# The Crystal and Molecular Structure of the Experimental Anticancer Agent 2-Hydroxy-2-phenyl-1-aziridinoethane

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The structure of the title compound, $C_{10}H_{13}NO$, has been determined by direct methods and refined to $R = 0.052$ from Cu $K\alpha$ diffractometer data. The space group is $Pna2_1$ with $a = 7.525$ (18), $b = 15.147$ (29), $c = 8.294$ (14) Å, $Z = 4$. The configuration at nitrogen is pyramidal (N lying 0.668 Å from the plane defined by its three substituents). The lengths of both C–N in the aziridine ring (1.457, 1.447 Å) agree well with the C–N single bond in the chain system (1.450 Å). In common with other structures having three-membered rings, the observed C–C bond length in the aziridine ring (1.465 Å) is considerably less than those found in unstrained compounds. The molecules are linked parallel to $y$ by hydrogen bonds between the hydroxyl group and the nitrogen of the aziridine ring with an O···N distance of 2.774 Å.

## Introduction

Neuroblastoma is one of the most frequent solid tumors in children, being most common in the first two years of life. This disease is associated with extensive metastasis, frequently present at the time of diagnosis. The tumor arises from primitive sympathetic neuroblasts of the neural crest, and as a result, exhibits a number of properties in common with normal nerve tissue. Clinically, the current drug therapy for neutroblastoma, consisting primarily of vincristine and cyclophosphamide, has not prolonged survival rates significantly (Schneider, 1974).

2-Hydroxy-2-phenyl-1-aziridinoethane (HPAE)
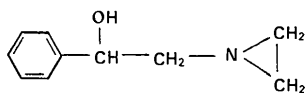
is currently being used as an experimental anticancer agent. Preliminary studies have shown that HPAE produces toxic effects in mouse neutroblastoma cells at a concentration of $10^{-6}$ $M$. These effects include a decrease in cell growth, increased detachment of the cells from the surface upon which they normally grow, and decreased viability of the cells (Johnston, Mandell & Schneider, 1974). A crystal structure determination was undertaken to ascertain the details of its molecular structure.

## Experimental

HPAE was synthesized* according to the procedure of Funke & Benoit (1953). In a 1:1 mole ratio, styrene oxide and aziridine were placed in a heavy-walled glass

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* Crystals of HPAE were synthesized by Dr Leon Mandell and Miss Judy Johnston, Chemistry Department, Emory University.

tube, a drop of water added, and the tube sealed and heated to 100°C for 30 min. The yellow-orange, syrupy product was vacuum-distilled (0.05 mm, 83°C experimental; 0.06 mm, 116°C reported by Funke) and the distillate recrystallized from hot pentane with benzene (about 30% yield), m.p.73–74°C.

Transparent white crystals of HPAE are not stable in air. Therefore, crystals were mounted in 0.3 mm sealed glass capillaries. A summary of physical and crystallographic data is given in Table 1.

Table 1. *Summary of physical and crystallographic data for HPAE*

$C_{10}H_{13}NO$
M.W. 163.1
Melting point: 73–74°C
Space group: $Pna2_1$
$a = 7.525$ (18) Å
$b = 15.147$ (29)
$c = 8.294$ (14)
$D_o = 1.151$ g cm$^{-3}$
$D_x = 1.144$
$Z = 4$
Reflections
  $F_o^2 > 2\sigma(I) = 850$
  Total $= 972$
$R$ (observed data) $= 0.052$
$R$ (all measured data) $= 0.089$

Two crystals were used for data collection on an automated Supper–Pace diffractometer possessing Weissenberg geometry. Two axes of diffraction data $(a, b)$ were measured with Ni-filtered Cu $K\alpha$ radiation. After Lp corrections the data were correlated (Simpson, 1963) to give 972 independent reflections, 850 of which were considered observed with $I > 2\sigma(I)$ (Parker, Flynn & Boer, 1968). An additional 118 high-angle reflections accessible in principle were not measured owing to physical limitations of the diffractometer.

The structure was solved by direct methods with the

Table 2. *Final atomic positions* ($\times 10^4$) *and temperature factors for HPAE*

$$T=\exp\,[-(\beta_{11}h^2+\beta_{22}k^2+\beta_{33}l^2+2\beta_{12}hk+2\beta_{13}hl+2\beta_{23}kl)\times 10^{-4}]\,.$$

| | $x/a$ | $y/b$ | $z/c$ | $\beta_{11}$ | $\beta_{22}$ | $\beta_{33}$ | $\beta_{12}$ | $\beta_{13}$ | $\beta_{23}$ |
|---|---|---|---|---|---|---|---|---|---|
| C(1) | 3168 (4) | 6574 (2) | 1198 (0) | 170 (5) | 34 (1) | 121 (3) | −12 (2) | 4 (4) | −2 (2) |
| C(2) | 2625 (5) | 6865 (3) | 9705 (5) | 249 (8) | 57 (2) | 131 (5) | −17 (3) | −5 (5) | 7 (2) |
| C(3) | 3536 (9) | 6620 (4) | 8329 (6) | 423 (14) | 75 (3) | 120 (5) | −71 (6) | 26 (8) | 2 (3) |
| C(4) | 4976 (9) | 6078 (4) | 8445 (8) | 395 (13) | 72 (3) | 235 (9) | −62 (5) | 177 (9) | −53 (4) |
| C(5) | 5513 (6) | 5790 (3) | 9914 (8) | 258 (9) | 63 (2) | 310 (10) | 5 (4) | 102 (9) | −35 (4) |
| C(6) | 4644 (4) | 6034 (2) | 1287 (6) | 199 (6) | 47 (2) | 202 (6) | 4 (3) | 25 (6) | −12 (3) |
| C(7) | 2136 (4) | 6817 (2) | 2692 (5) | 182 (5) | 34 (1) | 110 (4) | 3 (2) | 6 (5) | 3 (2) |
| C(8) | 585 (4) | 6190 (2) | 2903 (5) | 190 (6) | 42 (6) | 131 (5) | −2 (2) | 8 (5) | −1 (2) |
| C(9) | 8144 (5) | 5813 (3) | 4734 (6) | 233 (7) | 81 (2) | 199 (6) | −33 (4) | 41 (6) | 14 (4) |
| C(10) | 9637 (6) | 6090 (3) | 5748 (6) | 260 (8) | 63 (2) | 153 (5) | −1 (4) | 31 (6) | 21 (3) |
| N(11) | 9393 (3) | 6481 (2) | 4171 (5) | 179 (4) | 51 (1) | 142 (4) | 4 (2) | 32 (4) | 11 (2) |
| O(12) | 3175 (3) | 6791 (2) | 4103 (4) | 242 (5) | 57 (1) | 106 (3) | −25 (2) | −11 (3) | 4 (2) |

113 reflections with $E>1\cdot50$ and the program *MULTAN* (Germain, Main & Woolfson, 1971). Reflections in the starting set were 214, 140, 533, 220, 277, 343, and 260 with the first three used for origin and enantiomer specification. An $E$ map computed from one of the several sets of phases showing high figures of merit revealed the positions of the 12 non-hydrogen atoms ($R=0\cdot263$).

## Refinement

Eight cycles of full-matrix least-squares refinement with individual anisotropic temperature factors [*ORXFLS* (Busing, Martin & Levy, 1962)] reduced $R$ to $0\cdot108$. Five intense low-angle reflections (140, 040, 121, 120, and 002) affected by non-linearity of the proportional counter and secondary extinction were removed, thereby reducing $R$ to $0\cdot085$. A difference map revealed the positions of all 13 H atoms. Four additional cycles of full-matrix least-squares refinement of all positional and thermal parameters (individual isotropic temperature factors for H) produced a final $R=0\cdot052$ and $wR=0\cdot043$ where $R=\sum||F_o|-|F_c||/\sum|F_o|$ and $wR=[\sum w(|F_o|-|F_c|)^2/\sum w|F_o|^2]^{1/2}$. The weighting scheme $w=1/\sigma_F^2$ was employed. Scattering factors were taken from *International Tables for X-ray Crystallography* (1968). The final atomic coordinates and temperature factors and their estimated standard errors are listed in Table 2.* A final difference map contained no residual electron density above $0\cdot15$ e Å$^{-3}$.

## Discussion

Fig. 1 is an *ORTEP* II (Johnson, 1970) drawing of an HPAE molecule based on 50% probability thermal ellipsoids. Interatomic distances and angles [*ORFFE* (Busing, Martin & Levy, 1964)] are given in Tables 3 and 4. The high temperature factors of C(3), C(4), and C(5) indicate a strong vertical vibration of this portion

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* A list of structure factors has been deposited with the British Library Lending Division as Supplementary Publication No. SUP 30904 (8 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

Table 2 (*cont.*)

| | $x$ | $y$ | $z$ | $B$ |
|---|---|---|---|---|
| H(2) | 1644 (60) | 7233 (28) | 9655 (46) | 3·0 (0·8) |
| H(3) | 3032 (56) | 6830 (27) | 7421 (56) | 3·1 (0·8) |
| H(4) | 5715 (75) | 5886 (35) | 7682 (76) | 5·4 (1·1) |
| H(5) | 6383 (69) | 5420 (35) | 9964 (66) | 4·9 (1·0) |
| H(6) | 4954 (47) | 5792 (25) | 2317 (47) | 2·3 (0·7) |
| H(7) | 1670 (40) | 7397 (24) | 2552 (37) | 1·4 (0·5) |
| H(8A) | 9903 (50) | 6187 (24) | 1876 (53) | 2·9 (0·7) |
| H(8B) | 1030 (36) | 5598 (24) | 3129 (35) | 1·5 (0·6) |
| H(9A) | 6993 (73) | 6093 (29) | 4885 (60) | 4·7 (0·9) |
| H(9B) | 8369 (59) | 5170 (35) | 4014 (66) | 5·5 (1·0) |
| H(10A) | 9460 (74) | 6512 (35) | 6658 (71) | 5·6 (1·2) |
| H(10B) | 496 (50) | 5691 (26) | 5774 (42) | 2·3 (0·7) |
| H(O) | 3749 (67) | 7343 (40) | 4047 (80) | 5·8 (1·1) |

of the phenyl ring. C(9)–C(10) in the aziridine ring is significantly shorter than C(1)–C(7) and C(7)–C(8) in the chain, but its length agrees well with the C–C bonds in the three-membered ring compounds cyclopropanecarbohydrazide [1·478, 1·493, 1·520 Å (Chesnut & Marsh, 1958)], spiropentane [1·48 Å (Donohue, Humphrey & Schomaker, 1945)], ethylene oxide and
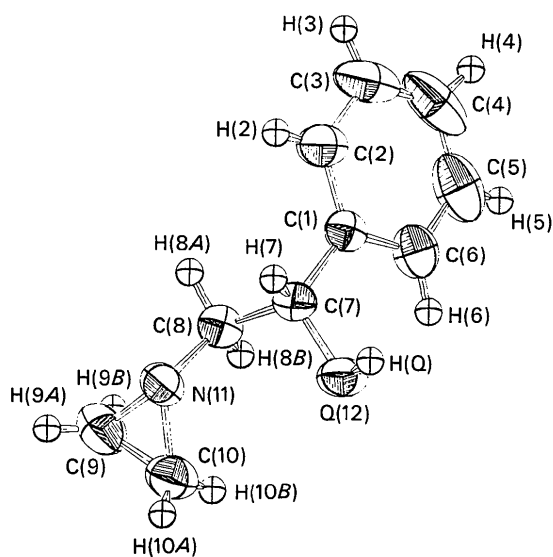


Fig. 1. An *ORTEP* II (Johnson, 1970) drawing of HPAE with thermal ellipsoids representing 50% probability.

ethylene sulfide [1·472, 1·492 Å (Cunningham, Boyd, Myers & Gwinn, 1951)]. This shortening is presumably a consequence of the inability of the orbitals of the C atom to rehybridize to about 60°. Consequently, the region of greatest orbital overlap does not lie exactly between the two C atoms but outside the ring. In order to have maximum orbital overlap, C(9) and C(10) therefore approach closer to each other than would be the case in an unstrained bonding situation. As a result, not only is C(9)–C(10) shorter, but its bond strength is weaker than those in normal aliphatic and alicyclic systems (Kilpatrick & Spitzer, 1946).

In general, distances and angles found in HPAE are similar to those found in other aziridine compounds. Table 5 presents for comparison selected bond lengths and angles from several aziridine structure determinations.

Fig. 2 is a stereoscopic drawing (Johnson, 1970) illustrating the molecular packing and hydrogen

bonding. The N atom is pyramidal, lying 0·668 Å from the plane defined by its three substituents. Molecules at the equivalent positions $(x,y,z)$ and $(\frac{1}{2}+x,\frac{1}{2}-y,z)$,

Table 3. *Interatomic distances and estimated standard errors for HPAE* (Å)

| | | | |
|---|---|---|---|
| C(1)—C(2) | 1·376 (5) | C(2)—H(2) | 0·926 (48) |
| C(1)—C(6) | 1·381 (4) | C(3)—H(3) | 0·901 (45) |
| C(2)—C(3) | 1·382 (6) | C(4)—H(4) | 0·891 (66) |
| C(3)—C(4) | 1·363 (9) | C(5)—H(5) | 0·863 (56) |
| C(4)—C(5) | 1·355 (8) | C(6)—H(6) | 0·959 (40) |
| C(5)—C(6) | 1·364 (6) | C(7)—H(7) | 0·953 (36) |
| C(1)—C(7) | 1·507 (4) | C(8)—H(8A) | 0·995 (43) |
| C(7)—C(8) | 1·514 (4) | C(8)—H(8B) | 0·976 (35) |
| C(7)—O(12) | 1·408 (4) | C(9)—H(9A) | 0·972 (53) |
| C(8)—N(11) | 1·450 (4) | C(9)—H(9B) | 1·155 (55) |
| C(9)—C(10) | 1·465 (6) | C(10)-H(10A) | 0·999 (59) |
| C(9)—N(11) | 1·457 (5) | C(10)-H(10B) | 0·885 (40) |
| C(10)-N(11) | 1·447 (4) | | |
| | | O(12)···N(11)′ | 2·774 (4) |
| O(12)-H(O) | 0·942 (61) | H(O)···N(11)′ | 1·849 (62) |

Table 4. *Interatomic angles and estimated standard errors for HPAE* (°)

| | | | |
|---|---|---|---|
| C(2)—C(1)—C(6) | 118·4 (3) | C(1)——C(6)—H(6) | 118·0 (2·1) |
| C(2)—C(1)—C(7) | 120·5 (3) | C(1)——C(7)—H(7) | 108·4 (1·8) |
| C(6)—C(1)—C(7) | 121·0 (3) | C(8)——C(7)—H(7) | 107·9 (1·8) |
| C(1)—C(2)—C(3) | 120·6 (4) | O(12)——C(7)—H(7) | 109·3 (1·9) |
| C(2)—C(3)—C(4) | 119·9 (4) | C(7)——C(8)—H(8A) | 107·5 (2·1) |
| C(3)—C(4)—C(5) | 119·6 (4) | C(7)——C(8)—H(8B) | 109·5 (1·6) |
| C(4)—C(5)—C(6) | 121·4 (4) | N(11)—C(8)—H(8A) | 107·7 (2·2) |
| C(5)—C(6)—C(1) | 120·1 (4) | N(11)—C(8)—H(8B) | 110·6 (1·7) |
| C(1)—C(7)—C(8) | 109·8 (2) | H(8A)—C(8)—H(8B) | 109·7 (2·7) |
| C(1)—C(7)—O(12) | 113·0 (2) | C(10)—C(9)—H(9A) | 119·0 (2·9) |
| C(8)—C(7)—O(12) | 108·3 (2) | C(10)—C(9)—H(9B) | 115·2 (2·3) |
| C(7)—C(8)—N(11) | 111·7 (2) | N(11)—C(9)—H(9A) | 108·3 (2·7) |
| C(10)-C(9)—N(11) | 59·4 (2) | N(11)—C(9)—H(9B) | 109·0 (2·4) |
| C(9)—C(10)-N(11) | 60·1 (2) | H(9A)—C(9)—H(9B) | 124·4 (3·7) |
| C(9)—N(11)-C(10) | 60·6 (2) | H(10A)-C(10)-H(10B) | 121·1 (4·0) |
| C(8)—N(11)-C(9) | 114·9 (3) | C(9)——C(10)-H(10A) | 121·0 (3·3) |
| C(8)—N(11)-C(10) | 116·9 (3) | C(9)——C(10)-H(10B) | 112·3 (2·3) |
| | | N(11)—C(10)-H(10A) | 113·8 (3·0) |
| C(1)—C(2)—H(2) | 118·0 (2·4) | N(11)—C(10)-H(10B) | 113·2 (2·3) |
| C(3)—C(2)—H(2) | 121·3 (2·4) | | |
| C(2)—C(3)—H(3) | 112·7 (2·8) | C(7)—O(12)——H(O) | 100·9 (3·8) |
| C(4)—C(3)—H(3) | 127·3 (2·8) | O(12)-H(O)····N(11)′ | 166·6 (4·9) |
| C(3)—C(4)—H(4) | 120·0 (3·3) | C(8)—N(11)···H(O)′ | 114·5 (1·9) |
| C(5)—C(4)—H(4) | 110·4 (3·4) | C(9)—N(11)···H(O)′ | 121·1 (1·6) |
| C(4)—C(5)—H(5) | 118·6 (3·8) | C(10)-N(11)···H(O)′ | 118·5 (2·1) |
| C(6)—C(5)—H(5) | 119·9 (3·8) | | |
| C(5)—C(6)—H(6) | 121·6 (2·1) | | |
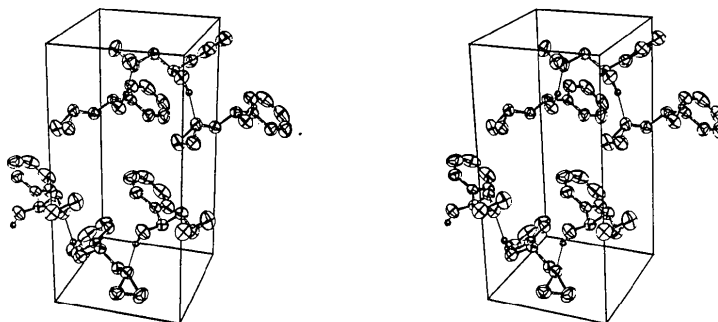


Fig. 2. A stereoscopic drawing (Johnson, 1970) of the contents of the unit cell of HPAE. Hydrogen bonds are drawn with thinner, solid lines. The horizontal axis is *a* and the vertical axis *b*.

Table 5. *Summary of selected distances and angles from several aziridine structures*

| 1. HPAE | This study |
|---|---|
| 2. *meso*-1,4-Diaziridinyl-2,3-butanediol | Gould & Pasternak (1961) |
| 3. α-Trichloromethyl-*N*-ethyleneiminocarbinol | Andrianov, Kostyanovskii, Shibaeva & Atovmyan (1967) |
| 4. *p*-Bromobenzoylethyleneimine | Shibaeva, Atovmyan & Kostyanovskii (1967) |
| 5. Aziridine borane | Ringertz (1969) |
| 6. Ethyleneimine | Turner, Fiora & Kendrick (1955) |

| | N–C(9) | N–C(10) | C(9)–C(10) | ∠NC(9)C(10) | ∠NC(10)C(9) | ∠C(9)NC(10) |
|---|---|---|---|---|---|---|
| 1. | 1·457 (5) | 1·447 (4) | 1·465 (6) | 59·4 (2) | 60·1 (2) | 60·6 (2) |
| 2. | 1·510 (11) | 1·468 (10) | 1·463 (12) | 58·9 | 59·1 | 58·9 |
| 3. | 1·50 | 1·49 | 1·49 | 59·8 | 60·4 | 59·9 |
| 4. | 1·48 | 1·48 | 1·51 | 59·5 | 59·5 | 61·0 |
| 5. | 1·450 (6) | 1·450 (6) | 1·460 (9) | 59·8 (2) | 59·8 (2) | 60·4 (4) |
| 6. | 1·488 | 1·488 | 1·480 | – | – | – |

| | N–C(8) | O–C(7) | O–H···N | ∠C(8)NC(9) | ∠C(8)NC(10) |
|---|---|---|---|---|---|
| 1. | 1·450 (4) | 1·408 (4) | 2·774 (4) | 114·9 (3) | 116·9 (3) |
| 2. | 1·501 (10) | 1·442 (8) | 2·874 (6) | 110·8 | 116·3 |
| 3. | 1·46 | 1·43 | 2·75 | 121·2 | 121·2 |
| 4. | 1·41 | 1·26* | – | 116·6 | 117·8 |

\* C=O rather than C–O⁻.

and at $(-x, -y, \frac{1}{2}+z)$ and $(\frac{1}{2}-x, \frac{1}{2}+y, \frac{1}{2}+z)$ are each linked alternately parallel to $y$ by hydrogen bonds O–H···N with O···N=2·774 Å and O–H···N= 166·6°. Other distances and angles involving the hydrogen bond are included in Tables 3 and 4.

The synthesis of HPAE leads to a racemic mixture; each single crystal is then either dextro- or levo-rotatory. Consequently no absolute configuration determination was undertaken.

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