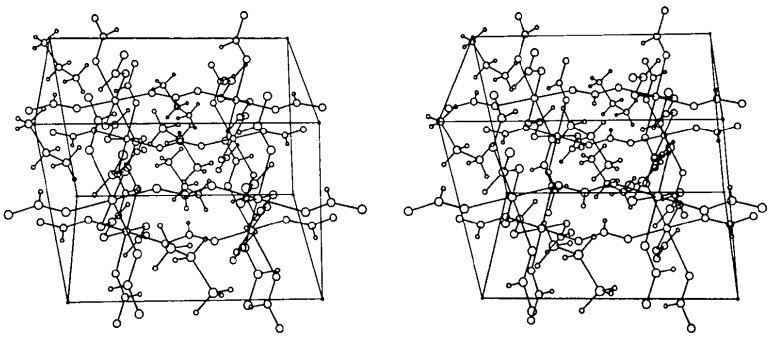

Fig. 4. A stereoscopic view of the molecular packing in the unit cell of dimethylammonium copper(II) formate.

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The Crystal and Molecular Structures of Reaction Products from γ-Irradiation of Thymine and Cytosine: *cis*-Thymine Glycol, $C_5H_8N_2O_4$, and *trans*-1-Carbamoyl-imidazolidone-4,5-diol, $C_4H_7N_3O_4$

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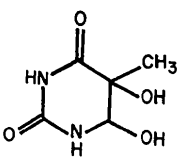
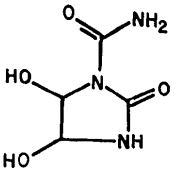
As part of a study on the mutagenetic effects of ionizing radiation on nucleic acids, solutions of thymine and cytosine were subjected to γ-radiation. In both cases the reaction conditions were the same; however, the products differed significantly. The product of the thymine reaction was *cis*-thymine glycol (I), $C_5H_8N_2O_4$ [space group $P2_12_12_1$ with $a=9{\cdot}745$ (6), $b=10{\cdot}806$ (6), $c=6{\cdot}282$ (4) Å]. The reaction on the cytosine molecule involved a rearrangement of the six-membered ring to give an imidazolidone derivative (II), $C_4H_7N_3O_4$ [space group *Pbca* with $a=13{\cdot}228$ (8), $b=13{\cdot}260$ (8), $c=7{\cdot}139$ (4) Å]. The calculated crystal densities are 1·61 g cm^{-3}for (I) and 1·71 g cm^{-3} for (II). Both structures were solved by the symbolic addition procedure. Intensities were collected on an automatic diffractometer (Cu $K\alpha$ radiation) and refined to final R values of 0·052 for (I) and 0·064 for (II). Hydrogen bonding plays a significant role in the packing systems of both molecules.





Introduction

The radiation chemistry of the nucleic acid bases, thymine, cytosine and uracil, has been the subject of extensive research in attempts to determine the molecular origin of biological radiation damage (Fahr, 1969). When solutions of thymine and cytosine were subjected to γ-radiation, under the same reaction con-

ditions, the products were expected to be *cis* and *trans* glycols of the reactant molecules (Ekert & Monier, 1960; Ekert, 1962; Khattak & Green, 1966). Isolation of the products of the thymine reaction was recently accomplished by Hahn & Wang (1972) who identified the products as *cis* and *trans* thymine glycols and characterized the stereochemistry of both isomers by chemical means. The structure of the *cis*-thymine glycol (I) was confirmed by X-ray analysis (this work). When the products from the cytosine reaction were isolated and purified by Hahn & Wang. it was found that the spectral evidence was not conclusive and an X-ray analysis was necessary for an unequivocal structure determination (Hahn, Wang, Flippen & Karle, 1973). The X-ray analysis was carried out on the *trans* isomer and showed it to be an imidazolidone derivative (II) This is the first time a photoreaction on a pyrimidine base has involved a rearrangement of the six-membered heterocyclic ring. These newly identified imidazolidones are analogs of synthetic nucleosides which have been shown to have broad spectrum antiviral activity (Sidwell, Huffman, Khare, Allen, Witkowski & Robins, 1972). The nucleosides of the imidazolidones, possibly produced in biological systems, may also possess antiviral activity (Hahn *et al.*, 1973).

Experimental

Crystals of both materials were kindly provided by Professor S. Y. Wang of the Johns Hopkins University.

Table 1. *Crystal data*

	Molecule I	Molecule II
Molecular formula	$C_5H_8N_2O_4$	$C_4H_7N_3O_4$
Crystal size	~(0·90 × 0·40 × 0·15mm)	~(0·25 × 0·25 × 0·12mm)
Space group	$P2_12_12_1$	*Pbca*
a	9·745 (6) Å	13·228 (8) Å
b	10·806 (6)	13·260 (8)
c	6·282 (4)	7·139 (4)
Molecules per unit cell	4	8
Density (calc.)	1·61 g cm^{-3}	1·71 g cm^{-3}
Source of data	Picker FACS-I diffractometer	
Radiation	Cu $K\alpha$(1·5418 Å) Ni filter	
Data collection technique	θ–2θ scan	
Scan width	$2·2° + 2\theta(\alpha_1) - 2\theta(\alpha_2)$	$1·5° + 2\theta(\alpha_1) - 2\theta(\alpha_2)$
Scanning speed	2 deg/min	1 deg/min
Background counting time	10 sec	
Maximum sin θ/λ	0·521	
Number of independent reflections	659	1024

Table 2. *Fractional coordinates and thermal parameters with standard deviations*

cis-Thymine glycol

The thermal parameters are of the form $T = \exp[-\frac{1}{4}(B_{11}h^2a^{*2} + B_{22}k^2b^{*2} + B_{33}l^2c^{*2} + 2B_{12}hka^*b^* + 2B_{13}hla^*c^* + 2B_{23}klb^*c^*)]$.

Standard deviations are based solely on least-squares parameters.

	x	*y*	*z*	B_{11}	B_{22}	B_{33}	B_{12}	B_{13}	B_{23}
N(1)	0·3064 (4)	0·1263 (3)	0·0384 (6)	3·0 (1)	2·2 (1)	2·5 (1)	−1·0 (1)	−0·0 (1)	0·2 (1)
C(2)	0·3080 (4)	0·1774 (4)	−0·1547 (6)	1·8 (1)	2·4 (1)	1·9 (1)	0·0 (1)	0·3 (1)	−0·4 (1)
O(2)	0·2507 (3)	0·1326 (3)	−0·3162 (5)	2·7 (1)	3·0 (1)	1·9 (1)	−0·3 (1)	−0·1 (1)	−0·6 (1)
N(3)	0·3788 (3)	0·2879 (3)	−0·1737 (6)	2·6 (1)	2·3 (1)	1·6 (1)	−0·2 (1)	−0·3 (1)	0·2 (1)
C(4)	0·4266 (4)	0·3577 (4)	−0·0061 (6)	2·1 (1)	1·9 (1)	2·0 (1)	0·3 (1)	−0·2 (1)	0·2 (1)
O(4)	0·4958 (3)	0·4498 (3)	−0·0322 (5)	3·0 (1)	2·3 (1)	2·7 (1)	−0·8 (1)	−0·5 (1)	0·4 (1)
C(5)	0·3772 (4)	0·3139 (4)	0·2134 (6)	2·1 (2)	2·6 (1)	1·4 (1)	−0·3 (1)	−0·0 (1)	−0·4 (1)
O(5)	0·4624 (3)	0·3657 (3)	0·3761 (4)	2·3 (1)	2·9 (1)	2·2 (1)	−0·0 (1)	−0·3 (1)	−0·7 (1)
C(6)	0·3853 (4)	0·1737 (4)	0·2142 (7)	2·4 (2)	2·7 (2)	1·9 (2)	−0·2 (1)	0·2 (1)	0·2 (1)
O(6)	0·5264 (3)	0·1438 (3)	0·1950 (5)	2·6 (1)	2·2 (1)	3·5 (1)	0·3 (1)	−0·2 (1)	0·5 (1)
C(7)	0·2325 (5)	0·3618 (5)	0·2544 (8)	2·4 (2)	4·2 (2)	3·2 (2)	0·3 (2)	0·3 (2)	−0·9 (2)

Table 2 (*cont.*)

	x	*y*	*z*
H(1)	0·283 (6)	0·054 (5)	0·065 (10)
H(3)	0·374 (6)	0·316 (5)	0·708 (10)
H(O5)	0·540 (7)	0·345 (5)	0·305 (10)
H(C6)	0·335 (6)	0·142 (6)	0·343 (10)
H(O6)	0·527 (6)	0·072 (6)	0·250 (11)
H(7*A*)	0·213 (6)	0·448 (6)	0·229 (11)
H(7*B*)	0·167 (7)	0·340 (7)	0·127 (12)
H(7*C*)	0·185 (7)	0·328 (6)	0·389 (12)

Table 3. *Fractional coordinates and thermal parameters with standard deviations*

trans-1-Carbamyl-imidazolidone-4,5-diol

The thermal parameters are of the form $T=\exp[-\frac{1}{4}(B_{11}h^2a^{*2}+B_{22}k^2b^{*2}+B_{33}l^2c^{*2}+2B_{13}hla^*c^*+2B_{12}hka^*b^*+2B_{23}klb^*c^*)]$.

Standard deviations are based solely on least-squares parameters.

	x	*y*	*z*	B_{11}	B_{22}	B_{33}	B_{12}	B_{13}	B_{23}
N(1)	0·4812 (2)	0·1487 (2)	0·1299 (3)	1·4 (1)	1·5 (1)	2·5 (1)	−0·0 (1)	0·0 (1)	0·3 (1)
C(2)	0·5177 (2)	0·0559 (2)	0·1930 (4)	2·4 (1)	2·0 (1)	2·0 (1)	−0·0 (1)	−0·2 (1)	−0·3 (1)
O(2)	0·6064 (1)	0·0285 (1)	0·1837 (3)	1·6 (1)	2·4 (1)	3·5 (1)	0·5 (1)	−0·0 (1)	0·2 (1)
N(3)	0·4396 (2)	0·0033 (2)	0·2606 (4)	1·9 (1)	1·8 (1)	3·2 (1)	−0·0 (1)	0·2 (1)	0·6 (1)
C(4)	0·3465 (2)	0·0606 (2)	0·2676 (4)	1·8 (1)	2·5 (1)	2·7 (1)	0·2 (1)	0·1 (1)	0·0 (1)
O(4)	0·3175 (2)	0·0855 (2)	0·4517 (3)	2·0 (1)	3·7 (1)	2·7 (1)	−0·0 (1)	0·2 (1)	0·2 (1)
C(5)	0·3708 (2)	0·1535 (2)	0·1474 (4)	1·6 (1)	2·0 (1)	2·8 (1)	0·1 (1)	−0·1 (1)	0·0 (1)
O(5)	0·3233 (1)	0·1517 (2)	−0·0298 (3)	2·1 (1)	2·4 (1)	2·8 (1)	0·4 (1)	−0·6 (1)	0·2 (1)
C(6)	0·5378 (2)	0·2339 (2)	0·0852 (4)	2·2 (1)	1·7 (1)	2·2 (1)	−0·3 (1)	−0·3 (1)	−0·1 (1)
N(6)	0·6365 (2)	0·2199 (2)	0·0584 (4)	1·7 (1)	2·3 (1)	5·0 (2)	−0·3 (1)	0·4 (1)	0·7 (1)
O(6)	0·4961 (1)	0·3164 (1)	0·0709 (3)	2·4 (1)	1·5 (1)	3·6 (1)	0·0 (1)	−0·2 (1)	0·2 (1)

Table 3 (*cont.*)

	x	*y*	*z*
H(N3)	0·447 (2)	−0·058 (2)	0·315 (5)
H(C4)	0·289 (2)	0·022 (2)	0·214 (4)
H(O4)	0·360 (3)	0·114 (3)	0·501 (6)
H(C5)	0·353 (2)	0·221 (2)	0·211 (5)
H(O5)	0·342 (2)	0·093 (2)	−0·086 (5)
H(N6*A*)	0·673 (2)	0·277 (3)	0·040 (5)
H(N6*B*)	0·664 (3)	0·160 (3)	0·080 (5)

Information on data collection and physical quanties for both molecules is given in Table 1. Lorentz and polarization corrections were applied and normalized structure factor magnitudes $|E|$, as well as structure factor magnitudes $|F|$, were derived.

The structure of *cis*-thymine glycol (I) was solved by the symbolic addition procedure for noncentrosymmetric crystals (Karle & Karle, 1966), The modified $B_3,0$ formula (Karle, 1970) was used to help confirm the assumption (made in the symbolic addition procedure) that the cosine invariants employed in the initial part of the phase determination are close to unity. The basic set of phases was then expanded by the tangent formula. The resulting molecule was properly oriented but misplaced with respect to a true origin for space group $P2_12_12_1$ and a translation function (Karle, 1972) was calculated which indicated a one-dimensional shift of ±1·150 Å in the *z* direction. The correct shift was −1·150 Å. The structure of the imidazolidone (II) was solved by routine application of the symbolic addition procedure for centrosymmetric crystals (Karle & Karle, 1966). Computer programs written by R. D. Gilardi & S. A. Brenner of this laboratory were used to facilitate use of the above procedures.

The structures were refined by full-matrix least-squares methods on *F* values. Program *ORFLS* (Busing, Martin & Levy, 1962) was used for (I) and program *ORXFLS3* (Busing *et al.*, 1971) was used for (II). The function minimized was $\sum w(|F_o|-|F_c|)^2$, where the weighting function *w* was calculated according to

$$w^{-1}=\sigma^2_{F|}=\left\{\frac{Q\cdot[P-t_f(B_1+B_2)]}{4\cdot \mathrm{Lp}}\right\}\left\{\frac{P+C^2P^2+t_f^2(B_1+B_2+C^2B_1^2+C^2B_2^2)}{[P-t_f(B_1+B_2)]^2}+\frac{\sigma_e^2}{Q}\right\}$$

where

Q = attenuator factor,
P = peak count,
B_1B_2 = background counts,
t_f = time factor to put background and peaks on same scale,
C = instrumental reliability factor (0·02).

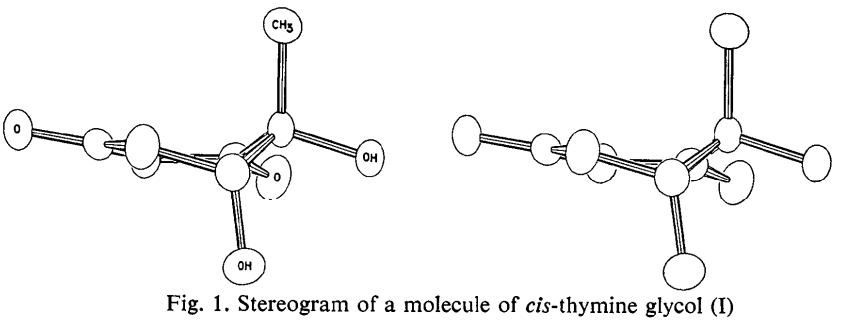
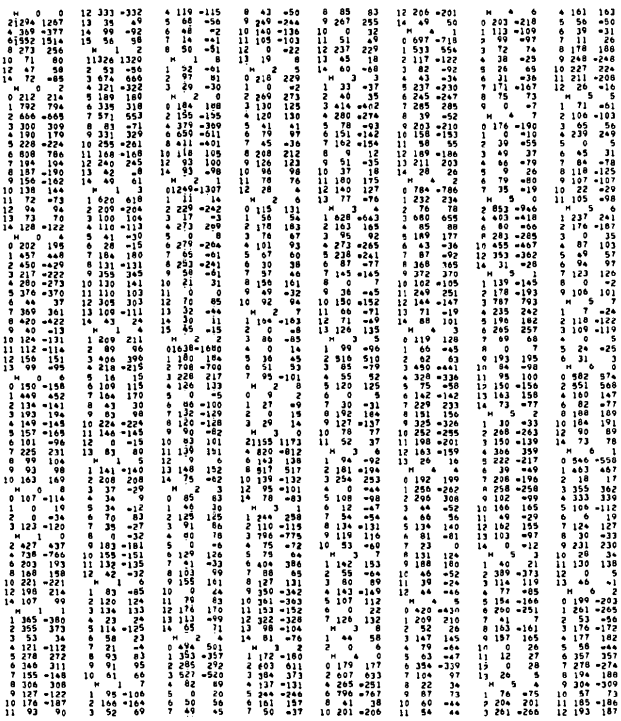


Fig. 1. Stereogram of a molecule of *cis*-thymine glycol (I)

Table 4. *Observed and calculated structure factors for cis-thymine glycol* (I)

The columns are the index h, $10|F_o|$, and $10|F_c|$.



A detailed derivation of the weighting function is given by Gilardi (1973).

The atomic scattering factors used were those listed in *International Tables for X-ray Crystallography* (1962). All the hydrogen atoms for both molecules were located from difference maps. Their positional parameters were refined and their assigned thermal parameters (set equal to those of the atoms to which they were bonded) were included in the refinement as constants. All data were included in the refinement, no reflections being considered unobserved. The final R values where $R=\sum||F_o|-|F_c||/\sum|F_o|$, were 0·052 for (I) and 0·064 for (II). The weighted R values where $R_w=[\sum w(|F_o|-|F_c|)^2/\sum wF_o^2]^{1/2}$, were 0·069 for (I) and 0·045 for (II). Fractional coordinates for all the atoms and thermal parameters for the C, N and O atoms are listed in Table 2 for (I) and in Table 3 for (II). The observed and calculated structure factors are given in Tables 4 and 5.

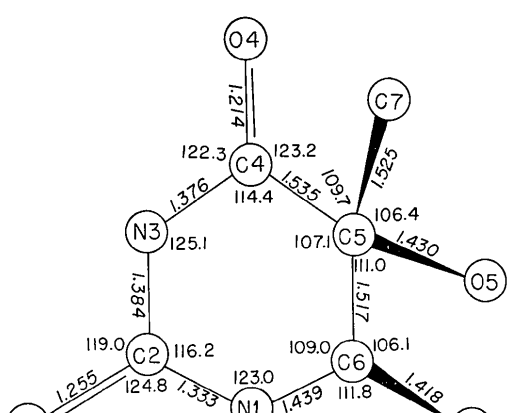


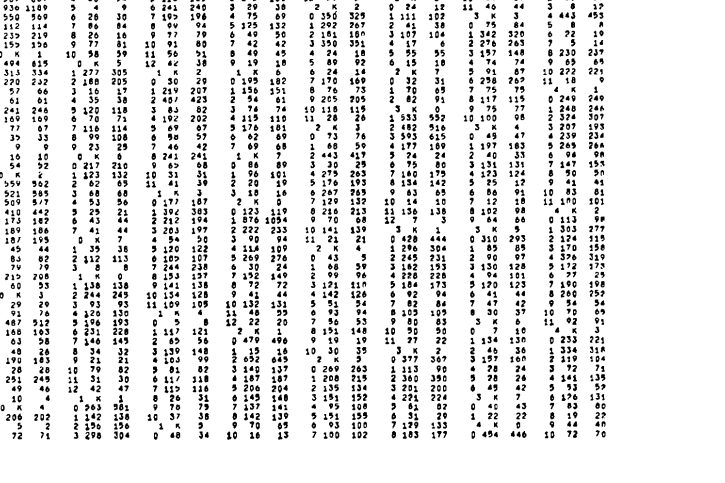
Fig. 2. Bond distance and angles for (*I*).

Discussion

The stereoconfiguration for the *cis*-thymine glycol (I) is illustrated in Fig. 1. Bond distances and angles are shown in Fig. 2. The six-membered ring has a half-chair conformation with atoms N(1), C(2), N(3) and C(4) planar to within ±0·05 Å, C(6) and C(5) having an average deviation of 0·37 Å from this plane. The methyl group on C(5) and the hydroxyl group on C(6) are axial to the ring while the hydroxyl group on C(5) is equatorial to the ring. The hydroxyl groups are *gauche* with respect to each other (pertinent torsion angles are listed in Table 6). The overall configuration of the *cis*-thymine glycol molecule is the same as that found for ring III in the thymine trimer (Flippen & Karle, 1971) and ring I in the thymine–thymine adduct (Karle, 1969). Values for comparable bond lengths and angles also agree quite well among the three molecules. The molecular packing of (I) is dominated by an extensive network of intermolecular hydrogen bonding which involves all available hydrogen atoms (see Fig. 3). Each molecule participates in seven hydrogen bonds, four of which are independent. The hydrogen bond distances are listed in Table 7. The hydroxyl group on C(5) acts as both an acceptor and a donor while N(1), N(3) and the hydroxyl group on C(6) are donors only. Of the

Table 5. *Observed and calculated structure factors for trans-1-carbamylimidazolidone-4,5-diol* (II)

The columns are the index k, $10|F_o|$, and $10\ F_c$.



two carbonyl oxygens, O(4) is the acceptor in one hydrogen bond and O(2) in two. Except for the hydrogen bond approaches there are no intermolecular contacts less than van der Waals distances.

The stereoconfiguration of the imidazolidone (II) is illustrated in Fig. 4. Bond distances and angles are shown in Fig. 5. Except for the hydroxyl groups the molecule is planar to within ±0·23 Å. The five-membered ring is a fairly flattened envelope with atoms N(1)–C(2)–N(3) and C(4) planar to within ±0·03 Å, C(5) being 0·22 Å from the plane. The plane of the amide group is at an angle of 13·3° to the best plane through the five-membered ring. The hydroxyl groups are approximately *trans* to one another. The carbonyl oxygen of the amide group is oriented so that the C=O bond is *synplanar* with respect to the C(5)–N(1) bond which is the preferred orientation for such a grouping (Dunitz, 1968). As in the thymine

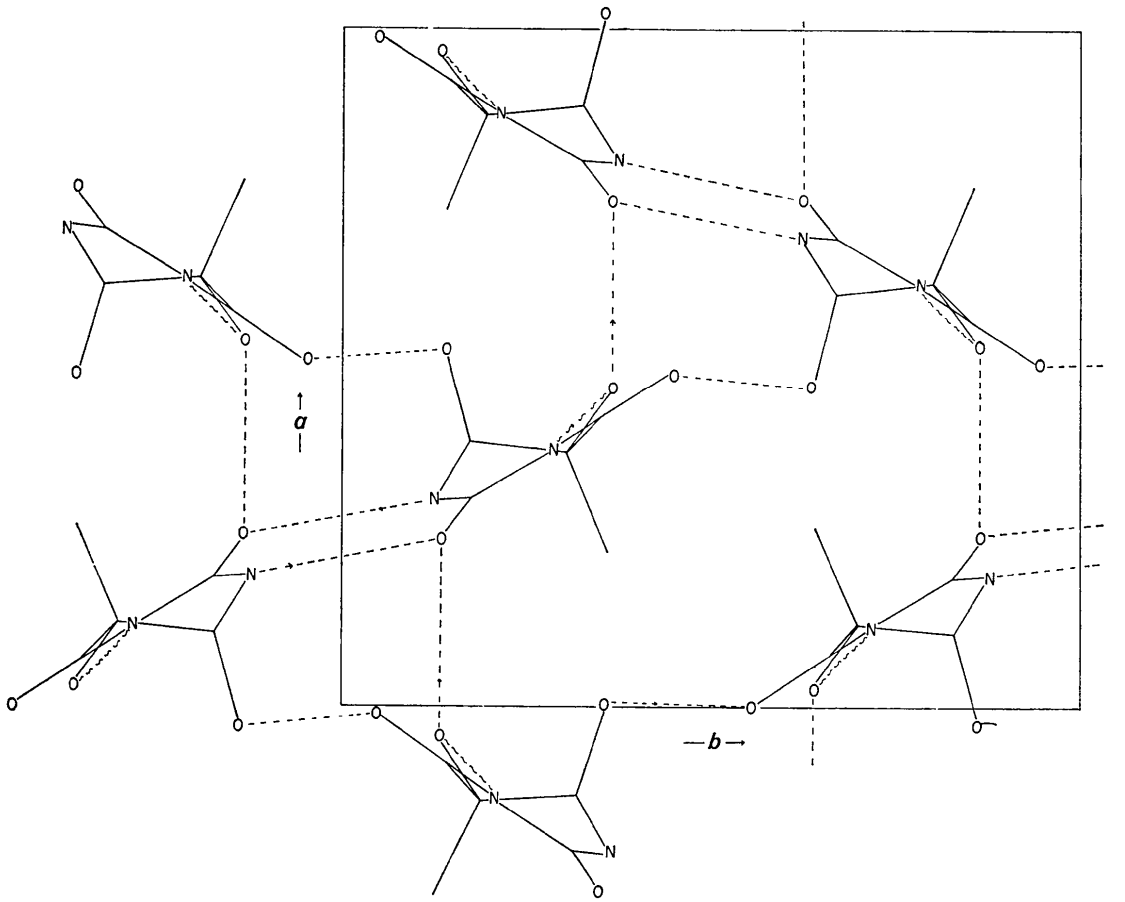


Fig. 3. A projection down **c** showing the packing in the unit cell for (I). The hydrogen bonds are shown as dotted lines.

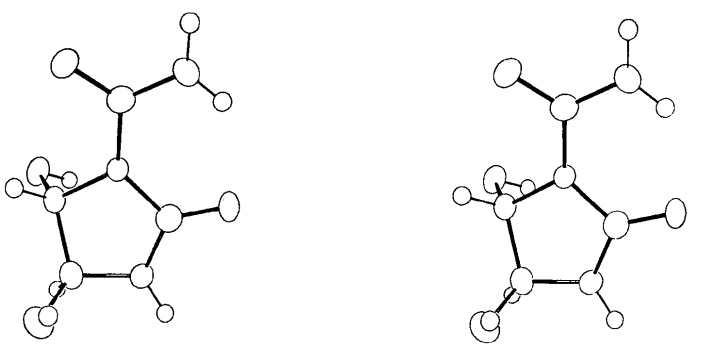


Fig. 4. Stereodiagram of a molecule of *trans*-1-carbamoylimidazolidone-4,5-diol (II).

glycol the molecular packing of (II) is dominated by an intricate network of hydrogen bonding involving the 5 available hydrogen atoms in 10 hydrogen bonds per molecule (see Fig. 6). Both carbonyl oxygen atoms are acceptors in two hydrogen bonds and both hydroxyl oxygens are donors in one and acceptors in a second hydrogen bond. The ring nitrogen atom is the donor in one hydrogen bond while the amide nitrogen participates in two hydrogen bonds, one of which is bifurcated. The bifurcated hydrogen bond has one intramolecular approach, N(6)···O(2) at 2·720 Å, and one intermolecular approach, N(6)···O(4) at 2·985 Å. The hydrogen atom was found to lie approximately along the bisector of the O(2)···N(6)···O(4) angle. An interesting feature of the molecule is the apparently strong electrostatic attraction between the ring C=O groups which are arranged in an anti-parallel fashion as shown in Fig. 7 with a C(2)···C(2′) separation of only 3·16 Å. A similar arrangement of C=O groups was noted by Przybylska (1972) in a tetracyclic diketone. However, in that case the closest approach of 3·18 Å was between a carbon atom of one C=O and the oxygen atom of C=O in an adjacent molecule. The attraction between the C=O groups, as well as the extensive hydrogen bonding which links the molecules in all directions, allow the molecules to pack quite closely together and explain, in part, the relatively high crystal density of 1·71 g cm^{-3}.

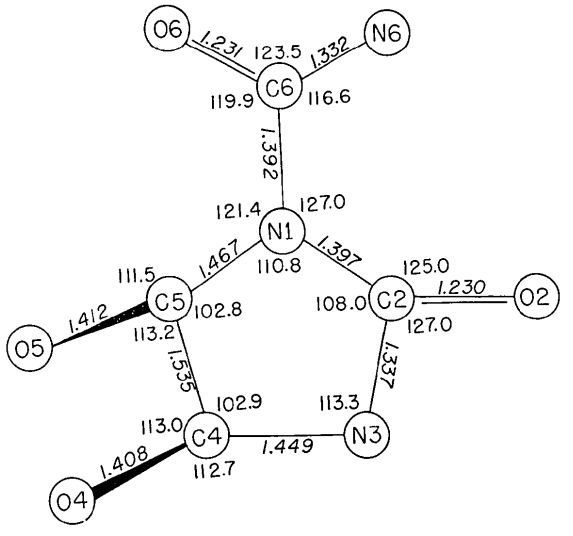


Fig. 5. Bond distances and angles for (II).

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Table 6. *Torsion angles*

Ring torsions			
(I)		(II)	
C(6)–N(1)–C(2)–N(3)	−6·8°	C(5)–N(1)–C(2)–N(3)	−3·9°
N(1)–C(2)–N(3)–C(4)	−11·3	N(1)–C(2)–N(3)–C(4)	−6·5
C(2)–N(3)–C(4)–C(5)	−8·6	C(2)–N(3)–C(4)–C(5)	13·3
N(3)–C(4)–C(5)–C(6)	41·8	N(3)–C(4)–C(5)–N(1)	−14·1
C(4)–C(5)–C(6)–N(1)	−55·8	C(4)–C(5)–N(1)–C(2)	11·6
C(5)–C(6)–N(1)–C(2)	41·6		
Torsional angles involving substituent atoms			
O(6)–C(6)–C(5)–O(5)	−55·2°	O(4)–C(4)–C(5)–O(5)	131·9°
O(6)–C(6)–C(5)–C(7)	−174·2	O(5)–C(5)–N(1)–C(6)	79·6
		O(2)–C(2)–N(1)–C(6)	−15·2
		C(5)–N(1)–C(6)–O(6)	4·5
		C(2)–N(1)–C(6)–N(6)	16·4

Table 7. *Hydrogen-bond lengths*

Donor	Acceptor	Distance (Å)	Symmetry operation on acceptor	
		(I)		
N(1)	O(2)	2·996	$\frac{1}{2}-x$, $\bar{y}$, $-\frac{1}{2}+z$	
N(3)	O(5)	3·061	x, y, $-1+z$	
O(5)	O(2)	2·835	$\frac{1}{2}+x$, $\frac{1}{2}-y$, $1-z$	
O(6)	O(4)	2·988	$1-x$, $-\frac{1}{2}+y$, $\frac{1}{2}-z$	
		(II)		
N(3)	O(6)	2·882	$1-x$, $-\frac{1}{2}+y$, $\frac{1}{2}-z$	
N(6)	O(2)	2·720	x, y, z	bifurcated
N(6)	O(4)	2·985	$\frac{1}{2}+x$, y, $\frac{1}{2}-z$	bifurcated
N(6)	O(5)	3·008	$\frac{1}{2}+x$, $\frac{1}{2}-y$, $\bar{z}$	
O(4)	O(6)	2·827	x, $\frac{1}{2}-y$, $\frac{1}{2}+z$	
O(5)	O(2)	2·789	$1-x$, $\bar{y}$, $\bar{z}$	

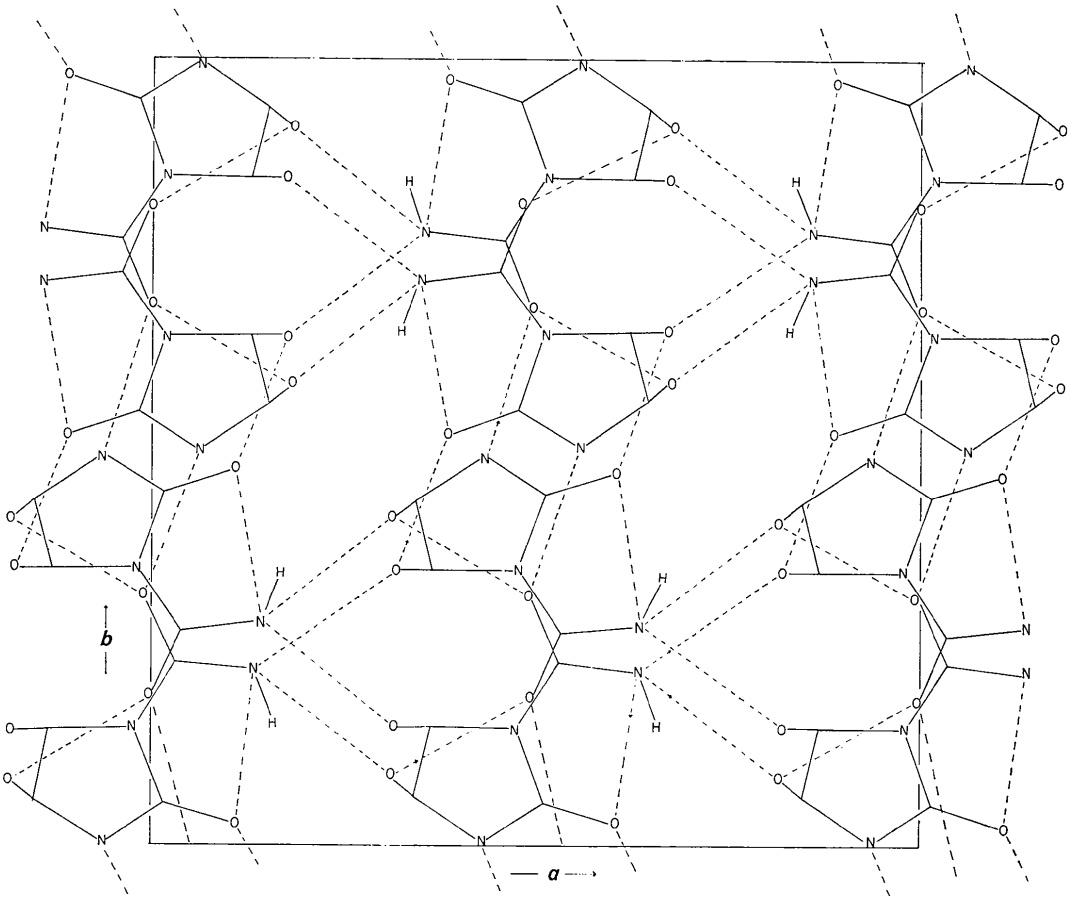

Fig. 6. A projection down **c** showing the packing in the unit cell for (II). The hydrogen bonds are shown as dotted lines. The hydrogen atom participating in the bifurcated hydrogen bonding is also illustrated at its refined position.

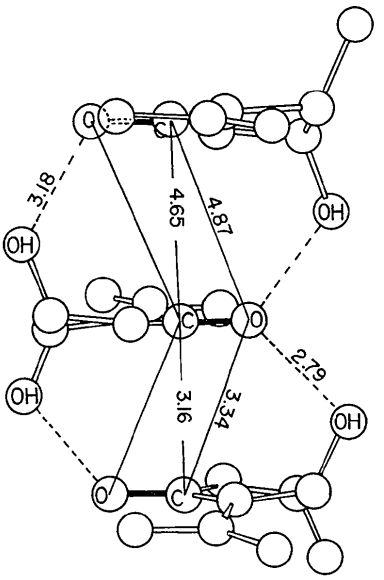

Fig. 7. Parallel arrangement of carbamoyl groups in crystal of (II).

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