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***cis*-5-Hydroxy-1,3-dimethyl-6-phenylthio-5,6-dihydrothymine,
cis-5-Hydroxy-6-(*p*-hydroxyphenyl)-1,3-dimethyl-5,6-dihydrothymine and
cis-5-Hydroxy-6-(*o*-hydroxyphenyl)-1,3-dimethyl-5,6-dihydrothymine**

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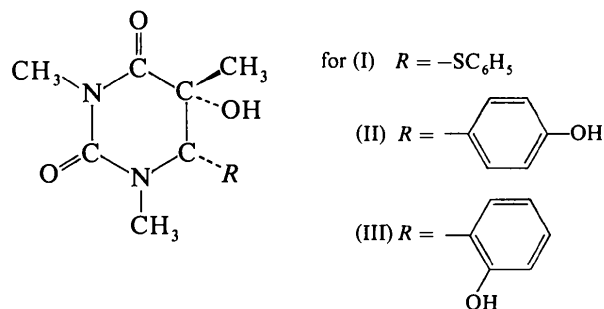
Abstract

The structures of three adducts formed by the photooxidation of dimethylthymine, with nucleophiles such as phenol and thiophenol, have been determined to help elucidate mechanistic pathways for such reactions. The reaction with thiophenol produced an adduct (I, C₁₃H₁₆N₂O₃S) which crystallizes in the monoclinic space group *P2₁/n* with *a* = 11.100 (3), *b* = 11.326 (3), *c* = 11.026 (3) Å, *β* = 96.2 (1)°, *Z* = 4, *V* = 1378.06 Å³ and *d_x* = 1.35 Mg m⁻³. The reaction with phenol yielded two products (II and III, C₁₃H₁₆N₂O₄) both of which showed unexpected carbon–carbon ring coupling indicating a different reaction mechanism from that which gave (I). (II) and (III) both crystallize in the monoclinic space group *P2₁/c* with cell dimensions of *a* = 13.056 (4), *b* = 8.317 (3), *c* = 13.478 (6) Å, *β* = 117.4 (1)°, *V* = 1299.35 Å³ and *d_x* = 1.35 Mg m⁻³ for (II) and *a* = 8.363 (3), *b* = 12.434 (3), *c* = 12.406 (5) Å, *β* = 103.6 (1)°, *V* = 1253.87 Å³ and *d_x* = 1.40 Mg m⁻³ for (III). *Z* = 4 for both (II) and (III). Final weighted *R* factors were 0.055 (2240 independent reflections) for (I), 0.092 (2111 independent reflections) for (II) and 0.073 (1274 independent reflections) for (III).

Introduction

Reactions involving post-irradiation treatment of photo-oxidized pyrimidines with various nucleophiles are being studied as possible mechanistic models for the

formation of protein–nucleic acid cross-linkages (Ryang & Wang, 1978). It was expected that treating dimethylthymine in this manner with phenol and thiophenol would give analogous products. However, this did not turn out to be the case indicating that the reaction pathway is dependent upon the nature of the attacking nucleophile (Burrows, Ryang, Wang & Flippen-Anderson, 1979). The reaction with thiophenol yielded a *cis* thiophenol adduct (*cis*-5-hydroxy-1,3-dimethyl-6-phenylthio-5,6-dihydrothymine, I) as expected while the reaction with phenol gave a 3:2 mixture of *cis*-5-hydroxy-6-(*p*- or *o*-hydroxyphenyl)-1,3-dimethyl-5,6-dihydrothymine (II and III) both of which turned out to be unexpected carbon–carbon coupling products. X-ray single-crystal studies have been performed on (I), (II) and (III) and are reported here. The X-ray structure work confirmed the structures and established the stereochemistry for molecules (I) and (II). For molecule (III) the X-ray results established both the structure and the stereochemistry.



Experimental

Crystals of all three materials were provided by S. Y. Wang and E. P. Burrows of the Johns Hopkins University. Details describing data collection are presented in Table 1. The structures were solved by application of the symbolic addition procedure for centrosymmetric crystals (Karle & Karle, 1966) and refined by full-matrix least-squares methods using program ORXFLS3 (Busing, Martin, Levy, Ellison, Hamilton, Ibers, Johnson & Thiessen, 1975). Atomic scattering factors used were those listed in *International Tables for X-ray Crystallography* (1962). The function minimized was $\sum w(|F_o| - |F_c|)^2$, where the weights, w (derived from e.s.d.'s of observed intensity), were calculated according to Gilardi (1973). All data were used in the refinements and corrections for isotropic extinction were calculated and applied by the least-squares program. All H atoms for molecules (I) and (II) were located in difference maps. For molecule

Table 1. Data-collection parameters

	(I)	(II)	(III)
Radiation	Cu K α (Ni filter)		Mo K α (Zr filter)
Data collection	Picker FACS-I diffractometer at room temperature with the θ - 2θ scan technique		
Scan width ($^\circ$)	2.0	2.0	1.3
Max. $\sin \theta/\lambda$ (\AA^{-1})	0.578	0.578	0.497
No. of independent reflections	2240	2111	1274
Final R factors R	0.061	0.062	0.097
R_w	0.055	0.092	0.073

Table 2. Fractional coordinates and equivalent isotropic thermal parameters for (I) with e.s.d.'s in parentheses

	x	y	z	B_{eq} (\AA^2)
S	0.09820 (7)	0.20967 (7)	0.44687 (6)	4.04 (5)
N(1)	0.1205 (1)	0.1987 (1)	0.6999 (1)	3.0 (1)
C(1)	0.2297 (2)	0.1416 (2)	0.7599 (2)	4.2 (2)
C(2)	0.0935 (2)	0.3080 (2)	0.7387 (2)	3.0 (1)
O(2)	0.1554 (1)	0.3603 (1)	0.8194 (1)	3.7 (1)
N(3)	-0.0126 (1)	0.3598 (1)	0.6801 (1)	3.3 (1)
C(3)	-0.0332 (2)	0.4863 (2)	0.7022 (2)	4.8 (2)
C(4)	-0.0987 (2)	0.3000 (2)	0.6062 (2)	3.5 (1)
O(4)	-0.1884 (1)	0.3481 (1)	0.5554 (1)	4.7 (2)
C(5)	-0.0788 (2)	0.1676 (2)	0.5948 (2)	3.7 (1)
O(5)	-0.1358 (1)	0.1242 (1)	0.4827 (1)	5.1 (2)
C(6)	0.0560 (2)	0.1464 (2)	0.5937 (2)	3.3 (1)
C(7)	-0.1293 (2)	0.1059 (2)	0.7029 (3)	5.0 (2)
C(8)	0.2534 (2)	0.2436 (2)	0.4894 (2)	4.0 (2)
C(9)	0.3412 (2)	0.1576 (2)	0.4802 (2)	5.2 (2)
C(10)	0.4623 (3)	0.1853 (3)	0.5139 (3)	6.2 (3)
C(11)	0.4955 (3)	0.2963 (3)	0.5558 (3)	6.7 (3)
C(12)	0.4073 (3)	0.3820 (3)	0.5646 (3)	6.4 (3)
C(13)	0.2870 (2)	0.3557 (2)	0.5311 (2)	4.8 (2)

Table 3. Fractional coordinates and equivalent isotropic thermal parameters for (II) with e.s.d.'s in parentheses

	x	y	z	B_{eq} (\AA^2)
N(1)	0.6485 (1)	0.3346 (2)	0.4134 (1)	3.0 (1)
C(1)	0.6201 (2)	0.1648 (2)	0.4124 (2)	4.2 (2)
C(2)	0.5649 (1)	0.4453 (2)	0.3871 (1)	3.1 (1)
O(2)	0.4634 (1)	0.4123 (2)	0.3550 (1)	4.4 (2)
N(3)	0.5996 (1)	0.6085 (2)	0.3981 (1)	3.1 (1)
C(3)	0.5161 (2)	0.7319 (3)	0.3928 (2)	4.5 (2)
C(4)	0.7084 (1)	0.6591 (2)	0.4226 (1)	3.1 (1)
O(4)	0.7385 (1)	0.7978 (2)	0.4443 (1)	4.3 (2)
C(5)	0.7871 (1)	0.5313 (2)	0.4144 (1)	3.0 (1)
O(5)	0.9018 (1)	0.5866 (1)	0.4763 (1)	3.5 (1)
C(6)	0.7716 (1)	0.3733 (2)	0.4652 (1)	2.8 (1)
C(7)	0.7578 (2)	0.5111 (3)	0.2906 (2)	4.0 (2)
C(8)	0.8279 (1)	0.3741 (2)	0.5927 (1)	2.8 (1)
C(9)	0.9293 (2)	0.2880 (2)	0.6516 (1)	3.1 (1)
C(10)	0.9865 (2)	0.2884 (2)	0.7671 (1)	3.1 (1)
C(11)	0.9413 (2)	0.3752 (2)	0.8257 (1)	3.2 (1)
O(11)	0.9974 (1)	0.3718 (2)	0.9401 (1)	4.3 (2)
C(12)	0.8391 (1)	0.4593 (2)	0.7692 (1)	3.9 (2)
C(13)	0.7830 (1)	0.4581 (2)	0.6531 (1)	3.6 (2)

Table 4. Fractional coordinates and equivalent isotropic thermal parameters for (III) with e.s.d.'s in parentheses

	x	y	z	B_{eq} (\AA^2)
N(1)	0.1731 (5)	0.1702 (3)	0.3952 (3)	3.1 (1)
C(1)	0.2602 (7)	0.1044 (4)	0.3296 (4)	4.8 (2)
C(2)	0.0275 (7)	0.1347 (5)	0.4099 (4)	3.4 (1)
O(2)	-0.0408 (5)	0.0527 (3)	0.3696 (3)	4.4 (2)
N(3)	-0.0505 (5)	0.2011 (3)	0.4745 (3)	3.0 (1)
C(3)	-0.1911 (7)	0.1566 (4)	0.5111 (4)	4.4 (2)
C(4)	-0.0091 (7)	0.3053 (4)	0.4988 (4)	3.3 (1)
O(4)	-0.0801 (5)	0.3607 (3)	0.5553 (3)	4.6 (2)
C(5)	0.1252 (6)	0.3506 (4)	0.4482 (4)	3.5 (1)
O(5)	0.2021 (4)	0.4395 (2)	0.5108 (3)	4.3 (2)
C(7)	0.0486 (7)	0.3862 (4)	0.3298 (4)	4.6 (2)
C(6)	0.2559 (6)	0.2646 (4)	0.4506 (4)	3.0 (1)
C(8)	0.3621 (7)	0.2377 (4)	0.5653 (4)	2.9 (1)
C(9)	0.4944 (7)	0.3040 (4)	0.6127 (4)	3.7 (2)
O(9)	0.5202 (5)	0.4004 (3)	0.5621 (3)	5.8 (3)
C(10)	0.6040 (7)	0.2762 (5)	0.7114 (5)	4.4 (2)
C(11)	0.5824 (8)	0.1819 (5)	0.7660 (4)	4.7 (2)
C(12)	0.4490 (8)	0.1170 (5)	0.7218 (4)	4.4 (2)
C(13)	0.3427 (7)	0.1442 (4)	0.6216 (4)	3.4 (1)

(III) the H atoms on methyl carbons C(1) and C(3) were put in at calculated positions and the H on hydroxyl C(9) was not found. H coordinates were included in the refinements as constant parameters. Final R factors are listed in Table 1. Tables 2–4 list the refined coordinates and B_{eq} values for the heavy atoms of molecules (I)–(III) respectively. Standard deviations for the coordinates, given in parentheses, are based solely on the least-squares results. The B_{eq} values were calculated according to the formula $B_{eq} = \frac{4}{3} \sum_i \sum_j \beta_{ij} \mathbf{a}_i \cdot \mathbf{a}_j$ where the β_{ij} 's are the final anisotropic

Table 5. *Approximate hydrogen coordinates*

H parameters given in this table are difference-map coordinates; they were not refined.

	(I)			(II)			(III)		
	x	y	z	x	y	z	x	y	z
H(1)	0.306	0.195	0.756	0.643	0.102	0.363	0.190	0.091	0.253
H(1)	0.227	0.134	0.849	0.530	0.157	0.376	0.284	0.029	0.367
H(1)	0.238	0.062	0.728	0.664	0.111	0.494	0.366	0.136	0.325
H(3)	-0.130	0.506	0.744	0.513	0.821	0.343	-0.295	0.197	0.477
H(3)	-0.008	0.530	0.632	0.552	0.782	0.475	-0.174	0.160	0.594
H(3)	0.023	0.517	0.782	0.434	0.694	0.352	-0.210	0.079	0.488
H(6)	0.076	0.053	0.592	0.803	0.286	0.432	0.352	0.289	0.401
H(7)	-0.116	0.020	0.693	0.762	0.630	0.258	-0.055	0.426	0.324
H(7)	-0.232	0.116	0.692	0.670	0.475	0.247	0.142	0.417	0.293
H(7)	-0.087	0.131	0.786	0.820	0.431	0.290	-0.016	0.318	0.280
H(9)	0.319	0.069	0.441	0.962	0.224	0.604			
H(10)	0.536	0.117	0.506	1.069	0.227	0.814	0.714	0.333	0.738
H(11)	0.588	0.322	0.592				0.659	0.154	0.857
H(12)	0.427	0.470	0.602	0.804	0.525	0.817	0.430	0.048	0.771
H(13)	0.219	0.419	0.541	0.705	0.522	0.613	0.238	0.092	0.600
HO(5)	-0.211	0.177	0.458	0.904	0.703	0.492			
HO(9)							Not found		
HO(11)*				0.996	0.470	0.976			

* Half weight.

thermal parameters. H coordinates for all three molecules are listed in Table 5.*

Discussion

The results of the X-ray analyses on molecules (I)–(III) are shown in the stereodiagrams in Figs. 1–3 respectively. In molecule (I), the thiophenol adduct, the two rings are linked by the S atom and are essentially parallel to one another. The phenylthio moiety is *trans* with respect to the methyl group on C(5) [C(7)–C(5)–C(6)–S = 172.7 (6)°] and *gauche* with respect to the hydroxyl on C(5) [O(5)–C(5)–C(6)–S = 51.2 (5)°]. In both (II) and (III) there is direct C–C bonding between C(6) and the aromatic ring of the phenol. The phenol moieties are *gauche* with respect to the hydroxyl group on C(5). In (II) the O(5)–C(5)–C(6)–C(8) torsion angle is 42.8 (5)° and in (III) this torsion angle is 49.2 (5)°. Similar bonding and geometry occur when thymine reacts with itself to form a thymine–thymine (T–T) adduct (Karle, 1969) and a trimer (Flippen & Karle, 1971). Torsion angles corresponding to those given above for (II) and (III) are 40.7° in the T–T adduct and 38.4° in the thymine trimer. In molecules (I)–(III), as well as in the T–T adduct, the trimer and *cis*-thymine glycol (Flippen,

* Lists of structure factors and anisotropic thermal parameters for the non-H atoms for the 3 molecules have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 36125 (34 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

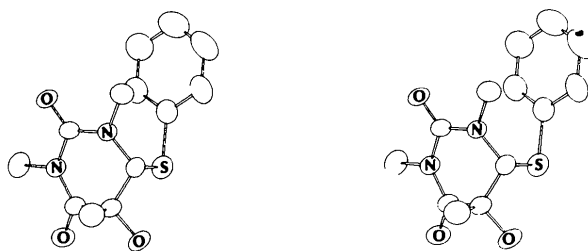


Fig. 1. Stereodiagram of (I) (Johnson, 1965). Atoms are shown at their final refined positions.

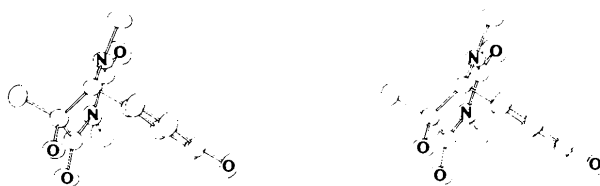


Fig. 2. Stereodiagram of (II). Atoms are shown at their final refined positions.

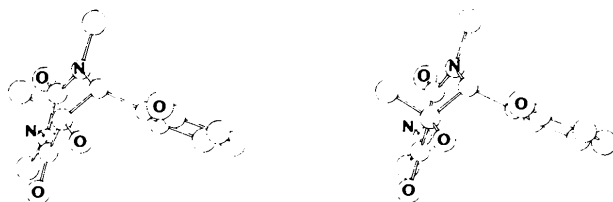


Fig. 3. Stereodiagram of (III). Atoms are shown at their final refined positions.

Table 6. Torsion angles for saturated thymine rings (°)

	(I)	(II)	(III)	<i>a</i>	<i>b</i>	<i>c</i>	<i>d</i>	<i>e</i>
C(6)–N(1)–C(2)–N(3)	9.2 (9)	8.2 (9)	6.2 (8)	15.4 (–14.0)	4.9	9.8	9.7	6.8
N(1)–C(2)–N(3)–C(4)	12.9 (8)	6.6 (9)	16.0 (8)	–1.9 (–1.9)	10.6	12.6	0.3	11.3
C(2)–N(3)–C(4)–C(5)	3.6 (11)	12.3 (9)	2.3 (13)	20.3 (–14.9)	8.9	1.0	17.4	8.6
N(3)–C(4)–C(5)–C(6)	–37.4 (8)	–41.9 (8)	–38.5 (8)	–46.9 (43.3)	–39.6	–33.6	–40.8	–41.8
C(4)–C(5)–C(6)–N(1)	55.1 (8)	52.2 (8)	54.9 (8)	57.9 (–55.5)	49.8	52.0	46.8	55.8
C(5)–C(6)–N(1)–C(2)	–44.1 (9)	–38.2 (8)	–41.7 (9)	–46.3 (43.8)	–35.3	–42.6	–34.1	–41.6

(I)–(III). This study. (*a*) Dihydrothymine (Furberg & Jensen, 1968). This molecule was disordered with mixtures of D and L isomers. Torsion angles are given for both configurations. (*b*) Thymine trimer (Flippen & Karle, 1971). (*c*) Dihydrothymidine (Konnert *et al.*, 1970). (*d*) Thymine–thymine adduct (Karle, 1969). (*e*) *cis*-Thymine glycol (Flippen, 1973).

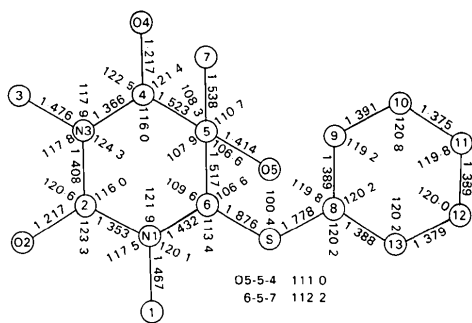


Fig. 4. Bond lengths (Å) and angles (°) for (I). Standard deviations are on the order of 0.004 Å for bond lengths and 0.2° for bond angles.

1973), the CH₃ group on C(5) is axial to the thymine ring and the OH group is equatorial. This contrasts with the configuration of saturated thymine rings without hydroxyl groups such as dihydrothymine (Furberg & Jensen, 1968) and dihydrothymidine (Konnert, Karle & Karle, 1970) in which the CH₃ group on C(5) is equatorial to the thymine ring.

Thymine itself is planar to within 0.008 Å (Gerdil, 1961). When the thymine ring is saturated such as in (I)–(III) and in the other compounds referred to in this discussion it assumes a half-chair conformation. The conformation of these saturated thymine rings seems to be fairly constant regardless of the type of substitution at C(5) and C(6) and also irrespective of whether or not there has been a substitution for the H atom on N(1) and/or N(3). Torsion angles describing the conformations of these saturated thymine rings are compared in Table 6. Bond lengths and angles for molecules (I)–(III) are shown in Figs. 4–6 respectively. The average O(5)–H(O5) distance is 1.04 Å. The O(11)–H(O11) distance in (II) is 0.96 Å. The average C–H distance for the three molecules is 1.06 Å. Distances and angles for the thymine ring lie within the ranges found for other nucleic acid bases (Karle, 1976).

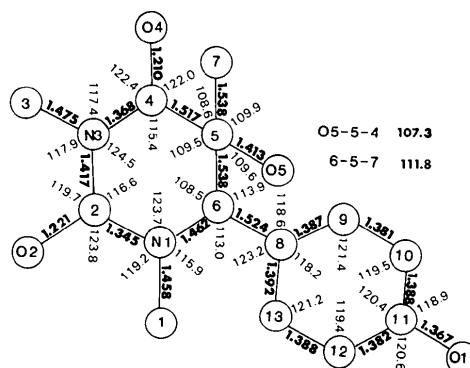


Fig. 5. Bond lengths (Å) and angles (°) for (II). Standard deviations are on the order of 0.003 Å for bond lengths and 0.2° for bond angles.

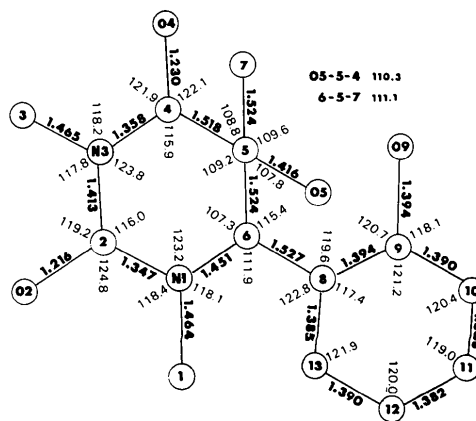


Fig. 6. Bond lengths (Å) and angles (°) for (III). Standard deviations are on the order of 0.007 Å for bond lengths and 0.5° for bond angles.

The average C=C bond length is 1.388 (4) for (I), 1.386 (3) for (II) and 1.408 (7) Å for (III). The average C=C=C angle is 120.0 (3)° for all three molecules.

Table 7. *Hydrogen bonding and close intermolecular approaches*

The average e.s.d. in O...O distances is 0.01 Å.

	Donor	Acceptor	Symmetry of acceptor	O—H	O...O	H...O	O—H...O	O...H...O	
Molecule (I)	O(5)	O(2)	$-\frac{1}{2} + x, \frac{1}{2} - y, -\frac{1}{2} + z$	1.04 Å	2.78 Å	2.05 Å	124.7 Å	87.0°	} Bifurcated
	O(5)	O(4)	x, y, z	1.04	2.74	2.21	109.3		
Molecule (II)	O(5)	O(11)	$2 - x, \frac{1}{2} + y, \frac{1}{2} - z$	0.99	2.75	1.84	142.6		
	O(11)	O(11)	$2 - x, 1 - y, 2 - z$	0.96	2.66	1.71	170.6		
	O(5)	O(5)	$2 - x, 1 - y, 1 - z$		2.75*				
Molecule (III)	O(5)	O(4)	$\bar{x}, 1 - y, 1 - z$	1.07	2.74	1.67	170.9		
	O(9)	O(9)	$1 - x, 1 - y, 1 - z$		2.89				

* Close intermolecular approach, not a hydrogen bond.

Packing for all three molecules is influenced by hydrogen bonding. Distances and angles describing hydrogen bonds and other close intermolecular approaches are given in Table 7. In (I) the only H available to participate in hydrogen bonding is on hydroxyl O(5) and it donates to both O(2) (intermolecular) and O(4) (intramolecular) to form a bifurcated hydrogen bond. In (II), the hydrogen on hydroxyl O(5) is the donor in an intermolecular hydrogen bond to hydroxyl O(11). A second hydrogen bond is formed between hydroxyl O(11) and one of its symmetry-related molecules. This O(11)...O(11) hydrogen bond forms across a center of symmetry and, therefore, the hydrogen on O(11) must be disordered, otherwise the H(O11)...H(O11) approach would be only 0.79 Å. The 'half' H along the bond was located in a difference map; however, a second 'half' position for this H was not found. There is also a close approach between hydroxyl O(5) and its equivalent across a center of symmetry (in molecule II). However, this is not a hydrogen bond since the H...O distance is 3.4 Å and the H atom is directed [away from the related O(5) atom] towards O(11). In molecule (III), there is a similar approach between O(9) and its equivalent across a center of symmetry. In this case, however, the H was not found and it is, therefore, not known whether this is merely a close intermolecular approach as with O(5)...O(5) in (II) or a hydrogen bond with a disordered H as in the O(11)...O(11) bond in (II).

Other than the distances quoted in Table 7 there are no intermolecular approaches less than van der Waals distances.

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