Acta Cryst. (1984). C**40**, 1078–1080

Structure of 2-Ethylsulfonyl-7-methyl-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-one, $C_8H_9N_3O_3S_2$

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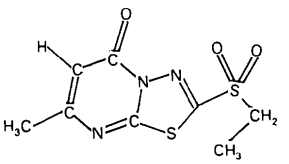
(*Received* 4 *November* 1983; *accepted* 8 *February* 1984)

Abstract. $M_r = 259{\cdot}31$, orthorhombic, *Pcab*, $a = 8{\cdot}362\ (3)$, $b = 11{\cdot}368\ (3)$, $c = 22{\cdot}776\ (6)$ Å, $V = 2165\ (2)$ Å^3, $Z = 8$, $D_m = 1{\cdot}592$, $D_x = 1{\cdot}591$ g cm^{-3}, $\lambda(\text{Mo } K\alpha) = 0{\cdot}71073$ Å, $\mu = 4{\cdot}465$ cm^{-1}, $F(000) = 1072$, $T = 297$ K. Final $R = 0{\cdot}053$ for 933 significant reflections. The analysis has established the chemical structure of the title compound. The thiadiazole and pyrimidinone portions are both essentially planar and the sulfone part, which is assumed to be responsible for the bioalkylation of DNA-dependent RNA polymerase, takes a staggered conformation around the fairly long S–C(aromatic) bond of 1·796 (5) Å.

Introduction. The title compound ($TPSO_2$-2, I) is a selective inhibitor of DNA-dependent RNA polymerase (Suiko, Taniguchi, Maekawa & Eto, 1980; Suiko, Hayashida & Nakatsu, 1982). The activity is susceptible to chemical modifications. An analogue (II), in which an ethylthio group is substituted for the sulfone, was not biologically active, and chlorination of the pyrimidine ring caused an increase in the inhibitory activity (Suiko & Maekawa, 1977). The present X-ray investigation was carried out to establish the molecular structure and to reveal the correlation between the biological activity and the structure.



(I)

Experimental. Colorless needles crystallized from $CHCl_3$ solution, D_m determined by flotation in CCl_4/hexane mixture, crystal dimensions 0·4 × 0·17 × 0·14 mm, Enraf–Nonius CAD-4 diffractometer, graphite-monochromatized Mo $K\alpha$. Cell parameters refined by least-squares methods on the basis of 25 θ values. Intensity measurement performed within a range of $2{\cdot}0 < \theta < 35{\cdot}0°$ (h: 0 to 13; k: 0 to 17; l: 0 to 34), ω–2θ scan technique, max. count time 60s, corrections for Lorentz–polarization, not for absorption. No significant variations in intensities of three standard reflections ($0\bar{3}8$, 008 and $1\bar{1}8$) monitored at intervals of 3600s. 4707 reflections measured, 3737 weak reflections, $I < 3\sigma(I)$, classified as unobserved, 933 observed unique reflections used for structure determination. Space group determined from extinction rule ($0kl$, $l = 2n + 1$; $hk0$, $k = 2n + 1$; $h0l$, $h = 2n + 1$). Positions of the two S atoms deduced from a Patterson map; starting with these positions, other non-H atoms determined stepwise from electron density maps and refined by full-matrix least squares with anisotropic thermal parameters, $\sum w\left|\,|F_o| - |F_c|\,\right|^2$ minimized, unit weights; max. shift on final cycle of refinement $0{\cdot}03\sigma$ for x coordinate of C(8); the H atom on the pyrimidinone ring found from a difference density map, others calculated; final $R = 0{\cdot}053$, $wR = 0{\cdot}059$, $S = 2{\cdot}5$ for 933 observed reflections; no peaks higher than 0·35 e Å^{-3} observed in final difference density map. Atomic scattering factors from *International Tables for X-ray Crystallography* (1974); structure analyzed by using an *SDP* system and program package (Frenz, 1978) on a PDP 11/34 computer.

Discussion. The final atomic parameters are listed in Table 1.† Bond distances and angles are given in Table 2. Fig. 1 shows a perspective view of the molecule, depicted by *ORTEP* (Johnson, 1965), with atomic numbering.

† Lists of structure factors, anisotropic thermal parameters, atomic parameters for H atoms, and least-squares planes have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 39255 (26 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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0108-2701/84/061078-03$01.50

Table 1. *Atomic coordinates and isotropic temperature factors of the non-H atoms*

	x	y	z	B_{eq}(Å^2)†
S(1)	0·1465 (4)	0·4577 (3)	0·5428 (1)	2·96 (5)
S(2)	0·1546 (4)	0·5093 (3)	0·6725 (1)	3·33 (5)
O(1)	0·282 (1)	0·5252 (9)	0·7115 (3)	4·7 (2)
O(2)	0·076 (1)	0·3974 (7)	0·6686 (4)	5·2 (2)
O(3)	0·554 (1)	0·7573 (8)	0·5334 (3)	3·9 (2)
N(1)	0·341 (1)	0·6111 (8)	0·5887 (3)	2·7 (2)
N(2)	0·363 (1)	0·6126 (8)	0·5294 (3)	2·6 (2)
N(3)	0·269 (1)	0·5318 (8)	0·4401 (3)	2·8 (2)
C(1)	0·230 (1)	0·5350 (11)	0·5997 (4)	2·9 (2)
C(2)	0·270 (1)	0·5387 (9)	0·4963 (4)	2·6 (2)
C(3)	0·475 (1)	0·6912 (9)	0·5030 (5)	2·8 (2)
C(4)	0·474 (1)	0·6817 (9)	0·4407 (5)	2·7 (2)
C(5)	0·375 (1)	0·6071 (10)	0·4127 (4)	2·9 (2)
C(6)	0·017 (1)	0·6241 (12)	0·6816 (5)	3·8 (3)
C(7)	0·093 (2)	0·7445 (13)	0·6891 (5)	4·5 (3)
C(8)	0·371 (2)	0·6003 (11)	0·3447 (4)	3·9 (3)

† $B_{eq} = 8\pi^2 U_{eq}$, where $U_{eq} = \frac{1}{3}\sum_i \sum_j U_{ij} a_i^* a_j^* \mathbf{a}_i . \mathbf{a}_j$.

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

S(1)–C(1)	1·713 (6)	N(2)–C(3)	1·428 (8)
S(1)–C(2)	1·744 (6)	N(3)–C(2)	1·284 (7)
S(2)–O(1)	1·400 (5)	N(3)–C(5)	1·384 (7)
S(2)–O(2)	1·435 (5)	O(3)–C(3)	1·216 (7)
S(2)–C(1)	1·796 (5)	C(3)–C(4)	1·422 (8)
S(2)–C(6)	1·755 (7)	C(4)–C(5)	1·343 (8)
N(1)–N(2)	1·364 (6)	C(5)–C(8)	1·551 (8)
N(1)–C(1)	1·296 (8)	C(6)–C(7)	1·518 (11)
N(2)–C(2)	1·370 (7)		

C(1)–S(1)–C(2)	87·0 (3)	S(1)–C(1)–N(1)	119·2 (4)
O(1)–S(2)–O(2)	120·2 (3)	S(2)–C(1)–N(1)	122·6 (4)
O(1)–S(2)–C(1)	107·4 (3)	S(1)–C(2)–N(2)	109·1 (4)
O(1)–S(2)–C(6)	109·3 (3)	S(1)–C(2)–N(3)	124·7 (5)
O(2)–S(2)–C(1)	104·4 (3)	N(2)–C(2)–N(3)	126·2 (6)
O(2)–S(2)–C(6)	111·3 (4)	N(2)–C(3)–O(3)	120·1 (6)
C(1)–S(2)–C(6)	102·6 (3)	N(2)–C(3)–C(4)	111·6 (6)
N(2)–N(1)–C(1)	107·3 (5)	O(3)–C(3)–C(4)	128·3 (6)
N(1)–N(2)–C(2)	117·4 (5)	C(3)–C(4)–C(5)	121·8 (6)
N(1)–N(2)–C(3)	121·0 (5)	N(3)–C(5)–C(4)	124·8 (5)
C(2)–N(2)–C(3)	121·6 (5)	N(3)–C(5)–C(8)	113·9 (6)
C(2)–N(3)–C(5)	114·0 (5)	C(4)–C(5)–C(8)	121·4 (6)
S(1)–C(1)–S(2)	118·2 (4)	S(2)–C(6)–C(7)	114·1 (5)

N(1)–C(1)–S(2)–C(6)	81·7 (1·8)	C(1)–S(2)–C(6)–C(7)	71·8 (2·3)

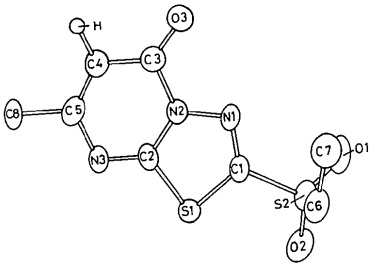

Fig. 1. An *ORTEP* drawing (Johnson, 1965) of the molecule with atom numbering. Thermal ellipsoids of the non-H atoms are scaled at 50% probability level. The pyrimidinone-ring H atom is represented by a circle of radius 0·2 Å. The other H atoms are omitted.

The arrangement of the bonds around the S(2) atom is a distorted tetrahedron with an O(1)–S(2)–O(2) angle of 120·2 (3)°. The O(1)···O(2) distance is 2·46 (1) Å, being comparable with the values 2·59 (1), 2·56 (1), 2·58 (1) and 2·64 (1) Å for C···O distances. The staggered conformation around the S(2)–C(6) bond is in contrast with the case of the planar zigzag ethylthio group in the biologically inactive analogue (II). The C(1)–S(2) bond is longer than the corresponding bond in (II) (Suiko, Nakatsu, Imada & Kiyose, 1984).

The dimensions of the thiadiazole portion are essentially the same as those of 1,3,4-thiadiazole, determined by microwave spectroscopy (Nygaard, Hansen & Sorensen, 1971) and electron diffraction (Markov & Stoelevik, 1970), except that the C(2)–N(2) bond of (I) is longer than that of the unsubstituted thiadiazole suggesting a single-bond nature. This tendency is confirmed by comparing (I) with the 5-benzoylimino-2,2-dimethyl-4-phenyl substituted 1,3,4-thiadiazole structure (Fukutani, Tsukihara, Okuda, Fukuyama, Katsube, Yamamoto & Gotoh, 1979), and 5,6-dimethylimidazo[2,1-*b*][1,3,4]thiadiazole (Schenetti, Taddei, Greci, Marchetti, Milani, Andreetti, Bocelli & Sgarabotto, 1980).

Shortening of the C(2)–N(3) bond in the pyrimidinone ring, in contrast to longer C(3)–N(2) and C(3)–C(4) bonds, is characteristic of pyrimidinone structures. An isolated pyrimidinone model structure, as well as its tautomers, *e.g.* pyrimidinol, was studied on the basis of MINDO/3 molecular-orbital calculations, with optimization of molecular geometry (Czerminski, Lesyng & Pohorille, 1979). Shortening of the corresponding bond was estimated on the basis of minimal energy. In this connection, the pyrimidinone ring of (I) seems to be in almost the same situation as that of guanine, on comparison of the molecular dimensions (Thewalt, Bugg & Marsh, 1970, 1971; Brennan, Weeks, Shefter, Rao & Sundaralingam, 1972; Ginel & Parthasarathy, 1978), except for the shortened C(4)–C(5) bond of (I).

Inhibition of the RNA polymerase by the $TPSO_2$-2 molecule is assumed to be caused mainly by bioalkylation, provoked by the scission of the S(2)–C(1) bond (Suiko *et al.*, 1980). This bond is longer than the S(2)–C(6) bond and is also longer than the corresponding bond in (II). The same situation was reported in the case of methyl phenyl sulfone (Vorontsova, 1965) in which the S–C(aromatic) is longer than its counterpart, S–C(methyl), while the latter is almost of the same order of length as in the case of dimethyl sulfone (Sands, 1963).

The authors are indebted to the Research Center for Material Analysis, Miyazaki University, for the use of a CAD-4–PDP 11/34a system.

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Acta Cryst. (1984). C**40**, 1080–1082

Structure of 2-Chloro-6-(*p*-chlorophenyl)-3-(*p*-tolyl)-3,4-dihydro-1,3,2-oxazaphosphorine 2-Oxide, $C_{16}H_{14}Cl_2NO_2P$*

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(*Received* 1 *November* 1983; *accepted* 13 *February* 1984)

Abstract. $M_r = 354{\cdot}2$, monoclinic, $P2_1/a$, $a = 10{\cdot}141\ (3)$, $b = 15{\cdot}113\ (3)$, $c = 10{\cdot}891\ (3)$ Å, $\beta = 93{\cdot}22\ (2)°$, $V = 1666{\cdot}4$ Å^3, $Z = 4$, D_m(flotation) = 1·41, $D_x = 1{\cdot}42$ g cm^{-3}, λ(Mo $K\alpha$) = 0·7107 Å, μ(Mo $K\alpha$) = 1·51 cm^{-1}, $F(000) = 728{\cdot}0$, $T = 293$ K. $R = 0{\cdot}067$ for 1334 reflections. The 1,3,2-oxazaphosphorine ring takes a half-chair conformation. The exocyclic chlorine and oxygen connected to phosphorus are in axial and equatorial positions respectively. The P—O distance of 1·468 (6) Å agrees with values found in other cyclophosphamide, isophosphamide and trophosphamide compounds.

Introduction. The perhydro-1,3,2-oxazaphosphorine cyclophosphamide and its analogues isophosphamide and trophosphamide are clinically useful anticancer drugs. Several recent studies have shown that the perhydro-1,3,2-oxazaphosphorine ring undergoes conformational changes due to steric and electronic influences of the substituents on phosphorus (Bajwa, Bentrude, Pantaleo, Newton & Hargis, 1979; Gorenstein & Rowell, 1979; Gorenstein, Rowell & Findlay, 1980; Maryanoff, Hutchins & Maryanoff, 1979) and of the substituents on the ring nitrogen (Chandrasekharan & Bentrude, 1980; Bajwa, Chandrasekharan, Hargis, Sopchik, Blatter & Bentrude, 1982). Carbon-substituted derivatives have also undergone extensive clinical and biological testing. We report here the influence of a ring constraint (3,4-dihydro) on the conformational flexibility of the oxazaphosphorine ring.

Experimental. The title compound was prepared following a general procedure (Sahasrabudhe, 1983). Orange, needle crystal from alcohol solution, approximate dimensions 0·45 × 0·40 × 0·55 mm; lattice parameters from 20 reflections ($12° < 2\theta < 35°$); intensity data collected on an Enraf–Nonius CAD-4F-11M single-crystal X-ray diffractometer, graphite-monochromated Mo $K\alpha$ radiation, $\omega/2\theta$ scan mode, scan speed 1° min^{-1}, $\theta \leq 24°$; of 2914 reflections collected 1334 were judged significant ($|F_o| > 3\sigma|F_o|$); intensities not corrected for absorption; structure solution by direct methods [*MULTAN*78 (Main, Hull, Lessinger, Germain, Declercq & Woolfson, 1978)]; full-matrix refinement of scale factor, positional and anisotropic thermal parameters (isotropic thermal parameters for H atoms,

* NCL communication No. 3333.

0108-2701/84/061080-03$01.50