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Structure of the Radiation Protection Agent *S*-3-(3-Methylaminopropylamino)propylphosphorothioic Acid (WR 151,327)

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Abstract. $C_7H_{19}N_2O_3PS.3H_2O$, $M_r = 296{\cdot}3$, triclinic, $P\bar{1}$, $a = 6{\cdot}859$ (2), $b = 7{\cdot}077$ (2), $c = 16{\cdot}326$ (5) Å, $\alpha = 96{\cdot}64$ (2), $\beta = 100{\cdot}66$ (2), $\gamma = 105{\cdot}82$ (2)°, $V = 737{\cdot}7$ Å^3, $Z = 2$, $D_x = 1{\cdot}337$ g cm^{-3}, Mo $K\alpha$, $\lambda = 0{\cdot}71073$ Å, $\mu = 3{\cdot}33$ cm^{-1}, $F(000) = 320$, room temperature, final $R = 8{\cdot}4\%$ for 1614 reflections with $|F_o| > 3\sigma$. The overall conformation of the molecule is linear with a bend at the terminal N atom. The molecule is a double zwitterion with the two phosphate hydrogens residing on the two N atoms, and the three P—O bonds are of equal length at approximately 1·51 Å. The S—P bond is unusually long at 2·13 Å. Each H atom on each N atom and in each water molecule participates in hydrogen bonding. Within the crystalline lattice the molecule forms head-to-tail dimers.

Introduction. The title compound is a member of a family of phosphorothioate compounds which have shown activity as a protective agent against the damaging and/or lethal effects of ionizing X- or γ-radiation (Sweeney, 1979). One-half of the maximum tolerated dose of WR 151,327 resulted in a dose reduction factor of 1·9 as indicated by 30 day survival following irradiation of mice with ^{137}Cs γ-rays (Brown, Pittock & Rubenstein, 1982). In more recent studies with higher-energy neutron radiation, WR 151,327 has demonstrated a dose reduction factor of 1·2 to 2·2 in mouse 6 to 100 day survival studies (Sigdestad, Grdina, Connor & Hanson, 1986; Steel, Jacobs, Giambarresi & Jackson, 1987).

The ultimate goal of the US Army radioprotection program is to provide field personnel with an orally effective non-toxic radioprotector. The best known and studied radioprotective agent, *S*-2-(3-aminopropylamino)ethylphosphorothioic acid (WR 2721, $C_5H_{15}N_2O_3PS$), has limitations with respect to limited radioprotection following oral administration and a relatively short duration of radioprotection (Davidson, Grenan & Sweeney, 1980). The three-dimensional crystal structure of WR 151,327 was established to compare the overall conformation and the interatomic distance between the potentially pharmacologically

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active N and S atoms with the corresponding features of WR 2721 (Karle & Karle, 1988), information which may lead to improved radioprotective agents.

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 colorless prism, 0·08 × 0·08 × 0·05 mm, containing small inclusions in the θ–2θ mode to a maximum 2θ value of 48° on the $R3m$/micro Nicolet four-circle diffractometer with a graphite monochromator. Range of indices: h 0→7, k −8→7, and l −18→18. The total number of independent reflections was 2324. The standard reflections 017, $\bar{3}\bar{1}2$ and $2\bar{4}2$ were monitored after every 60 intensity measurements. The standards remained constant within 4·9%. The lattice parameters were based on 25 centered reflections with 2θ values between 20 and 25°. No correction for absorption or extinction was used. The structure was solved routinely by direct phase determination (Karle & Karle, 1966). All of the non-hydrogen atoms were found in the first E map. All of the H atoms were found in subsequent difference maps. Least-squares refinement was performed using 1614 reflections with $|F_o| > 3\sigma(F)$. 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). Coordinates for the H atoms bonded to C were kept fixed in idealized positions. 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 190 parameters. Final $R = 8{\cdot}4\%$ and $wR = 7{\cdot}5\%$, $w = 1/[\sigma^2(|F|) + 0{\cdot}0005(F_o)^2]$; the relatively high R is attributed to the small specimen size. Final difference electron density $|\rho| < 0{\cdot}55$ e Å^{-3}. Atomic scattering factors were those incorporated in *SHELXTL*.

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 the C atoms was kept fixed at 0·96 Å throughout the refinement procedure.

As illustrated in Figs. 1 and 2(*a*), the overall configuration of WR 151,327 is linear except for a bend at the terminal N. This conformation is distinctly different from that of the radioprotector WR 2721 illustrated in Fig. 2(*b*). WR 2721, which has one less CH_2 group between S and N, crystallized in a folded conformation that contains an intramolecular hydrogen bond between a phosphate O and the secondary N atom (Karle & Karle, 1988). As in WR 2721, both of the N atoms in WR 151,327 are quaternary and

Table 1. *Fractional coordinates* (× 10^4) *and equivalent isotropic thermal parameters* U_{eq} (Å^2 × 10^3) *with e.s.d.'s in parentheses*

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

	x	y	z	U_{eq}*
S	1211 (3)	3819 (3)	3869 (1)	44 (1)
P	1759 (3)	3491 (3)	2626 (1)	28 (1)
O(1)	1191 (9)	1294 (7)	2268 (3)	43 (2)
O(2)	4049 (7)	4505 (7)	2693 (3)	36 (2)
O(3)	334 (8)	4547 (7)	2192 (3)	36 (2)
C(1)	2728 (12)	2378 (11)	4393 (4)	42 (3)
C(2)	2640 (12)	2585 (10)	5327 (4)	37 (3)
C(3)	3719 (13)	1269 (11)	5779 (4)	40 (3)
N(4)	3730 (10)	1612 (9)	6698 (4)	33 (3)
C(5)	4483 (12)	171 (11)	7181 (4)	40 (3)
C(6)	4173 (12)	543 (11)	8069 (4)	40 (3)
C(7)	4952 (12)	−722 (11)	8666 (5)	40 (3)
N(8)	3944 (12)	−2907 (10)	8390 (4)	37 (3)
C(9)	4296 (13)	−4010 (11)	9101 (5)	52 (4)
W(1)†	834 (13)	808 (13)	9352 (5)	73 (4)
W(2)†	10007 (10)	1931 (11)	6990 (4)	47 (3)
W(3)†	1137 (12)	6200 (10)	747 (4)	66 (3)
H(1*n*4)	2137 (129)	1766 (113)	6785 (49)	86 (26)
H(2*n*4)	4336 (76)	2666 (69)	6854 (29)	20 (13)
H(1*n*8)	2516 (134)	−3381 (117)	8116 (51)	78 (28)
H(2*n*8)	4580 (91)	−3331 (84)	8052 (37)	27 (18)
H(1*w*1)	299 (89)	597 (83)	9613 (38)	25 (17)
H(2*w*1)	390 (97)	154 (90)	8967 (42)	39 (19)
H(1*w*2)	9872 (119)	3430 (119)	7230 (49)	82 (25)
H(2*w*2)	9660 (99)	1436 (100)	7133 (40)	38 (20)
H(1*w*3)	994 (121)	5764 (113)	1113 (48)	76 (26)
H(2*w*3)	526 (189)	6827 (184)	717 (82)	57 (55)

* Coordinates and U_{iso} values have been refined only for H atoms in water molecules and those bonded to N(4) and N(8).

† O atom of water molecule.

Table 2. *Bond lengths* (Å), *bond angles* (°) *and torsion angles* (°) *involving the backbone atoms of WR* 151,327 *with e.s.d.'s in parentheses*

S–P	2·129 (3)	S–C(1)	1·818 (9)
P–O(1)	1·512 (5)	P–O(2)	1·516 (5)
P–O(3)	1·510 (6)	C(1)–C(2)	1·529 (10)
C(2)–C(3)	1·514 (12)	C(3)–N(4)	1·491 (9)
N(4)–C(5)	1·501 (11)	C(5)–C(6)	1·508 (11)
C(6)–C(7)	1·519 (11)	C(7)–N(8)	1·488 (9)
N(8)–C(9)	1·492 (11)		

P–S–C(1)	102·3 (3)	S–P–O(1)	109·0 (3)
S–P–O(2)	107·7 (2)	O(1)–P–O(2)	110·5 (3)
S–P–O(3)	100·7 (2)	O(1)–P–O(3)	114·2 (3)
O(2)–P–O(3)	114·0 (3)	S–C(1)–C(2)	109·2 (6)
C(1)–C(2)–C(3)	111·5 (7)	C(2)–C(3)–N(4)	110·0 (7)
C(3)–N(4)–C(5)	114·2 (6)	N(4)–C(5)–C(6)	108·2 (7)
C(5)–C(6)–C(7)	115·6 (7)	C(6)–C(7)–N(8)	114·3 (6)
C(7)–N(8)–C(9)	111·3 (5)		

C(1)–S–P–O(1)	54·8 (4)	C(1)–S–P–O(2)	−65·1 (3)
C(1)–S–P–O(3)	175·3 (3)	P–S–C(1)–C(2)	175·7 (4)
S–C(1)–C(2)–C(3)	174·9 (4)	C(1)–C(2)–C(3)–N(4)	176·1 (5)
C(2)–C(3)–N(4)–C(5)	171·5 (5)	C(3)–N(4)–C(5)–C(6)	−173·5 (5)
N(4)–C(5)–C(6)–C(7)	−177·1 (5)	C(5)–C(6)–C(7)–N(8)	−60·3 (9)
C(6)–C(7)–N(8)–C(9)	−163·4 (7)		

* 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 44806 (12 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

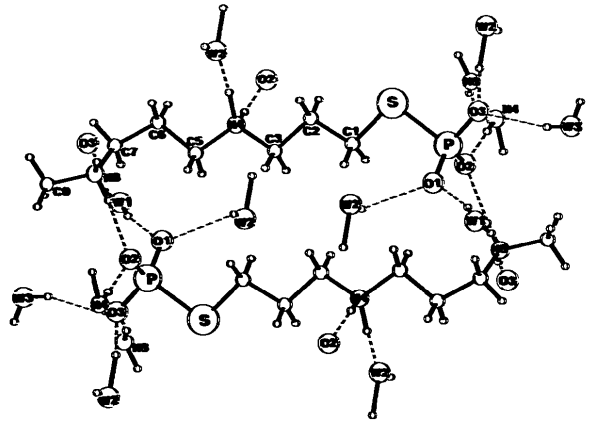

Fig. 1. Conformation of WR 151,327. The numbering of atoms is indicated. Hydrogen bonds between WR 151,327 molecules and between WR 151,327 and water molecules are depicted by the dashed lines. Two WR 151,327 molecules are shown in order to illustrate pairing of molecules within the crystalline lattice. The size of the circles was arbitrarily chosen to correspond roughly to the atomic weight of the atom.

Table 3. *Hydrogen-bond distances*

Donor atom	Hydrogen atom	Acceptor atom	Distance donor—acceptor* (Å)	Distance hydrogen—acceptor* (Å)	Symmetry equivalent of donor
N(4)	H(1*n*4)	*W*(2)	2·745	1·59	−1+*x*,*y*,*z*
N(4)	H(2*n*4)	O(2)	2·718	1·98	1−*x*,1−*y*, 1−*z*
N(8)	H(2*n*8)	O(2)	2·754	1·92	1−*x*, −*y*, 1−*z*
N(8)	H(1*n*8)	O(3)	2·778	1·79	−*x*, −*y*, 1−*z*
W(1)	H(2*w*1)	O(1)	2·783	2·10	−*x*, −*y*, 1−*z*
W(1)	H(1*w*1)†	*W*(1)′	2·799	2·21	−*x*, −*y*, 2−*z*
W(2)	H(2*w*2)	O(1)	2·708	2·25	1−*x*, −*y*, 1−*z*
W(2)	H(1*w*2)	O(3)	2·777	1·68	1−*x*, 1−*y*, 1−*z*
W(3)	H(1*w*3)	O(3)	2·830	2·12	*x*,*y*,*z*
W(3)	H(2*w*3)	*W*(1)‡	2·810	2·13	−*x*, 1−*y*, 1−*z*

* E.s.d.'s for the donor–acceptor and the hydrogen–acceptor distances are near 0·007 Å and 0·07 Å, respectively.

† Disordered across center of symmetry.

‡ Note that *W*(3)···*W*(3′) [across center of symmetry −*x*, 1−*y*, −*z*] = 2·731 Å. No H atom is available for forming a hydrogen bond.

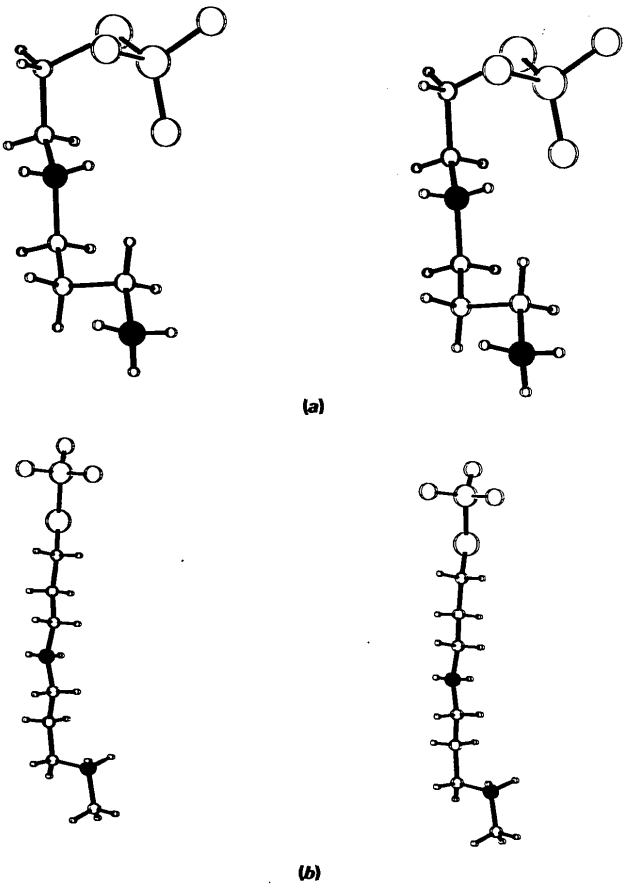

Fig. 2. Stereodiagram of (*a*) WR 151,327 [$CH_3NH_2^+(CH_2)_3$-$NH_2^+(CH_2)_3SPO_3^{2-}$] and (*b*) WR 2721 [$NH_3^+(CH_2)_3NH_2^+(CH_2)_2$-$SPO_3^{2-}$]. The size of the circles was arbitrarily chosen to correspond roughly to the atomic weight of the atom. The black spheres represent the N atoms.

positively charged with the phosphate hydrogens being found on the N atoms. The phosphate terminus of WR 151,327 has a double negative charge. As in WR 2721, the three P—O bonds are essentially equally long at approximately 1·51 Å, a bond length which is closer to a P=O double bond length of 1·42–1·50 Å than to a P—O single bond length of 1·58–1·64 Å (Gitany & McEwen, 1975; Sørensen, 1977; Kutschabsky, Messerschmidt & Sohr, 1979; Donohue & Mandel, 1981).

In both structures there are three H_2O molecules of crystallization per asymmetric unit that form a maximum number of hydrogen bonds. The crystalline structure of WR 151,327 includes ten hydrogen bonds (Fig. 1, Table 3). Each H atom attached to an N atom and each H atom in the water molecules is involved in hydrogen bonding. Each O atom attached to a P atom is involved in two or three hydrogen bonds. The relatively short distance of 2·72–2·83 Å between all of the donor and acceptor atoms indicates a strong attraction between WR 151,327 molecules and between the water and WR 151,327 molecules. Intermolecular hydrogen bonding between the hydrogen atoms attached to N(8) and the phosphate terminus forms head-to-tail dimers of WR 151,327 molecules.

The molecule contains an unusually long S—P bond at 2·13 Å [the typical S—P bond length appears to be 2·05–2·08 Å (Gitany & McEwen, 1975; Sørensen, 1977; Kutschabsky, Messerschmidt & Sohr, 1979; Donohue & Mandel, 1981)]. A long S—P bond of 2·12 Å was also observed for WR 2721. The length of the S—P bond may be a factor in the hydrolysis of this bond *in vivo*, a step presently felt necessary for the phosphorothioate compounds to exert their radioprotective properties.

In both WR 151,327 and WR 2721, the terminal N atom and the phosphate terminus are on the same face

of the molecule. The addition of a terminal *N*-methyl group in WR 151,327 does not affect the N···N distance. The intramolecular N···N distance of 4·48 Å in WR 151,327 is nearly identical to the N···N distance of 4·45 Å in WR 2721. However, the additional methylene group in WR 151,327 causes the N(4)···S distance of 5·19 Å and the N(8)···S distance of 9·41 Å to be considerably longer than the corresponding distances (3·49 Å and 7·14 Å, respectively) in the WR 2721 molecule. Radioprotection and toxicity studies (Sweeney, 1979) have demonstrated that these intramolecular distances, representing a separation of two or three C atoms between the S atom and the neighboring N atom and a separation of three C atoms between the N atoms, are optimal for radioprotection.

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Psilostachyin A

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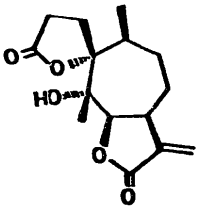
Abstract. $C_{15}H_{20}O_5$, $M_r = 280{\cdot}3$, orthorhombic, $P2_12_12_1$, $a = 7{\cdot}516\ (1)$, $b = 12{\cdot}817\ (1)$, $c = 14{\cdot}238\ (2)$ Å, $V = 1371{\cdot}7\ (3)$ Å^3, $Z = 4$, $D_x = 1{\cdot}357$ g cm^{-3}, λ(Mo $K\alpha$) = 0·71073 Å, $\mu = 0{\cdot}95$ cm^{-1}, $F(000) = 600$, $T = 298$ K, $R = 0{\cdot}045$ for 1577 observed reflections. The compound is a 4,5-seco-pseudoguaianolide containing a spiro-lactone. The conformations of both the spiro-lactone and the *cis*-fused lactone ring at C(6)–C(7) approximate envelopes, while the seven-membered ring approximates a twist chair with the pseudodiad axis passing through C(7) and the C(1)–C(10) bond. Intermolecular hydrogen bonds of length 2·883 (2) Å join the hydroxy group and the spiro-lactone carbonyl O atom along the **b** direction.

Introduction. Psilostachyin A is a 4,5-seco-pseudoguaianolide dilactone present in several species of the genus *Ambrosia* (Mabry, Miller, Kagan & Renold, 1966; Geissman & Matsueda, 1968; Herz, Anderson, Gibaja & Raulais, 1969; Higo, Hammam, Timmermann, Yoshioka, Lee, Mabry & Payne, 1971; Herz, Raulais & Anderson, 1973). The structure analysis was undertaken in order to confirm the relative configuration of the chiral centers assigned by Mabry *et al.* (1966) from NMR data, as well as to study the effect of the unique spiro-lactone on the conformation of the seven-membered ring.



Experimental. Title compound provided by T. J. Mabry, isolated from *Ambrosia psilostachya* D.C., collected on Galveston Island, Texas. Tabular, colorless

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