N atom and in each water molecule participates in hydrogen bonding. One of the N(7) hydrogen atoms forms a bifurcated intermolecular hydrogen bond to two of the phosphate O atoms.

Introduction. The title compound (WR 2721) was developed by the Walter Reed Army Institute of Research and the National Cancer Institute as a protective agent against the damaging and/or lethal effects of ionizing radiation (Sweeney, 1979). WR 2721 increases the radiation resistance of normal tissues to X- or γ-radiation by a factor of 1·2 to 3·4 (Yuhas, Spellman & Culo, 1980). Yuhas (1970) has demonstrated a dose reduction factor of 2·7 by WR 2721 against 30-day mortality in C57B1/6J mice. WR 2721 has been studied in clinical trials as a radioprotector of normal tissues in oncology radiation therapy (Constine, Zagars, Rubin & Kligerman, 1986) and has also been studied as an adjunctive therapy for alkylating agents in oncology patients (Glick, Glover, Weiler, Norfleet, Yuhas & Kligerman, 1984; Glover, Glick, Weiler, Fox, Turrisi & Kligerman, 1986) and for patients with cystic fibrosis (Tabachink, Peterson & Cerami, 1980). Through a route that bypasses the blood brain barrier, WR 2721 is being studied for its potential to provide radioprotection to healthy central nervous system tissues (Spence, Krohn, Edmondson, Steele & Rasey, 1986).

Although WR 2721 is the best known radioprotective agent, it has limitations for its proposed use as a radioprotectant for military personnel. Clinical trials of oncology patients show that most patients experience nausea and a small percentage (5%) experience significant hypotension (Kligerman *et al.*, 1984). The radioprotection of an oral dose, the desired route of administration for the military, of WR 2721 in large species such as the monkey is poor (Davidson, Grenan & Sweeney, 1980). In addition, the duration of radioprotection of WR 2721 in animal studies is relatively short, the best protection in the mouse occurring within 15 to 180 min post i.p. dosing with protection rapidly diminishing past 180 min (Davidson, Grenan & Sweeney, 1980). The three-dimensional structure of WR 2721 was established to provide information with respect to overall conformation and to the interatomic distance between potentially pharmacologically active N and S atoms, information which may lead to improved radioprotectants.

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Experimental. The title compound was synthesized and crystallized from ethanol/water on contract for the Walter Reed Army Institute of Research by Ash Stevens Inc. (Detroit, MI). Diffraction data were collected from a clear plate crystal, 0·08 × 0·15 × 0·03 mm, in the θ–2θ mode to a maximum 2θ value of 120° on the *R3M* Nicolet four-circle diffractometer (Nicolet Corp., Madison, WI) with a graphite monochromator. Range of indices: h 0→7, k 0→9 and l 0→24. The total number of independent reflections was 1181. The standard reflections 600, 060 and 0,0,14 were monitored after every 60 intensity measurements. The standards remained constant within 3·9%. The lattice parameters were based on 22 centered reflections with 2θ values between 24 and 86°. No correction for absorption or extinction was applied. The structure was solved routinely by direct phase determination (Karle & Karle, 1966). Ten non-hydrogen atoms were found in the first E map. The next cycle produced the remaining non-hydrogen atoms including the water molecules. All of the H atoms were found in difference maps. Least-squares refinement was performed using 1075 reflections with $|F_o| > 3\sigma(F_o)$. Coordinates for all atoms except the H atoms on the C atoms were refined (on F) by a blocked cascade program in the *SHELXTL* system (Sheldrick, 1980). Anisotropic thermal parameters for the C, N, O, P and S atoms and isotropic thermal parameters for H atoms were refined for a total of 169 parameters. Final $R = 3{\cdot}55\%$ and $wR = 3{\cdot}58\%$, $w = 1/\sigma^2(F)$. The other hand of the molecule had a final $R = 4{\cdot}4\%$. The absolute configuration of the molecules in the crystal studied was determined by anomalous scattering of the S and P atoms. The confidence level (Hamilton, 1965) is >99·5% that the model giving $R = 3{\cdot}55\%$ is the correct stereoisomer. Final difference electron density $|\rho| < 0{\cdot}39$ e Å^{-3}. Atomic scattering factors were those incorporated in *SHELXTL* (Sheldrick, 1980).

Discussion. Coordinates and U_{eq} values for the non-hydrogen atoms and coordinates for the refined H atoms are listed in Table 1.* Bond lengths, bond angles and torsion angles are listed in Table 2. The bond length of the H atoms attached to C atoms was kept fixed at 0·96 Å throughout the refinement procedure.

WR 2721 crystallized in a chiral space group which suggests that the molecules possess a chiral character. Although the molecule does not contain any asymmetric carbon atoms, it does possess a conformational chiral twist. All of the molecules in the crystal studied have the same chiral twist.

* Lists of structure factors, anisotropic thermal parameters and H-atom parameters have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 44288 (6 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 1. *Fractional coordinates* (×10⁴) *and equivalent isotropic thermal parameters* U_{eq} (×10³) *with e.s.d.'s in parentheses*

Coordinates and U_{iso} values have been refined only for hydrogen atoms in water molecules and those bonded to N(3) and N(7).

$U_{eq} = \frac{1}{3}\sum_i\sum_j U_{ij} a_i^* a_j^* \mathbf{a}_i.\mathbf{a}_j$.

	x	y	z	U_{eq}(Å²)
S	8808 (1)	4227 (1)	8255 (1)	33 (1)
P	7412 (1)	4894 (1)	9094 (1)	21 (1)
O(1)	6900 (3)	6638 (3)	9032 (1)	28 (1)
O(2)	8863 (4)	4609 (3)	9617 (1)	34 (1)
O(3)	5635 (4)	3813 (3)	9119 (1)	34 (1)
C(1)	11164 (5)	5274 (4)	8278 (2)	34 (1)
C(2)	11045 (6)	7033 (4)	8145 (2)	33 (1)
N(3)	10499 (4)	7957 (3)	8708 (1)	26 (1)
C(4)	10371 (6)	9697 (4)	8588 (2)	30 (1)
C(5)	10009 (5)	10611 (4)	9184 (2)	30 (1)
C(6)	7977 (5)	10314 (4)	9457 (2)	30 (1)
N(7)	7641 (4)	11326 (3)	10013 (1)	28 (1)
W(1)*	9033 (5)	1637 (4)	2938 (1)	52 (1)
W(2)*	8547 (4)	7270 (4)	446 (1)	45 (1)
W(3)*	9708 (6)	3440 (3)	1830 (1)	55 (1)
H(1*n*3)	11433 (60)	7823 (46)	8991 (19)	34 (2)
H(2*n*3)	9380 (57)	7612 (42)	8874 (17)	34 (2)
H(1*n*7)	7537 (62)	12361 (56)	9861 (17)	37 (2)
H(2*n*7)	8655 (61)	11000 (46)	10352 (17)	37 (2)
H(3*n*7)	6450 (43)	11165 (33)	10170 (12)	37 (2)
H(1*w*1)	8812 (76)	2182 (48)	3278 (14)	62 (3)
H(2*w*1)	9505 (75)	703 (35)	3059 (22)	62 (3)
H(1*w*2)	9706 (43)	7531 (50)	633 (20)	53 (3)
H(2*w*2)	8816 (67)	6518 (40)	162 (16)	53 (3)
H(1*w*3)	9625 (80)	2811 (46)	1503 (15)	65 (3)
H(2*w*3)	9625 (81)	2980 (51)	2202 (12)	65 (3)

* O atom of water molecule.

Table 2. *Bond lengths* (Å), *bond angles* (°) *and torsion angles* (°) *involving the backbone atoms of WR* 2721

S–P	2·116 (1)	S–C(1)	1·824 (4)
P–O(1)	1·521 (2)	P–O(2)	1·514 (2)
P–O(3)	1·511 (3)	C(1)–C(2)	1·518 (5)
C(2)–N(3)	1·491 (4)	N(3)–C(4)	1·497 (4)
C(4)–C(5)	1·520 (5)	C(5)–C(6)	1·515 (5)
C(6)–N(7)	1·490 (4)		

P–S–C(1)	103·7 (1)	S–P–O(1)	106·6 (1)
S–P–O(2)	107·7 (1)	O(1)–P–O(2)	111·5 (1)
S–P–O(3)	103·0 (1)	O(1)–P–O(3)	114·2 (1)
O(2)–P–O(3)	113·1 (1)	S–C(1)–C(2)	115·2 (3)
C(1)–C(2)–N(3)	111·9 (3)	C(2)–N(3)–C(4)	112·9 (3)
N(3)–C(4)–C(5)	111·3 (3)	C(4)–C(5)–C(6)	112·9 (3)
C(5)–C(6)–N(7)	110·8 (3)		

C(1)–S–P–O(1)	68·7 (2)	C(1)–S–P–O(2)	−51·1 (2)
C(1)–S–P–O(3)	−170·8 (1)	P–S–C(1)–C(2)	−75·2 (2)
S–C(1)–C(2)–N(3)	83·3 (3)	C(1)–C(2)–N(3)–C(4)	−180·0 (3)
C(2)–N(3)–C(4)–C(5)	−174·5 (3)	N(3)–C(4)–C(5)–C(6)	−68·2 (4)
C(4)–C(5)–C(6)–N(7)	−175·8 (3)		

As shown in Fig. 1, the overall configuration of the molecule is folded, thus making possible an internal hydrogen bond between O(1) and N(3) and containing close to an *antigauche* rather than a *trans* conformation about S–C(1)–C(2)–N(3) and a *gauche* rather than a *trans* conformation about N(3)–C(4)–C(5)–C(5) (see torsion angles in Table 2). Both of the N atoms are quaternary and positively charged with the phosphate hydrogens being found on the N atoms. The

phosphate terminus of the molecule has a double negative charge. The C(2)–N(3)–C(4) angle of 112·6° is similar to the backbone angles found around the carbon atoms (see Table 2). The three P–O bonds are essentially equally long at approximately 1·52 Å, a bond length which is between a single P–O bond of 1·58–1·64 Å and a double P=O bond of 1·42–1·50 Å (Gitany & McEwen, 1975; Sørensen, 1977; Kutschabsky, Messerschmidt & Sohr, 1979; Donohue & Mandel, 1981).

As illustrated in Figs. 1 and 2, one side of the molecule is polar, containing the divalent negative phosphate group and the two cationic nitrogen groups. All of the hydrogen bonding occurs on this side of the molecule. The other side is hydrophobic, exposing only the CH_2 groups and the large S atom.

The crystalline structure of WR 2721 includes 12 hydrogen bonds (Fig. 2 and Table 3). Each H atom attached to an N atom or a water molecule is involved in hydrogen bonding, and each O atom attached to a P atom is involved in three hydrogen bonds. One of the H atoms, H(1*n*7), is involved in a bifurcated hydrogen bond to O(2) and O(3). From their lengths all of the hydrogen bonds are quite strong, demonstrating a strong attraction between the WR 2721 molecule and the water molecules. The extensive hydrogen bonding most likely contributed to the rigidity of the structure as exhibited by the relatively low thermal factors and low *R* factor.

The WR 2721 molecule contains an unusually long S–P bond at 2·12 Å, the typical S–P bond length being 2·05–2·08 Å (Gitany & McEwen, 1975; Sørensen, 1977; Kutschabsky, Messerschmidt & Sohr, 1979; Donohue & Mandel, 1981). The length of the S–P bond in WR 2721 may be a factor in the ease of hydrolysis of this bond *in vitro* (half-life of 38 min at 37° C in 42·5 m*M* acetate buffer at pH 4·0) (Risley, Van Etten, Shaw & Bonner, 1986) and *in vivo* (Utley, Seaver, Newton & Fahey, 1984; Swynnerton, Huelle, Mangold & Ludden, 1986). The active radioprotectant species is presently felt to be the dephosphorylated (thiol) form of WR 2721 rather than WR 2721 itself. WR 2721 remains the drug of choice owing to the greater lack of oral efficacy by the thiol form (Sweeney, 1979).

A number of analogs of WR 2721 and its dephosphorylated analog *S*-2-(3-aminopropylamino)-ethylthiol (WR 1065) have been screened for their radioprotection properties (Sweeney, 1979). One of the factors affecting radioprotective efficacy is the chain length between the N atoms and between the S and its neighboring N atom which in WR 2721 and WR 1065 appears to be optimum. Increasing the chain length between S and N(3) from two to three carbons had little effect on relative radioprotective ability; however, with i.p. dosing, the toxicity increased. Analogs of WR 2721 and WR 1065 with a chain length of two to six carbons

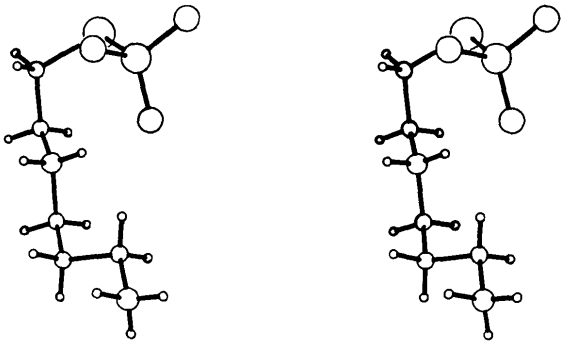

Fig. 1. Stereodiagram of WR 2721. The size of the spheres was arbitrarily chosen to correspond to the atomic weight of the atom. The numbering of the atoms is shown in Fig. 2.

Table 3. *Details of hydrogen bonds*

Donor (*D*)	Acceptor (*A*)	Distances (Å) *D*–H*	H···*A**	*D*···*A*†	Angle *D*H···*A** (°)	Symmetry equivalent of *D*
N(3)H1	*W*''(2)	0·89	1·88	2·759	173·9	*x*, *y*, *z*
N(3)H2‡	O(1)	0·89	1·90	2·766	165·6	*x*, *y*, *z*
W(1)H1	O(1)	0·88	1·97	2·843	175·6	1·5−*x*, 1−*y*, 0·5+*z*
W'(2)H1	O(1)	0·91	1·79	2·694	170·9	−0·5+*x*, 1·5−*y*, 1−*z*
N''(7)H1§	O(2)	0·94	2·17	3·021	150·8	*x*, −1+*y*, *z*
N'(7)H3	O(2)	0·89	1·92	2·791	166·4	0·5+*x*, 1·5−*y*, 2−*z*
W(2)H2	O(2)	0·90	2·00	2·883	166·8	*x*, *y*, 1+*z*
N''(7)H1§	O(3)	0·94	2·39	3·159	138·9	*x*, −1+*y*, *z*
N'''(7)H2	O(3)	1·04	1·77	2·760	158·6	−0·5+*x*, 1·5−*y*, 2−*z*
W(3)H1	O(3)	0·88	2·04	2·866	155·3	−0·5+*x*, 0·5−*y*, 1−*z*
W(3)H2	*W*''(1)	0·89	1·99	2·872	167·5	*x*, *y*, *z*
W'(1)H2	*W*(3)	0·89	2·00	2·879	168·1	2−*x*, 0·5+*y*, 0·5−*z*

* E.s.d.'s for *D*–H and H···*A* distances are near 0·04 Å and for the *D*H···*A* angles are between 2·5 and 4·0°.

† E.s.d.'s for the *D*···*A* distances are near 0·007 Å.

‡ Intramolecular hydrogen bond.

§ Bifurcated hydrogen bond with an angle of 67°.

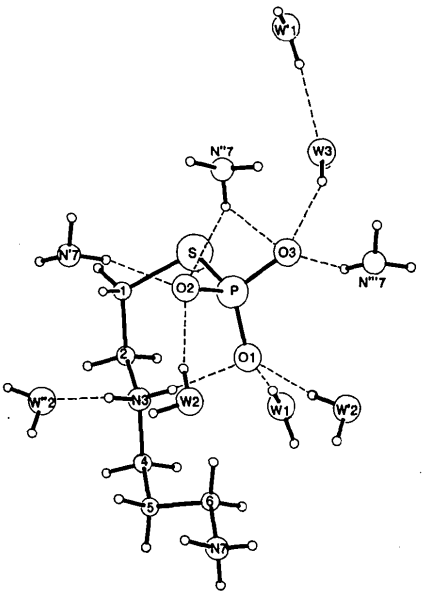

Fig. 2. Diagram illustrating the numbering scheme for the WR 2721 and water molecules. Eleven of the hydrogen bonds are depicted by the dashed lines. The $W(3)H2$ hydrogen bond to $W''(1)$ is not shown. Several fragments of surrounding WR 2721 molecules are shown in order to illustrate the hydrogen bonding which occurs between one WR 2721 molecule and its neighbors. The size of the circles was arbitrarily chosen to correspond to the atomic weight of the atom.

between the nitrogen atoms $[H_2N(CH_2)_nNH-]$ all demonstrate some radioprotection except for the WR 1065 analog with $n = 4$. Analogs of WR 1065 with $n = 7$ or greater are inactive. The most potent analog of WR 2721 is WR 2823 with $n = 5$, which showed essentially the same radioprotective strength as WR 2721; however, WR 2823 displayed more toxicity upon oral dosing. Thus, the interatomic distances found in the crystalline structure of WR 2721 between N(3) and N(7) of 4·45 Å and between N(3) and S of 3·49 Å are desirable for optimum radioprotective properties.

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Structure of 6,5′-Anhydro-6-hydroxy-2′,3′-*O*-isopropylideneuridine

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Abstract. $C_{12}H_{14}N_2O_6$, $M_r = 282·3$, orthorhombic, $P2_12_12_1$, $a = 10·412$ (2), $b = 14·936$ (2), $c = 16·651$ (3) Å, $V = 2589·46$ Å^3, $Z = 8$, $D_m = 1·450$, $D_x = 1·447$ Mg m^{-3}, λ(Cu $K\alpha$) = 1·5418 Å, $\mu = 0·902$ mm^{-1}, $F(000) = 1184·00$, $T = 293$ K, $R = 0·039$, $wR = 0·038$ for 2548 unique reflections with $F > 3\sigma(F)$. The two crystallographically independent molecules in the asymmetric unit have similar geome-

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