Table 4. *Bonding data in the oxetane rings for spirooxetanes and some derivatives*

Compound	O(2)—C(1)	O(2)—C(14)	C(1)—C(7)	C(7)—C(14)	Puckering angle	Reference
(I)–(IV) (average)	1·437 (3) Å	1·469 (3) Å	1·582 (3) Å	1·547 (4) Å	0·4 (2)–18·2 (4)°	*a*
Oxetane (90 K)	1·460 (1)		1·534 (2)		10·7 (1)	*b*
Oxetane (140 K)	1·443 (2)		1·517 (2)		8·7 (2)	*b*
3,5-Dinitrobenzoate of *threo*-3,3,4,4,α-pentamethyl-2-oxetanemethanol	1·437 (3)	1·445 (3)	1·558 (3)	1·550 (3)	22·9 (2)	*c*
2,2-Bis(*p*-ethoxyphenyl)-3,3-dimethyloxetane	1·47	1·48	–	–	16·0*	*d*
Dictyoxetane	1·50 (1)	1·48 (1)	1·55 (1)	1·57 (2)	9·0	*e*

References: (*a*) this work; (*b*) Luger *et al.* (1984); (*c*) Hospital *et al.* (1978); (*d*) Holan *et al.* (1973); (*e*) Pullaiah *et al.* (1985).

* Dihedral angle between the O—C—C planes.

Table 5. *Selected torsion angles* (°) *with e.s.d.'s in parentheses*

	(I)–(*A*)*	(I)–(*B*)	(II)*	(III)	(IV)
C(1)—C(7)—C(8)—C(9)/C(13)	66·3 (3)	−84·4 (3)	67·4 (6)	61·9 (2)	61·5 (8)
C(7)—C(14)—C(15)—C(16)/C(20)	−88·2 (4)	80·7 (4)	51·6 (6)	−47·9 (3)	−43·5 (8)

* Molecules with the symmetry code $-x, -y, -z$.

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1-(1-Aziridinyl)-3-(2-nitro-1-imidazolyl)-2-propanol [RSU-1069] (I) and 1-(2-Methyl-1-aziridinyl)-3-(2-nitro-1-imidazolyl)-2-propanol [RSU-1131] (II)

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Abstract. RSU-1069 (I): $C_8H_{12}N_4O_3$, $M_r = 212$, monoclinic, $P2_1/c$, $a = 9{\cdot}127$ (1), $b = 9{\cdot}763$ (1), $c = 11{\cdot}581$ (1) Å, $\beta = 103{\cdot}14$ (1)°, $V = 1004{\cdot}9$ (2) Å^3, $Z = 4$, $D_x = 1{\cdot}401$ Mg m^{-3}, Cu $K\alpha$, $\lambda = 1{\cdot}54178$ Å, $\mu = 0{\cdot}830$ mm^{-1}, $F(000) = 448$, $T = 298$ K, $R = 0{\cdot}064$ for 1469 unique observed reflections ($F > 6\sigma F$). RSU-1131 (II): $C_9H_{14}N_4O_3$, $M_r = 226$, triclinic, $P\bar{1}$, $a = 7{\cdot}111$ (2), $b = 9{\cdot}305$ (1), $c = 10{\cdot}395$ (2) Å, $\alpha = 62{\cdot}00$ (1), $\beta = 67{\cdot}80$ (1), $\gamma = 79{\cdot}66$ (1)°, $V = 562{\cdot}3$ (2) Å^3, $Z = 2$, $D_x = 1{\cdot}334$ Mg m^{-3}, Cu $K\alpha$, $\lambda = 1{\cdot}54178$ Å, $\mu = 0{\cdot}769$ mm^{-1}, $F(000) = 240$, $T = 298$ K, $R = 0{\cdot}051$ for 1827 unique observed reflections ($F > 6\sigma F$). The title compounds are 2-nitroimidazoles with current application as hypoxia-

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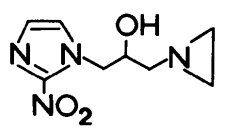
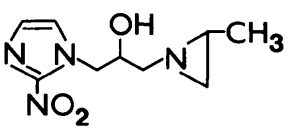
selective anticancer agents. In both compounds all bond lengths and angles have normal values; the planes of the nitro group and imidazole ring form dihedral angles of 19·4 (1) and 14·1 (1)° in (I) and (II) respectively. The aziridine rings form near-equilateral triangles with greater pyramidal character about the N15 atom in the case of (II).

Introduction. Considerable recent effort has been focused upon the development of 2-nitroimidazoles as hypoxic cell radiosensitizers and chemopotentiators in the treatment of human cancers (Adams & Stratford, 1986; Kennedy, 1987; Jenkins, 1989). The mixed-function compound 1-(1-aziridinyl)-3-(2-nitro-1-imidazolyl)-2-propanol [RSU-1069; NSC-347503] (I) is the most efficient compound of this class to have been examined, both *in vitro* and *in vivo*, and this activity has been ascribed to the presence of the aziridine moiety (Ahmed *et al.*, 1986; Chaplin, Durand, Stratford & Jenkins, 1986). Further, RSU-1069 shows, on a concentration basis, a 100-fold greater toxicity towards hypoxic cells relative to aerobic cells *in vitro* (Ahmed *et al.*, 1986; O'Neill, Jenkins, Stratford, Silver, Ahmed, McNeil, Fielden & Adams, 1987).



RSU-1069



RSU-1131

Molecular and cellular studies reveal that DNA is a major target for these compounds and that under aerobic conditions RSU-1069 acts as a monofunctional alkylating agent, whereas following reduction ('bioactivation') under hypoxic conditions it shows bifunctional character (Silver, O'Neill & Jenkins, 1985; Silver, McNeil, O'Neill, Jenkins & Ahmed, 1986; O'Neill, Jenkins, Stratford, Silver, Ahmed, McNeil, Fielden & Adams, 1987; Suzangar, White, Jenkins & Connors, 1987; Dale, Tocher & Edwards, 1988). Induction of interstrand DNA crosslinks by agents of this class may thus play a major role in their effectiveness as hypoxia-selective cytotoxins (O'Neill, McNeil & Jenkins, 1987; Jenkins, 1989). The introduction of a methyl group into the alkylating function, as in 1-(2-methyl-1-aziridinyl)-3-(2-nitro-1-imidazolyl)-2-propanol [RSU-1131] (II), moderates the differential hypoxic:aerobic cytotoxicity *in vitro* (O'Neill, Jenkins, Stratford, Silver, Ahmed, McNeil, Fielden & Adams, 1987). This behaviour has been ascribed to lower inherent alkylating reactivity and steric crowding of the alkylation site(s) (O'Neill, McNeil & Jenkins, 1987; Dale *et al.*, 1988).

Table 1. *Details of data collections and structure refinements*

	(I)	(II)
(*a*) Data collection		
Crystal dimensions	0·6 × 0·25 × 0·35 mm	0·5 × 0·2 × 0·15 mm
Cell parameter determination		
Number, θ range of reflections	25, 14–28°	25, 13–31°
Max. $(\sin\theta)/\lambda$ (Å^{-1})	0·588	0·609
Range h	−10,9	−7,8
k	0,11	−9,11
l	0,12	0,12
Standard reflections number, % variation	3, ±4%	3, ±3%
Number of intensity measurements	2090	2480
Number of unique reflections	1709	2139
Number of reflections omitted with $\lvert F_o\rvert \ll \lvert F_c\rvert$	4	1
Number of reflections with $F<6\sigma(F)$	236	311
(*b*) Structure refinement		
R	0·064	0·051
wR	0·076	0·063
Weighting scheme	$1/\{\lvert\sigma(F)\rvert^2 + aF^2\}$	
a	0·001	0·00025
$(\Delta/\sigma)_{max}$ in final cycle	0·71	0·26
Max. min. heights in final ΔF map (e Å^{-3})	0·41, −0·43	0·32, −0·3

Experimental. RSU-1069 and RSU-1131 were prepared by reflux condensation of the appropriate aziridine with 1-(2,3-epoxypropyl)-2-nitroimidazole as already described (Ahmed *et al.*, 1986; O'Neill, Jenkins, Stratford, Silver, Ahmed, McNeil, Fielden & Adams, 1987). The (±)-racemic compounds were recrystallized from 2-propanone containing 0·5% *v/v* triethylamine to inhibit acid-catalysed polymerization of the aziridine residues. RSU-1069 crystallized as pale-yellow needle-shaped crystals and had m.p. 393·5–394 K [lit: 393–394 K (Ahmed *et al.*, 1986)]; RSU-1131 crystallized as thin yellow plates in space group *Pbca* and had m.p. 383·5–384 K [lit: 382–384 K (Ahmed *et al.*, 1986)]. These latter crystals were found to diffract too weakly for the collection of good-quality intensity data; alternative crystallization of RSU-1131 from ethyl acetate containing 0·5% *v/v* triethylamine afforded triclinic material of unchanged melting point.

Details of data collections and structure refinements given in Table 1. Preliminary unit-cell dimensions and space-group information obtained from Weissenberg photographs. Intensity data collected using an Enraf–Nonius CAD-4 diffractometer with nickel-filtered Cu radiation and an ω–2θ scan mode. Reference reflections measured after every 60 min X-ray exposure time. Preliminary data reduction using *SDP* (Frenz, 1980). No correction made for absorption effects.

Structures solved by direct methods [*MULTAN*82 (Main *et al.*, 1982) for (I) and *SHELX*76 (Sheldrick, 1976) for (II)]. Full-matrix least-squares refinement

on F of overall scale factor and positional and anisotropic thermal parameters for non-H atoms carried out using *SHELX*76 (Sheldrick, 1976). H atoms located from a difference synthesis and subsequently fixed in positions calculated assuming idealized geometry and C—H distances 1·0 Å. In each case, the hydroxyl H atom (H13) was repositioned towards the end of refinement from a difference synthesis calculated with this atom omitted. All H atoms assigned fixed isotropic thermal parameters $U_{iso} = 0{\cdot}1$ Å^2. For both (I) and (II), a number of low-angle reflections had $|F_o| \ll |F_c|$. The discrepancies were attributed to secondary extinction and for (II) an extinction coefficient g, defined by $F_{corr} = F_{uncorr}(1 - gF^2_{uncorr}/\sin\theta)$, was introduced and refined with the other parameters. The final value of g was $5{\cdot}2\,(7) \times 10^{-6}$. Despite this correction, the 010 reflection still showed considerable discrepancy and was omitted from the refinement. For (I), no extinction coefficient was refined but four reflections which appeared to suffer from secondary extinction were omitted. Atomic scattering factors taken from *International Tables for X-ray Crystallography* (1974). Major computations performed on a VAX 11/750 computer at the Institute of Cancer Research.

Discussion. Atomic coordinates and equivalent isotropic thermal parameters for non-H atoms are given in Table 2.* The atomic numbering is indicated in Figs. 1(*a*) and 1(*b*) which also show bond lengths and angles, while Figs. 2(*a*) and 2(*b*) are stereodrawings of the molecules of (I) and (II) respectively.

In both compounds the imidazole rings are planar within experimental error and N21 and C11 both lie close to this plane; in (I) these atoms are 0·035 (5) and 0·005 (4) Å respectively from the least-squares plane defined by the ring atoms while the corresponding distances in (II) are 0·004 (3) and 0·001 (4) Å. Bond lengths and angles within the nitroimidazole moieties are in agreement with those found in the 1-alkyl-2-nitroimidazole, misonidazole (Jenkins & Walton, 1988).

Steric hindrance between O22 and H111 [nonbonded separation 2·32 Å in (I); 2·41 Å in (II)] is reduced by a twist about the C2—N21 bond and distortion of the exocyclic angles at N1. In (I) the dihedral angle between the planes defined by the imidazole ring atoms and the nitro group is 19·4 (1)° and the angle C2—N1—C11 is 130·8 (2)°. Corresponding values for (II) are 14·2 (1) and 131·5 (2)° and for misonidazole 7·9 (1) and 132·7 (2)°. Thus the angular distortion at N1 increases while the twist about the C2—N21 bond decreases; the values observed in any particular compound presumably depend on crystal packing constraints.

Table 2. *Fractional coordinates and equivalent isotropic thermal parameters for non-*H *atoms of RSU-*1069 (I) *and RSU-*1131 (II)

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

	x	y	z	U_{eq}(Å^2 × 10^3)
(I)				
N1	0·3575 (2)	0·2397 (2)	0·2388 (2)	45 (1)
C2	0·2363 (3)	0·3200 (3)	0·1973 (2)	49 (1)
N3	0·1157 (3)	0·2823 (3)	0·2309 (2)	68 (1)
C4	0·1602 (3)	0·1709 (4)	0·2985 (3)	73 (1)
C5	0·3087 (3)	0·1431 (3)	0·3059 (2)	61 (1)
N21	0·2417 (3)	0·4383 (2)	0·1242 (2)	62 (1)
O22	0·3437 (3)	0·4491 (2)	0·0737 (2)	68 (1)
O23	0·1439 (3)	0·5247 (3)	0·1198 (3)	111 (1)
C11	0·5112 (3)	0·2480 (2)	0·2222 (2)	45 (1)
C12	0·5327 (2)	0·1622 (2)	0·1175 (2)	38 (1)
O13	0·5366 (2)	0·0218 (2)	0·1497 (1)	44 (1)
C14	0·6785 (2)	0·2031 (2)	0·0850 (2)	45 (1)
N15	0·7057 (2)	0·1159 (2)	−0·0108 (2)	45 (1)
C16	0·8280 (3)	0·0155 (3)	0·0240 (2)	57 (1)
C17	0·8516 (3)	0·1405 (3)	−0·0412 (2)	58 (1)
(II)				
N1	0·3267 (2)	0·2808 (2)	0·5698 (2)	39 (1)
C2	0·4763 (3)	0·2824 (2)	0·6198 (2)	39 (1)
N3	0·4272 (3)	0·3569 (2)	0·7082 (2)	46 (1)
C4	0·2329 (4)	0·4070 (3)	0·7165 (3)	51 (1)
C5	0·1689 (3)	0·3611 (2)	0·6332 (3)	46 (1)
N21	0·6738 (3)	0·2110 (2)	0·5808 (2)	45 (1)
O22	0·7268 (2)	0·1729 (2)	0·4747 (2)	57 (1)
O23	0·7779 (3)	0·1949 (3)	0·6568 (2)	72 (1)
C11	0·3186 (3)	0·2115 (2)	0·4710 (2)	42 (1)
C12	0·3991 (3)	0·3311 (2)	0·2997 (2)	42 (1)
O13	0·2799 (3)	0·4755 (2)	0·2699 (2)	55 (1)
C14	0·3922 (4)	0·2541 (3)	0·2010 (3)	51 (1)
N15	0·5482 (3)	0·1284 (2)	0·2020 (2)	48 (1)
C16	0·6252 (5)	0·1053 (3)	0·0605 (3)	64 (1)
C17	0·7475 (4)	0·1934 (3)	0·0865 (3)	57 (1)
C18	0·9301 (4)	0·1190 (4)	0·1328 (3)	75 (2)

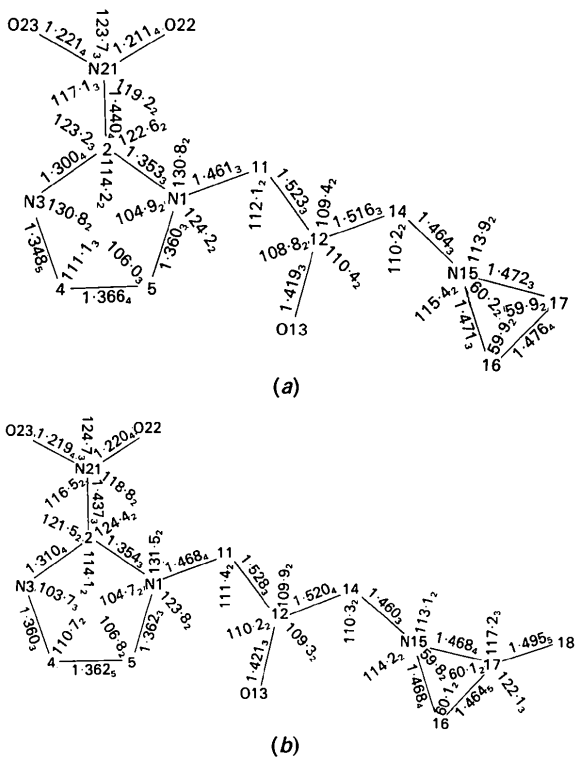
Bond lengths and angles in the 2-propanol side chains have normal values in both compounds and are in agreement with those found in misonidazole and in 2-(1-aziridinyl)-1-phenylethanol (Ko, Olansky & Moncrief, 1975).

The aziridine rings in (I) and (II) form nearly equilateral triangles as found in most other structures containing such rings [*e.g.* 2,4-dinitro-5-(1-aziridinyl)benzamide (Iball, Scrimgeour & Williams, 1975); 2-(1-aziridinyl)-1-phenylethanol (Ko *et al.*, 1975); 1-(1-aziridinyl)-2,4,6-trinitrobenzene (Barnes, Iball & Smith, 1977)]. In contrast, in 5-(1-aziridinyl)-3-nitro-1-(3-oxo-1-butyl)-1,2,4-triazole (McKenna, Jenkins & Neidle, 1988), the C—C bond of the aziridine ring [1·445 (4) Å] is significantly shorter than either N—C bond [1·473 (4) and 1·487 (4) Å]. Angles at N15 indicate a slightly more pyramidal geometry in (II) than in (I), in accord with the electron-releasing capacity afforded by the ring methyl substituent in (II), giving rise to altered sp^3 character of N15. Further, these observations are in

* 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 52403 (23 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

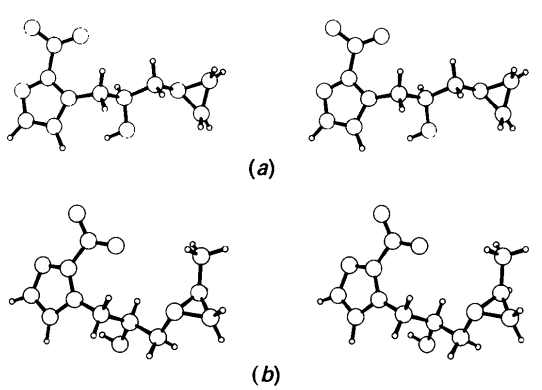
agreement with the increased basicity associated with (II) relative to (I) (O'Neill, Jenkins, Stratford, Silver, Ahmed, McNeil, Fielden & Adams, 1987; O'Neill, McNeil & Jenkins, 1987).

In neither compound are there any intermolecular distances which are significantly shorter than the sum of the appropriate van der Waals radii. In the crystal of (I), the molecules are arranged in layers parallel to the *bc* face of the unit cell. Each layer consists of pairs of molecules head-to-tail to one another with their longest dimension at approximately 30° to the normal to the *bc* face. Molecules in adjacent layers are head-to-head or tail-to-tail. However, owing to the spacing of the layers, there is no close proximity between aziridine moieties of neighbouring molecules. This may explain the observed radiation and chemical stability of the crystal in contrast with the limited stability of either amorphous material or (I) in solution (O'Neill, Jenkins, Stratford, Silver, Ahmed, McNeil, Fielden & Adams, 1987; Silver *et al*, 1986). In the crystal of (II), the molecules are arranged in a head-to-tail manner with no close intermolecular approaches.



(*a*) (*b*)

Fig. 1. Schematic diagrams of the molecules of (*a*) (I) and (*b*) (II), showing the atomic numbering, bond lengths (Å) and angles (°) with e.s.d.'s given as subscripts.



(*a*) (*b*)

Fig. 2. Stereodrawings of the molecules of (*a*) (I) and (*b*) (II).

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