Acta Cryst. (1991). C**47**, 1242–1245

Structure of the Radiation Protection Agent *S*-2-(5-Aminopentylamino)ethylphosphorothioic Acid (WR 2823) Dihydrate

BY JEAN M. KARLE

Department of Pharmacology, Division of Experimental Therapeutics,
Walter Reed Army Institute of Research, Washington, DC 20307-5100, *USA*

AND ISABELLA L. KARLE

Laboratory for the Structure of Matter, Naval Research Laboratory, Washington, DC 20375-5000, *USA*

(*Received* 1 *June* 1990; *accepted* 24 *September* 1990)

Abstract. $C_7H_{19}N_2O_3PS.2H_2O$, $M_r = 278\cdot3$, triclinic, $P\bar{1}$, $a = 6\cdot314\ (2)$, $b = 9\cdot616\ (2)$, $c = 12\cdot277\ (7)$ Å, $\alpha = 84\cdot73\ (4)$, $\beta = 75\cdot69\ (4)$, $\gamma = 73\cdot73\ (3)°$, $V = 693\cdot1$ Å^3, $Z = 2$, $D_x = 1\cdot333$ g cm^{-3}, Cu $K\alpha$, $\lambda = 1\cdot54178$ Å, $\mu = 32\cdot6$ cm^{-1}, $F(000) = 300$, room temperature, final $R = 6\cdot5\%$ for 1904 reflections with $|F_o| > 3\sigma(F)$. WR 2823 crystallized as a double zwitterion with the two phosphate H atoms residing on the two N atoms. An intramolecular hydrogen bond between O(1) and N(3) causes the molecule to bend at the phosphate end. The S—P bond length is 2·126 (1) Å, and the three P—O bonds are of nearly equal length at 1·50 (1) Å. The WR 2823 molecules pack head to tail with hydrogen bonds between neighboring amine and phosphate groups and to water molecules.

Introduction. The crystal and molecular structure of WR 2823 was determined as part of our continuing study of the aminophosphorothioate radioprotective agents (Karle & Karle, 1988*a*,*b*). WR 2823 is one of a family of radioprotectants which share the common formula $X\mathrm{NH(CH_2)}_n\mathrm{NH(CH_2)}_{n'}\mathrm{SPO_3H_2}$ (neutral form) where $X = \mathrm{H}$ or $\mathrm{CH_3}$. For WR 2823, $n = 5$, $n' = 2$ and $X = \mathrm{H}$. WR 2823 fully protected mice against a lethal dose of ionizing radiation (10 Gy) when given as a single intraperitoneal dose of 150 mg kg^{-1} 15 to 30 min prior to irradiation (Piper, Stringfellow, Elliott & Johnston, 1969). In a similar experiment, WR 2823 also protected >50% of the mice after a single oral dose of 500 mg kg^{-1} (Sweeney, 1979). On a molar basis WR 2823 is more protective than the structurally smaller compounds aminoethylphosphorothioate and aminopropylphosphorothioate against the lethal effects of ionizing radiation (Kollmann, Martin & Shapiro, 1971; Piper *et al.*, 1969).

In addition to the radioprotective properties of these aminophosphorothioate compounds, these compounds also preserve the steroid binding capacity of the glucocorticoid receptor in 100 000 x g supernatants of rat liver homogenate and in intact rat hepatocytes (Karle, Olmeda, Ridder, Park & Nielsen, 1989). For both the radioprotective properties and the steroid-binding preservation, the active moiety appears to be the dephosphorylated sulfhydryl form of the molecules with the phosphorylated form serving as a prodrug. The phosphorothioate compounds are dephosphorylated both in whole animals and in tissue preparations (Kollmann *et al.*, 1971; Risley, Van Etten, Shaw & Bonner, 1986; Swynnerton, Huelle, Mangold & Ludden, 1986; Utley, Seaver, Newton & Fahey, 1984).

We determined the crystal structure of WR 2823 to ascertain whether this series of compounds possesses common structural features in terms of zwitterion formation, S—P distance and overall conformation.

Experimental. The title compound was synthesized and crystallized on contract for the Walter Reed Army Institute of Research by Ash Stevens (Detroit, MI). Diffraction data were collected from a colorless cloudy plate crystal, 0·5 × 0·3 × 0·1 mm, in the θ–2θ mode to a maximum 2θ value of 120° on the *R*3*m*/micro Nicolet four-circle diffractometer (Siemens Corporation, Madison, WI) with a graphite monochromator. Range of indices: h 0→7, k −9→10 and l −13→13. The total number of reflections measured was 2131, and the number of independent reflections was 2005. The standard reflections 300, $0\bar{4}0$ and 004 were monitored after every 60 intensity measurements. The standards varied by up to 7·7%. The lattice parameters were based on 25 centered reflections with 2θ values between 30 and 48°. No correction for absorption or extinction was applied. The structure was solved routinely by direct phase determination (Karle & Karle, 1966). All of the non-H atoms except for the water molecules were

0108-2701/91/061242-04$03.00

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

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

	x	y	z	U_{eq}
P	164 (1)	1688 (1)	6924 (1)	36 (1)
S	−127 (2)	3847 (1)	6285 (1)	59 (1)
O(1)	635 (5)	1631 (1)	8062 (2)	57 (1)
O(2)	2073 (4)	728 (3)	6101 (2)	50 (1)
O(3)	−2133 (4)	1521 (3)	6897 (3)	51 (1)
C(1)	2700 (7)	4093 (5)	6080 (4)	57 (2)
C(2)	3247 (7)	4488 (5)	7102 (4)	56 (2)
N(3)	3711 (5)	3227 (4)	7899 (3)	49 (1)
C(4)	3822 (10)	3659 (6)	9003 (4)	71 (2)
C(5)	4118 (11)	2380 (6)	9775 (4)	79 (3)
C(6)	3825 (13)	2839 (6)	10985 (4)	89 (3)
C(7)	3928 (12)	1577 (6)	11795 (4)	86 (3)
C(8)	3372 (8)	2042 (5)	13015 (3)	57 (2)
N(9)	3547 (6)	717 (4)	13748 (3)	42 (1)
W(1)†	2128 (7)	7904 (4)	5686 (3)	82 (2)
W(2)†	339 (23)	9351 (14)	9608 (11)	124 (4)‡
W(3)†	1183 (40)	6317 (26)	369 (21)	136 (7)‡
W(4)†	1296 (65)	7638 (43)	8174 (34)	148 (12)‡
H(1*n*3)	2824 (64)	2726 (41)	8012 (32)	46 (10)‡
H(2*n*3)	5051 (66)	2666 (43)	7620 (34)	49 (10)‡
H(1*n*9)	2821 (62)	27 (41)	13548 (32)	46 (10)‡
H(2*n*9)	2890 (66)	869 (44)	14491 (35)	52 (11)‡
H(3*n*9)	4931 (62)	223 (37)	13641 (29)	29 (9)‡

† *W*(1), *W*(2), *W*(3) and *W*(4) represent the O atoms of water molecules and were weighted 100, 40, 25 and 16%, respectively.

‡ These atoms were refined isotropically. The values represent U_{iso}.

Table 2. *Bond lengths* (Å), *bond angles* (°) *and torsion angles* (°) *with e.s.d.'s in parentheses*

P—S	2·126 (1)	P—O(1)	1·492 (3)
P—O(2)	1·507 (2)	P—O(3)	1·512 (3)
S—C(1)	1·819 (5)	C(1)—C(2)	1·488 (8)
C(2)—N(3)	1·496 (6)	N(3)—C(4)	1·477 (7)
C(4)—C(5)	1·479 (7)	C(5)—C(6)	1·541 (8)
C(6)—C(7)	1·494 (8)	C(7)—C(8)	1·530 (7)
C(8)—N(9)	1·485 (5)		
S—P—O(1)	107·2 (1)	S—P—O(2)	106·5 (1)
O(1)—P—O(2)	112·7 (2)	S—P—O(3)	100·6 (1)
O(1)—P—O(3)	115·8 (2)	O(2)—P—O(3)	112·6 (2)
P—S—C(1)	104·8 (1)	S—C(1)—C(2)	115·3 (3)
C(1)—C(2)—N(3)	112·5 (4)	C(2)—N(3)—C(4)	112·7 (4)
N(3)—C(4)—C(5)	110·0 (5)	C(4)—C(5)—C(6)	110·9 (5)
C(5)—C(6)—C(7)	111·8 (5)	C(6)—C(7)—C(8)	112·2 (5)
C(7)—C(8)—N(9)	108·0 (4)		
O(1)—P—S—C(1)	66·6 (2)	O(2)—P—S—C(1)	−54·3 (2)
O(3)—P—S—C(1)	−171·9 (2)	P—S—C(1)—C(2)	−83·1 (3)
S—C(1)—C(2)—N(3)	75·3 (4)	C(1)—C(2)—N(3)—C(4)	−169·0 (4)
C(2)—N(3)—C(4)—C(5)	175·9 (4)	N(3)—C(4)—C(5)—C(6)	−170·2 (5)
C(4)—C(5)—C(6)—C(7)	175·3 (6)	C(5)—C(6)—C(7)—C(8)	−173·5 (6)
C(6)—C(7)—C(8)—N(9)	−179·3 (5)		

found in the first *E* map. The H atoms attached to the N atoms were found in subsequent difference maps. The H atoms attached to the C atoms were placed in idealized positions. Least-squares refinement was performed using 1904 reflections with $|F_o| > 3\sigma(F)$ ($R_{merge} = 0{\cdot}013$). 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 and P atoms of WR 2823 and one water oxygen, and isotropic thermal parameters for the H atoms attached to the N atoms and the O atom of the second water molecule located in three different positions weighted 0·4, 0·25 and 0·16 were refined for a total of 172 parameters. Final $R = 6{\cdot}5\%$ and $wR = 7{\cdot}2\%$, $w = 1/[\sigma^2(|F|) + 0{\cdot}0006(F_o)^2]$. $S = 2{\cdot}9$. $(\Delta/\sigma)_{max} = 0{\cdot}022$. Final difference electron density $|\rho|_{max} = 0{\cdot}59$ and $|\rho|_{min} = -0{\cdot}62\ \text{e Å}^{-3}$. Atomic scattering factors were those incorporated in *SHELXTL*.*

Discussion. Table 1 lists the coordinates and U_{eq} values for the non-H atoms and coordinates for the refined H atoms. Table 2 lists bond lengths, bond angles and torsion angles for WR 2823. The bond length for the H atoms attached to the C atoms was kept fixed at 0·96 Å throughout the refinement procedure.

WR 2823 (Fig. 1) crystallized as a double zwitterion with a double negative charge on the phosphate group and a positive charge on both of the N atoms. The two H atoms from the phosphate group are located on the N atoms causing both N atoms to be in the form of primary or secondary amine salts. The long S—P bond length of 2·126 (1) Å is characteristic of the phosphorothioate radioprotection agents as it is equivalent to the S—P bond length of 2·116 (1) Å found in WR 2721 (where $n = 3$, $n' = 2$ and $X = \text{H}$) and of 2·129 (3) Å in WR 151,327 (where $n = n' = 3$ and $X = \text{CH}_3$) (Karle & Karle, 1988*a*,*b*). The three P—O bonds are nearly equal in length at 1·50 (1) Å and are also similar to the P—O bond lengths found in WR 2721 and WR 151,327 of 1·51–1·52 Å. The P—O bonds appear to have more double- than single-bond character since a typical single P—O bond ranges from 1·58–1·64 Å, and a typical double P=O bond ranges from 1·42 to 1·50 Å (Gitany &

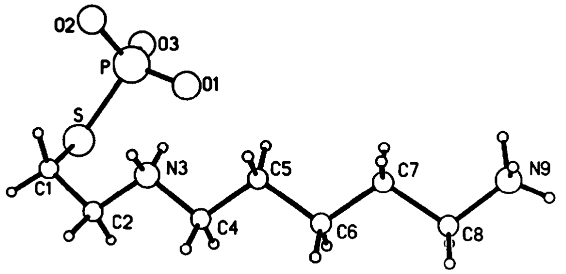

Fig. 1. Conformation and numbering scheme of WR 2823. The size of the spheres was arbitrarily chosen to approximate the atomic weight of each atom.

---

* 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 53603 (16 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

McEwen, 1975; Sørensen, 1977; Kutschabsky, Messerschmidt & Sohr, 1979; Donohue & Mandel, 1981).

Despite the nearly equally long P—O bonds, the three S—P—O bond angles ranged from 100·6 (1) to 107·2 (1)°. An even larger variation of S—P—O bond angles from 100·7 (2) to 109·0 (3)° was observed for WR 151,327 (Karle & Karle, 1988*b*). The S—P—O bond angles in WR 2721 were closer to each other ranging from 103·0 (1) to 107·7 (1)° (Karle & Karle, 1988*a*).

An intramolecular hydrogen bond between a phosphate O atom and N(3) causes the molecule to bend at the sulfur end of the molecule and assume a *gauche*-staggered conformation. This conformation is nearly identical to the conformation of the identical portion of the WR 2721 molecule (Karle & Karle, 1988*a*). WR 2721 differs from WR 2823 only by the number of methylene groups between the N atoms. The crystal structure of mercaptoethylamine hydrochloride, $H_3N^+(CH_2)_2SH.Cl^-$, which has no intramolecular hydrogen bond, also assumes a bent *gauche*-staggered conformation (Jandacek & Swartz, 1970). The N—C—C—S torsion angles for WR 2823, WR 2721 and mercaptoethylamine are 75·3 (4), 83·3 (3) and 59·3 (17)°, respectively. Likewise, phosphorylethanolamine, $H^-O_3PO(CH_2)_2N^+H_3$, also crystallizes in a *gauche*-staggered conformation with an O—C—C—N torsion angle of −59·9 (1)° without the involvement of an intramolecular hydrogen bond (Weber, McMullan, Swaminathan & Craven, 1984). WR 151,327 which has three instead of two methylene groups between the S and N atoms does not contain an intramolecular hydrogen bond (Karle & Karle, 1988*b*) and is essentially linear in this region of the molecule.

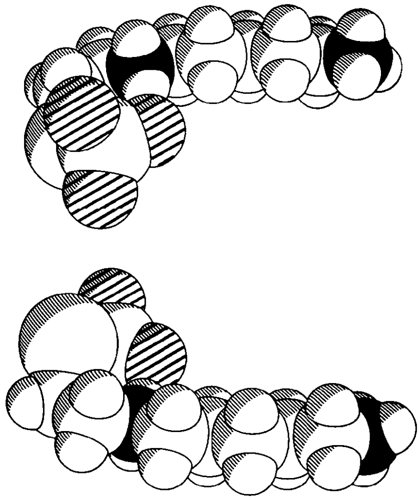

Fig. 2. Hydrophilic (top diagram) and hydrophobic (bottom diagram) sides of the WR 2823 molecule. The hydrophilic side contains the N—H groups and the phosphate O atoms. The hydrophobic side contains only methylene groups and the S atom. The N atoms are colored black, and the O atoms are striped. The radii of the spheres is 75% of the van der Waals radii. The figure was drawn using the *SHELXTL* program package.

Table 3. *Hydrogen-bond geometry* (Å, °)

D	H	*A*	*D*—*A**	H···*A**	*D*—H···*A**	Symmetry equivalent of *D*
N(3)	H(1*n*3)	O(1)	2·755	1·95	171·5	*x*,*y*,*z*
N(3)	H(2*n*3)	O(3)	2·730	1·86	174·9	−1 + *x*,*y*,*z*
N(9)	H(1*n*9)	O(3)	2·792	1·83	166·9	−*x*, −*y*,2−*z*
N(9)	H(2*n*9)	O(2)	2·808	1·92	165·2	*x*,*y*, −1 + *z*
N(9)	H(3*n*9)	O(2)	2·769	1·95	161·4	1 − *x*, −*y*,2 − *z*
W(1)	†	O(2)	2·798	†	†	*x*, −1 + *y*,*z*
W(1)	†	O(3)	3·168	†	†	−*x*,1 − *y*,1 − *z*
W(2)	†‡	O(1)	2·781	†	†	*x*, −1 + *y*,*z*
W(2)	†‡	O(1)	2·901	†	†	−*x*,1 − *y*,2 − *z*
W(3)	†‡	W(2)	2·923	†	†	*x*,*y*,1 + *z*
W(3)	†‡	O(1)	2·694	†	†	−*x*,1 − *y*,1 − *z*
W(4)	†‡	W(1)	2·968	†	†	*x*,*y*,*z*
W(4)	†‡	W(3)	2·865	†	†	*x*,*y*, −1 + *z*

* E.s.d.'s for the *D*—*A* and H···*A* distances are near 0·007 and 0·07 Å, respectively, and for the *D*—H···*A* angle are near 0·4°.

† The H atoms of the water molecules were not located in the difference maps.

‡ Partial occupancy of 0·4 for *W*(2), 0·25 for *W*(3) and 0·16 for *W*(4).

The remainder of the WR 2823 molecule between the two N atoms is essentially linear. This conformation differs from the WR 2721 and WR 151,327 molecules where $n' = 3$ instead of 5. Both of these molecules display a bent conformation between the two N atoms. Despite the different configurations at the amine end of the molecules, WR 2823, like WR 2721, has a hydrophilic side and a hydrophobic side (Fig. 2).

All of the H atoms attached to the N atoms form hydrogen bonds with the phosphate O atoms either within the same molecule, N(3)···O(1), or to neighboring molecules (Table 3). All of the phosphate O atoms participate in multiple hydrogen bonds with the water molecules and the amine groups. Although none of the H atoms on the water molecules were located in the difference maps, all of the water O atoms are spaced from the phosphate O atoms and other water O atoms at distances appropriate for hydrogen bonding.

The WR 2823 molecules pack in a head-to-tail manner with N(9) hydrogen bonding to O(2) at the head of a neighboring molecule (Fig. 3). Atom O(1) participates in the intramolecular hydrogen bond with N(3), and the third O atom of the phosphate group forms an intermolecular hydrogen bond with a neighboring molecule, N(3)···O(3). The water molecules form a channel of disordered molecules with partial occupancy for atoms *W*(2), *W*(3) and *W*(4). *W*(4) cannot be present when *W*(2) is present because of the short interatomic distance of 2·29 (1) Å. Likewise, both *W*(2) atoms across the center of symmetry

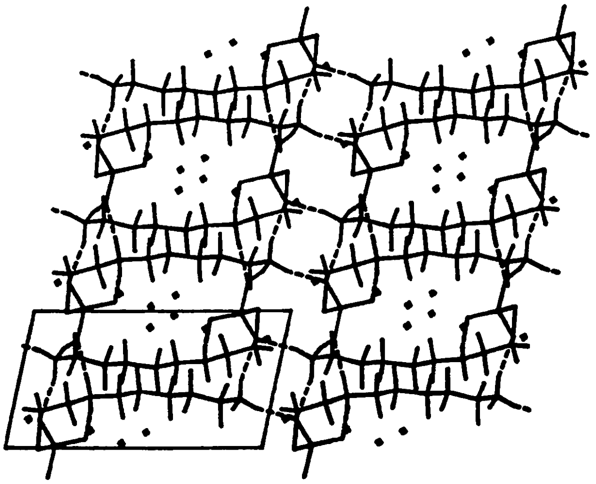

Fig. 3. Packing diagram of WR 2823 dihydrate viewed down the *b* axis. The intramolecular hydrogen bond and hydrogen bonds between WR 2823 molecules are depicted by the dotted lines. The small crosses represent the location of the O atoms of the water molecules *W*(1) to *W*(4). The hydrogen bonds involving the water molecules are not illustrated. The figure was drawn using *SYBYL* (Tripos Associates, 1989).

cannot be present simultaneously since they would be only 1·71 (1) Å apart. The WR 2823 molecules pack such that the hydrophobic sides of the molecules face each other and the hydrophilic sides of the molecules face the water channels.

In summary, from studying this series of radioprotective agents, we have discovered that the S—P bond length is longer than usual, but of consistent length. These molecules all crystallized as zwitterions in the presence of two or three molecules of water per radioprotectant. This results in P—O bonds of essentially equal length. An intramolecular hydrogen bond forms when $n' = 2$, although the *gauche*-staggered nature of the —S—CH$_2$—CH$_2$—N— segment of the molecule is not dependent upon this hydrogen bond. Finally, the linear or bent nature of the molecule is apparently dependent on the numerical values of n and n'.

References

Donohue, J. & Mandel, N. (1981). *J. Cryst. Mol. Struct.* **11**, 189–196.

Gitany, R. & McEwen, R. S. (1975). *J. Chem. Soc. Perkin Trans.* 2, pp. 57–59.

Jandacek, R. J. & Swartz, H. M. (1970). *Radiat. Res.* **44**, 523–530.

Karle, J. & Karle, I. L. (1966). *Acta Cryst.* **21**, 849–859.

Karle, J. M. & Karle, I. L. (1988*a*). *Acta Cryst.* C**44**, 135–138.

Karle, J. M. & Karle, I. L. (1988*b*). *Acta Cryst.* C**44**, 1218–1221.

Karle, J. M., Olmeda, R., Ridder, W. E., Park, A. S. & Nielsen, C. J. (1989). *J. Steroid Biochem.* **33**, 503–513.

Kollmann, G., Martin, D. & Shapiro, B. (1971). *Radiat. Res.* **48**, 542–550.

Kutschabsky, L., Messerschmidt, A. & Sohr, H. (1979). *Tetrahedron*, **35**, 499–503.

Piper, J. R., Stringfellow, C. R., Elliott, R. D. & Johnston, T. P. (1969). *J. Med. Chem.* **12**, 236–243.

Risley, J. M., Van Etten, R. L., Shaw, L. M. & Bonner, B. (1986). *Biochem. Pharmacol.* **35**, 1453–1458.

Sheldrick, G. M. (1980). *SHELXTL. An Integrated System for Solving, Refining and Displaying Crystal Structures from Diffraction Data.* Univ. of Göttingen, Germany.

Sørensen, A. M. (1977). *Acta Cryst.* B**33**, 2693–2695.

Sweeney, T. R. (1979). *A Survey of Compounds from the Antiradiation Drug Development Program of the US Army Medical Research and Development Command.* Washington, DC: Walter Reed Army Institute of Research.

Swynnerton, N. F., Huelle, B. K., Mangold, D. J. & Ludden, T. M. (1986). *Int. J. Radiat. Oncol. Biol. Phys.* **12**, 1495–1499.

Tripos Associates (1989). *SYBYL.* Molecular modeling software. Version 5.3. Tripos Associates, St Louis, Missouri, USA.

Utley, J. F., Seaver, N., Newton, G. L. & Fahey, R. C. (1984). *Int. J. Radiat. Oncol. Biol. Phys.* **10**, 1525–1528.

Weber, H.-P., McMullan, R. K., Swaminathan, S. & Craven, B. M. (1984). *Acta Cryst.* B**40**, 506–511.

Acta Cryst. (1991). C**47**, 1245–1247

A Novel Aminotriol: 4-Amino-4-(3-hydroxy-1-propyl)-1,7-heptanediol

By Melanie Broussard, Booker Juma, Frank R. Fronczek and Steven F. Watkins

Department of Chemistry, Louisiana State University, Baton Rouge, Louisiana 70803-1804, *USA*

and George R. Newkome and Charles N. Moorefield

Department of Chemistry, University of South Florida, Tampa, Florida 33620-5250, *USA*

(*Received* 22 *January* 1990; *accepted* 25 *October* 1990)

Abstract. $C_{10}H_{23}NO_3$, $M_r = 205{\cdot}30$, orthorhombic, $P2_12_12_1$, $a = 8{\cdot}314\,(2)$, $b = 9{\cdot}539\,(1)$, $c = 14{\cdot}512\,(3)$ Å, $V = 1150{\cdot}9\,(6)$ Å^3, $Z = 4$, $D_x = 1{\cdot}185$ g cm^{-3}, λ(Mo $K\alpha$) = 0·71073 Å, $\mu = 0{\cdot}8$ cm^{-1}, $F(000) = 456$, $T = 293\,(2)$ K, 1926 unique reflections measured, final $R = 0{\cdot}034$ for 1681 reflections with I

0108-2701/91/061245-03$03.00