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Structures of Three DNA Cross-Linking Agents, Ethane-1,2-di(methylsulfonate), Propane-1,3-di(methylsulfonate) and *n*-Butane-1,4-di(methylsulfonate)

BY R. MCKENNA AND S. NEIDLE*

Cancer Research Campaign, Biomolecular Structure Unit, Institute of Cancer Research, Sutton, Surrey SM2 5NG, England

R. KURODA

Department of Chemistry, College of Arts and Sciences, The University of Tokyo, Komaba, Meguro, Tokyo 153, Japan

AND B. W. FOX

Patterson Institute for Cancer Research, Christie Hospital and Holt Radium Institute, Manchester M20 9BX, England

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Abstract. (I): $C_4H_{10}O_6S_2$, $M_r = 218{\cdot}25$, $P2_1/c$, $a = 7{\cdot}2611\ (9)$, $b = 5{\cdot}8726\ (4)$, $c = 10{\cdot}6628\ (19)$ Å, $\beta = 103{\cdot}95\ (1)°$, $V = 441{\cdot}3\ (2)$ Å^3, $Z = 2$, $D_m = 1{\cdot}65$, $D_x = 1{\cdot}642$ Mg m^{-3}, λ(Cu $K\alpha$) = 1·54184 Å, $\mu = 5{\cdot}43$ mm^{-1}, $F(000) = 228$, $R = 0{\cdot}0336$ and $wR = 0{\cdot}0346$ for 745 unique reflections with $F \geq 3\sigma(F)$, $T = 298$ K. (II): $C_5H_{12}O_6S_2$, $M_r = 232{\cdot}28$, $P2_1/c$, $a = 11{\cdot}030\ (1)$, $b = 8{\cdot}452\ (1)$, $c = 11{\cdot}162\ (1)$ Å, $\beta = 104{\cdot}65\ (1)°$, $V = 1006{\cdot}8\ (3)$ Å^3, $Z = 4$, $D_m = 1{\cdot}54$, $D_x = 1{\cdot}532$ Mg m^{-3}, λ(Cu $K\alpha$) = 1·54184 Å, $\mu = 4{\cdot}79$ mm^{-1}, $F(000) = 488$, $R = 0{\cdot}0418$ and $wR = 0{\cdot}0430$ for 1666 unique reflections with $F \geq 3\sigma(F)$, $T = 298$ K. (III): $C_6H_{14}O_6S_2$, $M_r = 246{\cdot}30$, $P\bar{1}$, $a = 5{\cdot}6147\ (9)$, $b = 6{\cdot}8343\ (6)$, $c = 7{\cdot}5434\ (6)$ Å, $\alpha = 110{\cdot}61\ (1)$, $\beta = 92{\cdot}08\ (1)$, $\gamma = 76{\cdot}15\ (1)°$, $V = 262{\cdot}7\ (3)$ Å^3, $Z = 1$, $D_m = 1{\cdot}56$, $D_x = 1{\cdot}557$ Mg m^{-3}, λ(Cu $K\alpha$) = 1·54184 Å, $\mu = 4{\cdot}79$ mm^{-1}, $F(000) = 130$, $R = 0{\cdot}0397$ and $wR = 0{\cdot}0425$ for 907 unique reflections with $F \geq 3\sigma(F)$, $T = 298$ K. All three compounds have a common conformation in the $C.O.SO_2.CH_3$ part of the molecules due to weak O···H interactions. Compounds (I) and (III) have a *trans* conformation about the central C—C bond, whereas (II) is *cis*.

Introduction. Several members of the series of dimethanesulfonic acid esters of general formula $CH_3.SO_2.O.(CH_2)_n.O.SO_2.CH_3$ ($n = 1$–10) have long been known to be active against a number of proliferating cell systems in experimental animals (Fox, 1975). Their antitumour and immunosuppressive activities vary greatly with the length of the central methylene chain. Antitumour activity was observed in the case of the four-carbon chain member, BDMS ($n = 4$), against the Walker 256 rodent carcinoma (Haddow & Timmis, 1951). More recent work has shown that maximum *in vitro* cytotoxicity against Yoshida lymphosarcoma cells occurs with hexanedimethanesulfonate ($n = 6$), and the highest *in vivo* antitumour therapeutic index is for octanedimethanesulfonate ($n = 8$) (Bedford & Fox, 1983). With the exception of EDMS ($n = 2$), DNA cross-linking has been observed with all the other members of this series (Bedford & Fox, 1983; Hartley & Fox, 1986). The relationship between this cross-linking and the antitumour and cytotoxic properties of

* Author to whom correspondence should be addressed.

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the members of this series is still unclear, however. Molecular and crystal structures have been determined for three members of short chain length ($n = 2,3,4$) of the series, EDMS (I), PDMS (II) and BDMS (III), as an aid to understanding the possible mechanisms of interactions of these compounds with DNA and associated proteins.

Experimental. Prismatic translucent crystals were obtained from ethanol–water solution for all three compounds, and densities were measured by flotation. X-ray photographs were taken to determine crystal class, and accurate cell dimensions were determined by least squares from 25θ values in the range $15 < \theta < 25°$ on an Enraf–Nonius CAD-4 diffractometer with graphite-monochromated Cu $K\alpha$ radiation. For data collection, the ω–2θ scan mode was used up to $\theta = 72°$ ($-8 \le h \le 8$, $0 \le k \le 7$, $0 \le l \le 13$) for (I), up to $\theta = 70°$ ($0 \le h \le 13$, $0 \le k \le 10$, $-13 \le l \le 13$) for (II), and up to $\theta = 70°$ ($0 \le h \le 6$, $-8 \le k \le 8$, $-9 \le l \le 9$) for (III). The crystal sizes were approximately $0{\cdot}25 \times 0{\cdot}18 \times 0{\cdot}33$ mm for (I), $0{\cdot}24 \times 0{\cdot}25 \times 0{\cdot}22$ mm for (II) and $0{\cdot}28 \times 0{\cdot}20 \times 0{\cdot}31$ mm for (III). Three standard reflections were monitored at intervals of 3600 s in each case and no crystal decay was observed during the data collection. The systematic absences were: (I) and (II): $h0l$, $l = 2n$; $0k0$, $k = 2n$; (III): none. 912 reflections were recorded for (I), 745 with $F \ge 3\sigma(F)$ were used for the refinement. For (II) and (III), 1666 and 907 reflections with $F \ge 3\sigma(F)$ were employed for the refinement out of 1830 and 993 reflections measured respectively.

All three structures were solved by direct methods (*MULTAN*80; Main *et al.*, 1980) and refined on F with full-matrix least-squares techniques. All the H-atom positions were located from difference Fourier syntheses and their positional and isotropic thermal parameters were refined in the case of compound (III). For (I), all the H atoms except two of the methyl hydrogen atoms (H1*A* and H1*B*) were located from the difference Fourier maps and their parameters refined. The two methyl H atoms were generated assuming an ideal geometry and their parameters fixed during the refinement. All the H atoms of compound (II) were revealed in the difference Fourier maps and their parameters were included in the refinement except those of H(1*C*), H(2*B*) and H(5*C*), which were fixed. Anisotropic and isotropic thermal parameters were assumed for the non-hydrogen and H atoms, respectively. Final difference maps showed $\Delta\rho$ within $\pm 0{\cdot}247$, $\pm 0{\cdot}243$ and $\pm 0{\cdot}232$ e Å^{-3} for (I), (II) and (III), respectively. $R(wR) = 0{\cdot}0336$ ($0{\cdot}0346$) for (I), $0{\cdot}0418$ ($0{\cdot}0430$) for (II), $0{\cdot}0397$ ($0{\cdot}0425$) for (III), $w = [\sigma(I)^2 + (0{\cdot}03I)^2]^{-1/2}$; there was a zero shift/e.s.d. in the final least-squares cycle for the three structures. Empirical absorption (Walker & Stuart, 1983) and extinction corrections of the form $[1+(10^{-5}|I_c|)]$ were applied and atomic scattering factors were taken from *International Tables for X-ray Crystallography* (1974). The maximum and minimum absorption correction factors were $0{\cdot}88$, $1{\cdot}10$ for (I), $0{\cdot}91$, $1{\cdot}12$ for (II) and $0{\cdot}87$, $1{\cdot}14$ for (III). All computations were performed on a VAX 11/750 computer using the *SDP* program system (Frenz, 1980).

Table 1. *Final unit-cell coordinates for the non-hydrogen atoms and their average thermal parameters with e.s.d.'s in parentheses*

$B_{eq} = \frac{4}{3}\sum_i\sum_j a_i^* a_j^* \mathbf{a}_i.\mathbf{a}_j$

	x	y	z	B_{eq}(Å^2)
Compound (I)				
S(1)	0·74269 (9)	0·0535 (1)	0·19762 (6)	2·62 (1)
O(1)	0·8057 (3)	0·0654 (4)	0·3345 (2)	3·79 (5)
O(2)	0·6065 (3)	−0·1159 (4)	0·1420 (2)	4·04 (5)
O(3)	0·9287 (3)	0·0166 (4)	0·1499 (2)	3·18 (4)
C(1)	0·6632 (5)	0·3197 (6)	0·1344 (3)	3·68 (7)
C(2)	0·9120 (4)	−0·0444 (6)	0·0155 (3)	3·15 (6)
Compound (II)				
S(1)	0·05308 (7)	0·4345 (1)	0·20415 (7)	3·47 (2)
S(2)	−0·41327 (7)	0·5071 (1)	0·35102 (7)	3·33 (2)
O(1)	0·1382 (2)	0·5611 (3)	0·2027 (2)	4·88 (6)
O(2)	0·0726 (2)	0·2857 (3)	0·1529 (2)	4·71 (6)
O(3)	−0·0779 (2)	0·5032 (3)	0·1345 (2)	3·42 (4)
O(4)	−0·3626 (2)	0·4581 (3)	0·2369 (2)	3·96 (5)
O(5)	−0·3549 (2)	0·6506 (3)	0·4034 (2)	5·49 (6)
O(6)	−0·3992 (2)	0·3673 (3)	0·4252 (2)	5·11 (6)
C(1)	0·0406 (4)	0·4086 (5)	0·3562 (3)	4·88 (9)
C(2)	−0·1827 (3)	0·3927 (4)	0·0901 (3)	3·30 (6)
C(3)	−0·2972 (3)	0·4951 (4)	0·0526 (3)	3·41 (7)
C(4)	−0·3311 (3)	0·5799 (4)	0·1568 (3)	3·34 (6)
C(5)	−0·5726 (3)	0·5399 (5)	0·2876 (3)	4·23 (8)
Compound (III)				
S(1)	0·1277 (1)	−0·1690 (1)	0·17663 (9)	2·68 (1)
O(1)	0·1816 (5)	0·0366 (3)	0·2249 (4)	4·55 (6)
O(2)	0·2130 (5)	−0·3280 (4)	−0·0048 (3)	3·91 (5)
O(3)	0·2400 (4)	−0·2551 (3)	0·3359 (3)	2·94 (4)
C(1)	−0·1875 (6)	−0·1359 (5)	0·2055 (5)	3·38 (7)
C(2)	0·2654 (6)	−0·4835 (4)	0·3080 (4)	2·72 (6)
C(3)	0·3708 (5)	−0·5150 (4)	0·4845 (4)	2·67 (6)

Discussion. Final atomic parameters are listed in Table 1* and the molecular structures of (I), (II) and (III) are shown in Fig. 1 with the numbering scheme employed. Molecules (I) and (III) have $\bar{1}$ symmetry, with the midpoints of the central C—C bonds lying on crystallographic inversion centres. Bond lengths and angles are compared in Table 2. The two terminal S—O bonds, S—O_t, compare well with overall mean S=O bonds in sulfonate esters [1·423 (8) Å (Allen *et al.*, 1987)] in all three structures and thus have considerable π-bond character, employing vacant d orbitals of the S atom.

* Tables of structure factors, H-atom coordinates and isotropic temperature factors, and anisotropic temperature factors for non-hydrogen atoms, for compounds (I), (II) and (III), have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 51409 (22 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Hence the O(1)–S(1)–O(2) bond angle is widened in all three structures, from the regular tetrahedral value of 109·5° to a mean value of 119·1 (5)°. The ester O_e–S and S–C bonds have less π-bond character and accordingly the O_e–S–C angles are considerably smaller. The two S–O_t bonds have very similar bond lengths in each structure [in (I) and (III) they are symmetry equivalent]; however the O_e–S–O_t angle has a smaller value of *ca* 104·5° when the O_t–S bond is *trans* to the O_e–C bond, while the other O_e–S–O_t angle is *ca* 109°. Similar bond length–bond angle relationships have been observed in many phosphate compounds (Saenger, 1983). The termini of all three compounds are closely similar in terms of conformation (Table 2) as well as in terms of bond geometry. This may be due to favourable weak attractive interactions between H atoms and O lone-pair electrons as indicated by short H···O distances – O(2)··· H(2*b*): (I) 2·77 (3), (II) 2·66 (2), (III) 2·54 (4) Å; O(3)···H(3*a*) [H(2*a*) in the case of (I)]: (I) 2·52 (3); (II) 2·43 (3), (III) 2·42 (4) Å; O(4)···H(4*b*) [H(3*b*) in the case of (II)]: (II) 2·59 (4), (III) 2·66 (3) Å. There appears to be no restriction on the conformation of the carbon chains and the compounds can either be stretched [(I), (III)] or bent [(II)], depending on whether the torsion angles for the central C–C bonds are *trans* or *gauche*.

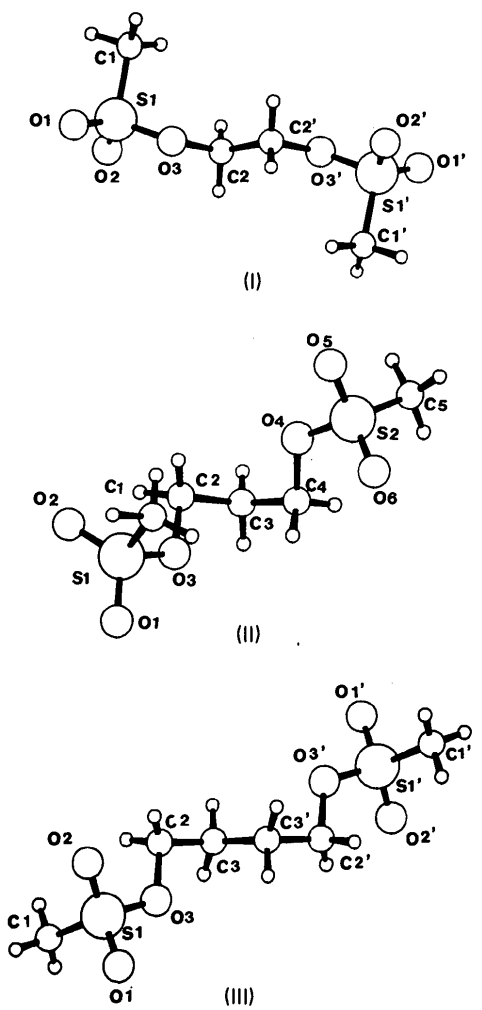

Fig. 1. Molecular structures of (I), (II) and (III).

Table 2. *Bond lengths* (Å), *bond angles* (°) *and torsion angles* (°) *for the non-hydrogen atoms with e.s.d.'s in parentheses*

(I) and (III) have a crystallographic centre of inversion, and hence only half of the molecule is indicated.

	(I)	(II)	(III)
S(1)–O(1)	1·422 (2)	1·426 (3)	1·4264
S(2)–O(6)		1·429 (3)	
S(1)–O(2)	1·427 (2)	1·420 (3)	1·427 (4)
S(2)–O(5)		1·427 (3)	
S(1)–O(3)	1·569 (2)	1·569 (2)	1·566 (3)
S(2)–O(4)		1·570 (3)	
S(1)–C(1)	1·745 (3)	1·751 (4)	1·741 (6)
S(2)–C(5)		1·743 (3)	
O(3)–C(2)	1·453 (3)	1·471 (4)	1·472 (5)
O(4)–C(4)		1·462 (4)	
C(2)–C(2)	1·489 (1)		
C(2)–C(3)		1·500 (4)	1·506 (6)
C(3)–C(4)		1·491 (5)	
C(3)–C(3)			1·514 (9)
O(1)–S(1)–O(2)	118·7 (1)	119·5 (2)	118·6 (3)
O(5)–S(2)–O(6)		119·6 (2)	
O(1)–S(1)–O(3)	104·5 (1)	104·1 (1)	104·7 (2)
O(6)–S(2)–O(4)		104·0 (2)	
O(1)–S(1)–C(1)	110·3 (2)	108·6 (2)	109·6 (3)
O(6)–S(2)–C(5)		108·5 (2)	
O(2)–S(1)–O(3)	109·5 (1)	110·0 (1)	109·6 (2)
O(5)–S(2)–O(4)		109·9 (2)	
O(2)–S(1)–C(1)	109·4 (1)	109·7 (2)	108·9 (3)
O(5)–S(2)–C(5)		109·6 (2)	
O(3)–S(1)–C(1)	103·2 (2)	103·8 (2)	104·5 (2)
O(4)–S(2)–C(5)		104·0 (1)	
S(1)–O(3)–C(2)	118·7 (2)	118·6 (2)	118·9 (3)
S(2)–O(4)–C(4)		119·9 (2)	
O(3)–C(2)–C(2)	105·1 (2)		
O(3)–C(2)–C(3)		105·2 (3)	106·6 (4)
O(4)–C(4)–C(3)		106·5 (3)	
C(2)–C(3)–C(4)		114·8 (2)	
C(2)–C(3)–C(3)			113·5 (5)
O(1)–S(1)–O(3)–C(2)	168·9 (2)	164·2 (2)	166·7 (2)
O(6)–S(2)–O(4)–C(4)		−164·0 (2)	
O(2)–S(1)–O(3)–C(2)	40·7 (2)	35·0 (2)	38·6 (2)
O(5)–S(2)–O(4)–C(4)		−34·8 (2)	
C(1)–S(1)–O(3)–C(2)	−75·7 (2)	−82·3 (2)	−78·0 (2)
C(5)–S(2)–O(4)–C(4)		82·5 (2)	
S(1)–O(3)–C(2)–C(2)	152·4 (2)		
S(1)–O(3)–C(2)–C(3)		168·7 (2)	−178·4 (2)
S(2)–O(4)–C(4)–C(3)		−175·2 (2)	
O(3)–C(2)–C(2)–O(3)	180·0 (0)		
O(3)–C(2)–C(3)–C(3′)			−65·5
O(3)–C(2)–C(3)–C(4)		−66·8 (2)	
O(4)–C(4)–C(3)–C(2)		−63·9 (2)	
C(2)–C(3)–C(3)–C(2)			180·0 (0)

Primed atoms are related to the corresponding unmarked atoms by centre of inversion.

The series as a whole can alkylate DNA since the alkyl–oxygen bonds readily undergo fission. The possible bisalkylation range of distances (O_{ester}–O_{ester} distance) is 3·56, 3·62 and 4·99 Å for (I), (II) and

(III) respectively, in the conformations found in the crystal structures. The range can increase to 4·7 Å for (II) if the central dihedral angle is altered to a *trans* value of 180° rather than the crystallographically observed *gauche* value of *ca* 65° (Table 2). In the case of (III), the *gauche*$^-$, *trans*, *gauche*$^-$ conformation for the three central C—C bonds would have to be changed to *trans*, *trans*, *trans* for a maximum extended distance of 6 Å to be achieved. Even so, the potential alkylation distances are too short for the compounds to (inter-strand) span the distance between N(7) or O(6) atoms of adjacent guanosine nucleotides on opposite DNA strands. Thus, the high biological activity observed for BDMS may be due to its ability to form intra-strand rather than inter-strand cross-linking, which is geometrically quite feasible. Molecular modelling studies on these cross-linking possibilities will be reported elsewhere.

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Structure of 1-(3,4-Dichlorophenyl)-4-methylthiosemicarbazide

BY D. CHATTOPADHYAY AND S. K. MAZUMDAR

Crystallography and Molecular Biology Division, Saha Institute of Nuclear Physics, Block 'AF', Sector I, *Bidhannagar, Calcutta*-700 064, *India*

T. BANERJEE

Department of Physics, Calcutta University, 92 *Acharya Prafulla Chandra Road, Calcutta*-700 009, *India*

AND W. S. SHELDRICK

Fachbereich Chemie, Universität Kaiserslautern, Erwin-Schrödinger Straße, 6750 *Kaiserslautern, Federal Republic of Germany*

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Abstract. $C_8H_9Cl_2N_3S$, $M_r = 250{\cdot}14$, monoclinic, $P2_1/n$, $a = 6{\cdot}477$ (1), $b = 27{\cdot}079$ (5), $c = 6{\cdot}266$ (1) Å, $\beta = 96{\cdot}84$ (2)°, $V = 1091{\cdot}2$ (3) Å^3, $Z = 4$, $D_m = 1{\cdot}54$, $D_x = 1{\cdot}523$ g cm^{-3}, λ(Mo $K\alpha$) = 0·7107 Å, $\mu = 7{\cdot}438$ cm^{-1}, $F(000) = 512$, $T = 293$ K, final R 0·038 with 1542 observed reflections. The molecule is in the *trans* conformation. The extent of conjugation between the phenyl ring and the thiosemicarbazide side chain is considerable. The charge density, calculated by the *CNDO*/2 method, on the hydrazinic N atom is less than in the 4-phenylthiosemicarbazides.

Introduction. The biological activities possessed by thiosemicarbazides and thiosemicarbazones (Agrawal, Cushley, Lipsky, Wheaton & Sartorelli, 1972; Nandi, Sheldrick & Ghosh, 1986; Chattopadhyay, Mazumdar, Banerjee, Ghosh & Mak, 1988; Chattopadhyay, Mazumdar, Banerjee & Mak, 1988, and references therein) are generally associated with their metal chelating ability (Umapathy, Budhkar & Dorai, 1986). Since the S and hydrazinic N atoms take part in metal chelation, the biological activity of the ligands is thought to be centred around these two atoms. The

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