Crystal Structure of the Growth Inhibitor, 'Maleic Hydrazide' (1,2-Dihydropyridazine-3,6-dione)

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The crystal structure of the title compound (I) has been determined by symbolic-addition and rotation-function procedures and refined by full-matrix least-squares methods to R 0.063 for 568 observed reflections. Crystals are triclinic, space group $P\bar{1}$, with $Z = 2$ in a cell of dimensions $a = 5.83(2)$, $b = 5.78(2)$, $c = 7.31(2)$ Å, $\alpha = 79.0(3)$, $\beta = 99.5(3)°$, $\gamma = 107.2(3)°$. Analysis of the molecular structure suggests that maleic hydrazide could act as a pyrimidine or a purine analogue.

'MALEIC HYDRAZIDE' (1,2-dihydropyridazine-3,6-dione) is widely used as a growth inhibitor in agriculture and because of its close structural similarity to the pyrimidine base uracil, the replacement of uracil in the nucleic acid structure has been postulated as its mode of action.[1] The crystal structure of maleic hydrazide was investigated to determine the feasibility of this replacement. The biological implications of this work have already been reported.[2]

EXPERIMENTAL

Crystal Data.—$C_4H_4N_2O_2$, $M = 112.09$. Triclinic, $a = 5.83(2)$, $b = 5.78(2)$, $c = 7.31(2)$ Å, $\alpha = 79.0\ (3)$, $\beta = 99.5(3)$, $\gamma = 107.2(3)°$, $U = 229.4$ Å^3, $D_c = 1.62$, $Z = 2$, $D_m = 1.63$ g cm^{-3}, $F(000) = 116$. Space group $P\bar{1}$, no systematic absences. Cu-K_α radiation, $\lambda = 1.5418$ Å; $\mu(\text{Cu-}K_\alpha) = 11.6$ cm^{-1}.

Crystallographic Measurements.—The crystal morphology suggested a monoclinic cell and the crystal was mounted about the apparent symmetry axis. Rotation and Weissenberg photographs showed the Laue symmetry to be $\bar{1}$ and space group $C\bar{1}$ with cell dimensions (measured from precession films and refined from 34 powder lines) of $a = 9.350(26)$, $b = 6.889(19)$, $c = 7.306(21)$ Å, $\alpha = 88.8(5)$, $\beta = 102.8(2)$, $\gamma = 89.4(1)°$. The crystal used for data collection was a prism ($0.3 \times 0.18 \times 0.18$ mm) with rhombic cross-section, the c axis being parallel to the long dimension. Intensity data were collected photographically with the crystal rotating about the b ($C\bar{1}$) axis, and were measured by the SRC Microdensitometer service † (see ref. 3 for details). Because of the large variation in cross-section of the crystal rotating in the beam, data were corrected for absorption by the procedure of Busing and Levy.[4] The final intensities were obtained by averaging equivalent reflections and correcting for Lorentz and polarisation effects. A total of 568 reflections was obtained.

TABLE 1

Atom parameters ($\times 10^4$, for H $\times 10^3$) with estimated standard deviations in parentheses

Atom	x	y	z	β_{11} †	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
O(1)	9 667(5)	12 598(5)	3 551(5)	117(10)	758(12)	173(8)	10(9)	44(6)	29(7)
O(2)	743(5)	7 087(7)	1 831(5)	135(10)	177(13)	194(8)	−20(10)	−73(7)	36(7)
N(1)	6 785(6)	9 017(6)	3 691(5)	120(11)	212(14)	136(9)	56(11)	−26(8)	−3(8)
N(2)	4 547(6)	7 465(6)	3 333(5)	132(11)	136(12)	125(8)	15(10)	−13(7)	17(7)
C(1)	7 528(7)	11 410(8)	3 099(6)	104(13)	171(15)	94(8)	−2(12)	15(8)	−14(9)
C(2)	5 718(7)	12 427(8)	1 931(6)	165(14)	142(15)	107(9)	44(13)	−10(9)	8(9)
C(3)	3 485(7)	11 019(8)	1 520(6)	162(14)	220(17)	112(9)	87(14)	−30(9)	11(9)
C(4)	2 979(7)	8 482(8)	2 260(6)	127(13)	199(15)	93(9)	38(12)	−20(8)	3(9)
				B_{iso}/Å^2					
H(C2)	627(9)	1 419(10)	160(7)	3.63(98)					
H(C3)	199(11)	1 147(11)	66(8)	5.76(131)					
H(N1)	789(8)	855(8)	459(6)	2.54(77)					
H(O2)	48(11)	549(13)	226(9)	5.13(140)					

† β_{ij} is a symmetric tensor defined by the expression exp $- h_r h_s \beta^{rs}$.

For the structure determination a primitive cell was chosen from a plot of the a^*b^* reciprocal lattice net, the transformation in reciprocal space being given by the matrix:

$$\begin{pmatrix} 1 & 1 & 0 \\ \bar{1} & 1 & 0 \\ 0 & 0 & 1 \end{pmatrix}.$$

By transformation of the metric tensor of the centred cell, the primitive cell given in the crystal data was obtained. The observed structure factors were transformed to this cell which was used throughout the determination. All results are reported in terms of the primitive cell.

Structure Determination.—The structure was solved by the symbolic-addition procedure [5] and orientation information provided by the rotation function.[6] For the latter calculation, a non-planar model of symmetry 2 was placed in space group $P222$. The orientation corresponding to the largest peak in the function was accepted as the molecular orientation and this proved to be correct despite the fact that the initial assumption of a non-planar molecule was incorrect. The symbolic-addition procedure was employed to determine the phases of all reflections having $|E| > 1.1$, using three origin phases and three symbols. 52 Reflections were determined having probability values $P^+ > 0.97$ and a further 29 were accepted on the basis of four or more consistent phase indications. There were no

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† Atlas computer laboratory, Chilton, Didcot, Berkshire OX11 0QY.

[1] D. Coupland and A. J. Peel, *Physiol. Plant.*, 1971, **25**, 141.

[2] P. D. Cradwick, *Nature*, 1975, **258**, 774.

[3] P. A. Machin and M. Elder, 'Notes for Weissenberg Film Processing,' S.R.C. Microdensitometer Service, 1974.

[4] W. Busing and K. Levy, *Acta Cryst.*, 1957, **10**, 180.

[5] J. Karle and I. L. Karle, *Acta Cryst.*, 1966, **21**, 849.

[6] M. G. Rossmann and D. M. Blow, *Acta Cryst.*, 1962, **15**, 24.

inconsistent indications within this set of 81 reflections. Seven E maps were computed by assigning phases to the symbols and all generally showed a close-packed array of peaks in a small region of the unit cell. Since the molecular plane in all maps corresponded to that observed in the rotation function, prospective models were considered only in the rotation function orientation. One map could be interpreted by considering only the largest peaks, and structure factors calculated for this model gave a conventional R factor of 0.46. Refinement as a rigid body reduced R to 0.33 and then to 0.148 on removing this restriction. Introduction of anisotropic temperature factors resulted in R 0.096 and when the refinement was continued allowing hydrogen atom parameters to vary (initial values were obtained by calculation), R converged at 0.063.

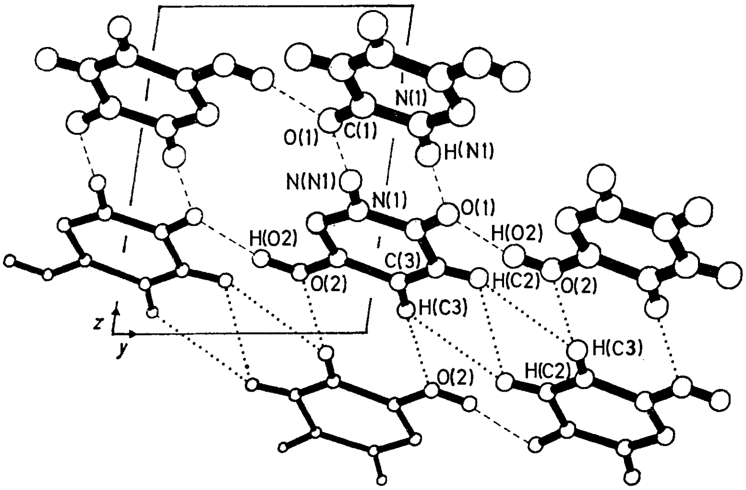

FIGURE 1 Intermolecular interactions projected on the *yz* plane. Hydrogen bonds are shown by broken lines, C–H · · · O and H · · · H contacts by dotted line

TABLE 2

Analysis of thermal motion tensors referred to crystal axes

Atom	Root-mean displacements (Å) along principal axes	Direction cosines		
O(1)	0.12	0.866 4	−0.032 0	0.320 9
	0.14	0.002 1	−0.844 9	0.323 4
	0.25	0.499 3	−0.533 8	−0.890 1
O(2)	0.11	0.804 2	0.188 4	0.315 6
	0.15	−0.152 8	0.802 6	−0.431 2
	0.28	−0.574 3	0.565 9	0.845 2
N(1)	0.12	0.873 6	0.257 7	0.329 6
	0.17	−0.223 6	−0.781 1	−0.298 0
	0.21	0.432 0	0.568 6	0.895 8
N(2)	0.13	0.386 3	0.731 2	−0.183 8
	0.14	−0.761 5	0.367 [illegible]	−0.466 7
	0.21	−0.520 3	0.575 0	0.865 0
C(1)	0.12	0.822 8	0.297 3	−0.095 9
	0.16	−0.104 9	0.101 0	−0.938 4
	0.18	−0.558 5	0.949 4	0.331 7
C(2)	0.13	0.409 7	−0.715 9	0.489 1
	0.15	−0.676 1	−0.466 3	−0.222 2
	0.19	0.612 3	−0.519 5	−0.843 4
C(3)	0.12	0.702 1	−0.447 0	0.495 5
	0.18	−0.561 7	−0.568 6	0.274 1
	0.20	0.436 6	−0.690 4	−0.824 2
C(4)	0.12	0.728 1	−0.184 8	0.551 5
	0.16	−0.455 4	−0.556 2	0.472 9
	0.20	0.512 1	−0.810 1	−0.687 1

Scattering factors were taken from ref. 7(*a*) for non-hydrogen atoms, and from ref. 7(*b*) for the hydrogen atoms. Refinement cycles were computed by use of RBLS.[8] Table 1 gives the final atomic parameters with estimated standard deviations in the last digits in parentheses. The r.m.s. displacements and direction cosines of the principal axes of the β_{ij} tensors (referred to crystallographic axes) are given in Table 2, torsion angles in Table 3, and intermolecular distances in Table 4. The molecular geometry is shown in Figure 2 while Figure 1 shows the packing and molecular interactions.

TABLE 3

Comparison of the torsion angles of maleic hydrazide (I) with those of dichloromaleic hydrazide (II) *

		(II)	
	(I)	(1)	(2)
N(2)–N(1)–C(1)–C(2)	−0.54	−0.93	−0.29
N(1)–C(1)–C(2)–C(3)	0.48	−1.13	−0.05
C(1)–C(2)–C(3)–C(4)	−0.73	1.34	−0.58
C(2)–C(3)–C(4)–N(2)	1.09	−1.36	1.18
C(3)–C(4)–N(2)–N(1)	−1.08	1.07	−0.97
C(4)–N(2)–N(1)–C(1)	0.84	0.93	−0.23
N(2)–N(1)–C(1)–O(1)	180.0	178.73	178.57
O(1)–C(1)–C(2)–C(3)	179.87	178.53	178.75
C(2)–C(3)–C(4)–O(2)	−179.61	178.51	−178.45
O(2)–C(4)–N(2)–N(1)	179.63	−178.79	178.64
H(N1)–N(1)–C(1)–O(1)	11.68	4.84	−0.45
H(N1)–N(1)–C(1)–C(2)	−168.9	−174.83	−179.34
H(N1)–N(1)–N(2)–C(4)	168.05	173.79	178.75
O(1)–C(1)–C(2)–X_1 †	−5.05	0.74	0.69
N(1)–C(1)–C(2)–X_1	175.57	−178.92	−178.14
X_1–C(2)–C(3)–C(4)	−175.11	−179.03	−177.36
C(1)–C(2)–C(3)–X_2	−177.50	−178.36	179.95
X_2–C(3)–C(4)–N(2)	178.41	178.35	−179.29
X_2–C(3)–C(4)–O(2)	−2.29	−1.76	1.06
X_1–C(2)–C(3)–X_2	8.12	−0.67	−2.13
C(3)–C(4)–O(2)–H(02)	177.10	170.04	−175.15
N(2)–C(4)–O(2)–H(02)	−3.56	−10.07	5.20

* Columns (1) and (2) represent the two independent molecules in the structure.[10] † X_1 and X_2 refer to H(C2) and H(C3) for maleic hydrazide and to the chlorine atoms for dichloromaleic hydrazide.

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[7] (*a*) 'International Tables for *X*-Ray Crystallography,' vol. III, Kynoch Press, Birmingham, 1962; (*b*) R. Mason and G. B. Robertson, *Adv. Struct. Res. Diffraction Methods*, 1966, **2**, 35.

[8] P. D. Cradwick, *J.C.S. Dalton*, in the press.

TABLE 4

Intermolecular geometry

(*a*) Intermolecular contacts (Å)

	Found	Calc.*
$O(1) \cdots O(2^{I})$	2.599	
$H(C2) \cdots O(2^{I})$	2.647	2.670
$H(C2) \cdots H(C2^{II})$	2.715	2.363
$H(C2) \cdots H(C3^{II})$	2.737	2.470
$H(C3) \cdots H(C3^{III})$	2.599	2.861
$O(1) \cdots N(1^{IV})$	2.873	
$H(N1) \cdots H(N1^{IV})$	2.580	2.688
$H(N1) \cdots C(1^{IV})$	2.909	2.872
$O(2) \cdots H(C3^{V})$	2.406	2.385
$H(O2) \cdots H(C2^{VI})$	2.341	2.412

(*b*) Geometry of the hydrogen interactions (distances Å, angles °)

	X–H	H · · · Y	X · · · Y	Angle at H
(i) Found				
$O(2)-H(02) \cdots O(1)$	0.894	1.726	2.599	164.9
$N(1)-H(N1) \cdots O(1)$	0.904	1.971	2.874	176.5
$C(3)-H(C3) \cdots O(2)$	1.05	2.406	3.441	166.8
(ii) Calc.*				
$N(1)-H(N1) \cdots O(1)$	0.99	1.906	2.874	165.0
$C(3)-H(C3) \cdots O(2)$	1.08	2.385	3.441	165.3

* These values obtained with H atoms in calc. positions. Roman numerals refer to the following equivalent positions:

I $1 + x, 1 + y, z$
II $1 - x, 3 - y, -z$
III $-x, 2 - y, -z$
IV $2 - x, 2 - y, 1 - z$
V $-x, 2 - y, -z$
VI $x - 1, y - 1, z$

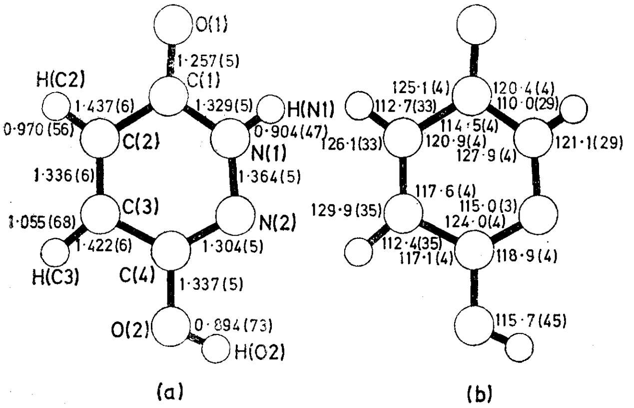
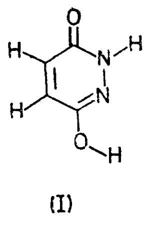


FIGURE 2 Molecular geometry: (a) bond lengths (Å) and (b) angles (°)

DISCUSSION

The pattern of bond lengths and angles permits the designation of the molecule as (I), in confirmation of both



(I)

the spectral evidence[9] and that obtained from the crystal structure of 'dichloromaleic hydrazide' (II).[10] Detailed comparison of the bond lengths with those of the dichloro-compound (II) shows that the main effect of substituting chlorine for hydrogen atoms is to increase the lengths of the C(2)–C(3) and C(3)–C(4) bonds. These effects, which are significant at the α 0.01 level, are more likely due to the high electronegativity of the chlorine atoms than to steric repulsion. If the latter were the more important effect, the torsion angle about the C(2)–C(3) bond should be greater in the dichloro-compound (II) than in maleic hydrazide: the reverse is actually found, this angle being 8.12° for maleic hydrazide and −0.67 and −2.13° for the two independent molecules in (II).[10] The atoms of maleic hydrazide other than hydrogens are planar as shown by the first ten torsion angles listed in Table 3. The equation of the mean plane through these atoms is $0.4937X - 0.3115Y - 0.8119Z = -2.8401$ (where X and Z are parallel to a and c^* respectively, and Y lies in the ab plane), the largest deviation of any atom from the plane being 0.0057 Å. For the hydrogen atoms, however, the deviations are considerably larger: namely H(C2) −0.071, H(C3) 0.031, and H(N1) −0.165 Å. To investigate the reason for these distortions, intermolecular geometry calculations were made with these hydrogen atoms located at ideal positions, *i.e.* assuming 120° angles at C(2), C(3), N(1) and C–H 1.08, N–H 0.99 Å (see Table 4).

The values in Table 4 indicate that the distortion involving H(N1) is the result of hydrogen-bond formation rather than steric interactions. Table 4(*b*) shows that the hydrogen bond $N(1)-H(N1) \cdots O(1)$ is nearly linear in the crystal but is clearly non-linear with H(N1) in its idealized position. The out-of-plane distortions of H(C2), H(C3), are caused by mutual repulsion interactions. The idealized positions for these atoms give rise to $H \cdots H$ separations close to or less than the van der Waal's separation of 2.4 Å and these are increased by the distortions.

The molecular packing is stabilized mainly by the two hydrogen bonds involving the ketonic oxygen O(1), with N(1) and with O(2) (see Figure 2), although weaker interactions are also present. H(C3) is separated from O(2) by 2.41 Å, which is considerably less than the van der Waal's distance of 2.6 Å. This suggests the presence of a hydrogen-bond type of interaction between O(2) and C(3); the geometry given in Table 4(*b*) is consistent with this assumption. Interactions between unsaturated carbon and more electronegative atoms have been reported previously (ref. 11 and references therein) and are common in the structure of molecules similar to maleic hydrazide, *e.g.* uracil,[12] 1-methylthymine,[13] and the molecular complex 9-ethyladenine–parabanic acid–oxaluric acid.[14]

Although the molecular geometry of the aromatic nucleus shows a close correspondence to that of the pyrimidine bases uracil and thymine, maleic hydrazide,

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[9] J. Druey, K. Meier, and K. Eichenberger, *Helv. Chim. Acta*, 1954, **37**, 1299.

[10] T. Ottersen, *Acta Chem. Scand.*, 1973, **27**, 797.

[11] J. C. Calabrese, A. T. McPhail, and G. A. Sim, *J. Chem. Soc.* (*B*), 1966, 1235.

[12] R. F. Stewart and L. H. Jensen, *Acta Cryst.*, 1967, **23**, 1102.

[13] K. Hoogsteen, *Acta Cryst.*, 1963, **16**, 28.

[14] Huey-Sheng Sheih and D. Voet, *Acta Cryst.*, 1975, **B31**, 2192.

in order to have directly comparable biological activity, would need to form a nucleoside analogue by condensation with ribose through C(4) by removal of the OH group from the ring nucleus. The biological conditions for normal nucleoside formation (condensation through a nitrogen atom by removal of a hydrogen atom) would however tend to favour condensation either through N(1) or O(2). As pointed out previously,[2] nucleoside formation through O(2) would enable maleic hydrazide to act as a purine analogue forming base pairs with uracil or thymine, while the alternative possibility [nucleoside formation through N(1)] enables it to act as a pyrimidine analogue forming base pairs with adenine.

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