

## Secondary Metabolites from the Patulin Pathway. I. Phyllostine (5,6-Epoxygentisylquinone) at 208 K

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**Abstract.**  $C_7H_6O_4$ ,  $M_r = 154.12$ , monoclinic,  $P2_1$ ,  $a = 6.9996$  (19),  $b = 4.2366$  (06),  $c = 11.4252$  (33) Å,  $\beta = 98.717$  (13)°,  $V = 334.89$  (14) Å<sup>3</sup>,  $Z = 2$ ,  $D_x = 1.528$  Mg m<sup>-3</sup>,  $\mu(\text{Mo } K\alpha) = 0.1379$  mm<sup>-1</sup>,  $F(000) = 160$ ,  $T = 208$  (2) K,  $R = 0.031$  for 779 contributing reflections. Phyllostine has a slightly flattened boat conformation. The carbonyl groups are bowed away from the oxirane ring. The hydroxyl group is involved in an intermolecular hydrogen bond.

**Introduction.** Phyllostine is a photosensitive polyketide from the postgentisaldehyde portion of the patulin pathway in *Penicillium urticae* isolated by thin-layer chromatography from the patulin-negative mutant, J1 (Sekiguchi & Gaucher, 1978). It possesses roughly 80% of the antibiotic activity of patulin against *Bacillus subtilis*. Purification by high-pressure liquid chromatography with solvent programming (90% hexane/10% ethyl acetate to 20% hexane/80% ethyl acetate in 45 min) and subsequent recrystallization from 80% hexane/20% ethyl acetate.

**Experimental.** Pale-yellow needle (cut),  $0.10 \times 0.15 \times 0.35$  mm, Enraf-Nonius CAD-4F diffractometer, graphite-monochromated Mo  $K\alpha$  radiation; lattice parameters from least-squares refinement of 24 reflections with  $8.6 \leq \theta \leq 18.8^\circ$ . Cooling provided by N<sub>2</sub> gas stream and monitored by thermocouple approximately 5 mm upstream of crystal. Scan range,  $\Delta\omega = 1.5(0.66 + 0.347 \tan\theta)^\circ$  in  $\omega/2\theta$  mode; three standard reflections monitored every 1000 s; 702 of 828 unique reflections observed with  $I > 3.0\sigma(I)$ . Structure solved using *MULTAN* (Germain, Main & Woolfson, 1971); refined by full-matrix least squares minimizing  $\sum w|F_o - F_c|^2$  with  $w = (\sigma^2 F + 0.0008F^2)^{-1}$  to  $R = 0.031$  and  $wR = 0.032$  for 779 contributing reflections [reflections with  $I \leq 3.0\sigma(I)$  included if  $F_o \leq F_c$ ];  $[\sum w\Delta^2/(m-n)]^{1/2} = 1.000$ ; scattering factors and anomalous-dispersion terms (real part only) from *International Tables for X-ray Crystallography* (1974). Hydrogen atoms refined isotropically; max.  $\Delta/\sigma = 0.0016$ ; average  $\Delta/\sigma = 0.00030$ ; max. residual electron density  $0.14 \text{ e } \text{Å}^{-3}$ ; *XRAY76* programs (Stewart, 1976).

Table 1. Fractional atomic coordinates and (equivalent) isotropic thermal parameters ( $\times 10^4$ )

	$U_{eq} = \frac{1}{3}(U_{11} + U_{22} + U_{33})$ .			
	<i>x</i>	<i>y</i>	<i>z</i>	$U_{eq}/U_{iso}(\text{Å}^2)$
C(1)	1117 (3)	5558 (9)	1501 (2)	262 (12)
C(2)	1519 (3)	4403 (12)	2741 (2)	255 (12)
C(3)	3235 (3)	4972	3395 (2)	310 (13)
C(4)	4779 (3)	6640 (10)	2910 (2)	310 (12)
C(5)	4711 (3)	6552 (10)	1598 (2)	284 (12)
C(6)	2821 (3)	6019 (12)	870 (2)	277 (12)
C(7)	-146 (4)	2871 (10)	3213 (2)	328 (14)
O(1)	-505 (2)	6169 (12)	1023 (1)	398 (10)
O(4)	6042 (2)	8113 (12)	3524 (2)	502 (12)
O(6)	4220 (2)	3535 (8)	1064 (1)	318 (8)
O(7)	393 (3)	1737 (12)	4378 (2)	388 (12)
H(3)	3481 (29)	4433 (63)	4191 (20)	248 (62)
H(5)	5598 (30)	7736 (64)	1293 (19)	213 (58)
H(6)	2591 (28)	6824 (71)	82 (20)	259 (59)
H(71)	-1203 (39)	4372 (82)	3145 (22)	447 (84)
H(72)	-585 (35)	1175 (91)	2690 (22)	418 (76)
H(O7)	378 (46)	3102 (95)	4867 (30)	535 (109)

Final atomic coordinates in Table 1;\* bond lengths, bond angles and torsional angles in Table 2; rigid-body thermal parameters in Table 3. Fig. 1 is a perspective view of the molecule.

**Discussion.** Phyllostine can be regarded as a substituted *p*-benzoquinone in which the 5,6 double bond has been replaced by an epoxy group. Both in the pure sample and in complexes, *p*-benzoquinones are flat molecules (Bernstein *et al.*, 1975). By contrast, Fig. 2 clearly shows that the six-membered ring is strongly bowed with the two carbonyls bent away from the oxirane system in a flattened boat conformation with the carbon about 0.28 Å and the oxygens 0.78 Å out of the plane defined by C(2)C(3)C(5)C(6). The oxirane ring is about 89° out of that plane on the side opposite the carbonyls.

There are no short contacts between the epoxy oxygen and the carbonyl groups. The bowing is caused by electronic rather than steric effects and has been

\* Lists of structure factors, anisotropic thermal parameters, and bond angles and torsional angles involving hydrogen have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 42816 (9 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 2. Bond distances (Å), bond angles (°) and selected torsion angles (°)

	Observed	Corrected*		
C(1)–C(2)	1.484 (3)	1.489	C(1)–C(2)–C(7)	116.1 (2)
C(2)–C(3)	1.337 (3)	1.342	C(3)–C(2)–C(7)	123.8 (2)
C(2)–C(7)	1.504 (4)	1.507	C(1)–C(2)–C(3)	119.9 (2)
C(3)–C(4)	1.469 (3)	1.472	C(2)–C(3)–C(4)	121.7 (2)
C(3)–H(3)	0.93 (2)		C(3)–C(4)–C(5)	117.0 (2)
C(4)–C(5)	1.493 (3)	1.497	C(3)–C(4)–O(4)	122.8 (2)
C(4)–O(4)	1.215 (4)	1.217	C(5)–C(4)–O(4)	120.2 (3)
C(5)–C(6)	1.469 (3)	1.475	C(4)–C(5)–C(6)	117.5 (2)
C(5)–O(6)	1.436 (5)	1.441	C(4)–C(5)–O(6)	114.7 (3)
C(5)–H(5)	0.91 (2)		O(6)–C(5)–C(6)	59.0 (2)
C(6)–O(6)	1.432 (4)	1.437	C(5)–C(6)–C(1)	117.5 (2)
C(6)–H(6)	0.95 (2)		O(6)–C(6)–C(5)	59.3 (2)
C(6)–C(1)	1.497 (3)	1.501	O(6)–C(6)–C(1)	113.9 (2)
C(1)–O(1)	1.211 (3)	1.214	C(6)–C(1)–O(1)	121.1 (2)
C(7)–O(7)	1.411 (3)	1.415	C(6)–C(1)–C(2)	116.9 (2)
C(7)–H(71)	0.97 (3)		C(2)–C(1)–O(1)	122.0 (2)
C(7)–H(72)	0.96 (3)		C(5)–O(6)–C(6)	61.7 (2)
O(7)–H(7)	0.81 (4)		C(2)–C(7)–O(7)	112.0 (2)
C(1)–C(2)–C(3)–C(4)	–2.0 (4)		C(3)–C(4)–C(5)–C(6)	24.3 (5)
C(1)–C(2)–C(7)–O(7)	177.6 (3)		C(3)–C(4)–C(5)–O(6)	–42.2 (4)
C(1)–C(6)–C(5)–C(4)	–0.9 (6)		C(4)–C(3)–C(2)–C(7)	–176.4 (3)
C(1)–C(6)–C(5)–O(6)	102.9 (4)		C(4)–C(3)–C(2)–O(7)	–103.8 (4)
C(1)–C(6)–O(6)–C(5)	–108.9 (4)		C(4)–C(5)–O(6)–C(6)	108.4 (4)
C(2)–C(1)–C(6)–C(5)	–23.9 (5)		C(5)–C(6)–C(1)–O(1)	154.6 (4)
C(2)–C(1)–C(6)–O(6)	42.6 (4)		C(6)–C(1)–C(2)–C(7)	–159.0 (3)
C(2)–C(3)–C(4)–C(5)	–23.7 (4)		C(6)–C(5)–C(4)–O(4)	–153.8 (4)
C(2)–C(3)–C(4)–O(4)	154.3 (3)		C(7)–C(2)–C(1)–O(1)	22.5 (5)
C(3)–C(2)–C(1)–C(6)	26.2 (5)		O(1)–C(1)–C(6)–O(6)	–138.9 (4)
C(3)–C(2)–C(1)–O(1)	–152.3 (4)		O(4)–C(4)–C(5)–O(6)	139.7 (4)
C(3)–C(2)–C(7)–O(7)	–7.8 (5)			

\* Corrected for thermal libration.

Table 3. Rigid-body thermal parameters for phyllostine

Referred to orthogonal axis defined with **A** parallel to **a** and **B** in the *ab* plane. The r.m.s.  $\Delta U_{ij}$  is  $0.0022 \text{ \AA}^2$ .  $R = \sum |\Delta U_{ij}| / \sum |U_{ij}| = 0.0896$ . The diagonal component of the cross tensor **S** arbitrarily set to zero is indicated by \*.

<b>T</b> =	$\begin{bmatrix} 256 (10) & & \\ & 52 (9) & \\ & 246 (15) & \end{bmatrix}$	$\begin{bmatrix} & & 35 (8) \\ & -6 (10) & \\ & 226 (11) & \end{bmatrix}$	$\text{\AA} \times 10^{-4}$
<b>L</b> =	$\begin{bmatrix} 10.9 (1.9) & & \\ & 2.8 (9) & \\ & 9.7 (1.1) & \end{bmatrix}$	$\begin{bmatrix} & & -7.6 (7) \\ & 0.5 (8) & \\ & 13.3 (1.5) & \end{bmatrix}$	deg <sup>2</sup>
<b>S</b> =	$\begin{bmatrix} -46 (77) & & \\ 71 (29) & & \\ 159 (41) & & \end{bmatrix}$	$\begin{bmatrix} & & 9 (46) \\ & -141 (32) & \\ & 9 (59) & -92 (27) \\ & & & 37 (*) \end{bmatrix}$	rad $\text{\AA} \times 10^{-5}$

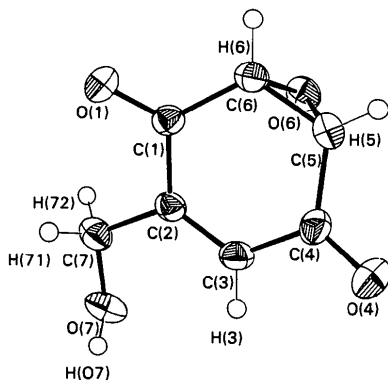


Fig. 1. Perspective view of phyllostine showing the numbering scheme and the orientation of the thermal ellipsoids (50% probability).

discussed by a number of authors (Hoffmann, 1970; Lauber & Ibers, 1975; Jason & Ibers, 1977; Allen, 1980). The Walsh (1949) model for bonding in cyclopropane provides valuable insight. Rauk (1981) has shown that the HOMO of the oxirane system is a set of dumb-bell-shaped orbitals whose lobes at carbon are approximately perpendicular to the bisector of the opposite side of the triangle. Although his diagrams show slightly different orientations of the orbitals in aziridine and oxirane, Rauk fails to comment on this point. Allen (1982) has attempted to quantify the effect in his study of  $C_2X$  rings using the Cambridge Crystallographic Data File. He shows that both the C–C distance and the bent back angle,  $\gamma$ , decrease as the electronegativity of the hetero-atom increases. His 'average' oxirane ring has the dimensions C–C =  $1.467 (2)$ , C–O =  $1.447 (2) \text{ \AA}$ ,  $\angle \text{COC} = 60.9 (2)$ ,  $\angle \text{CCX} = 59.5 (2)^\circ$  with  $\gamma = 21.6^\circ$ . In phyllostine the corresponding (uncorrected) dimensions are C–C =  $1.469 (3)$ , C–O =  $1.432 (4)$ ,  $1.436 (5) \text{ \AA}$ ,  $\angle \text{COC} = 61.6 (2)$ ,  $\angle \text{CCO} = 59.0 (2)$ ,  $59.3 (2)^\circ$ , with  $\gamma = 24.6^\circ$  at C(5) and  $22.9^\circ$  at C(6), indicating that the overlap between the LUMO of the carbonyl and the HOMO of the oxirane system is nearly optimal in phyllostine.

There is little conjugation between the double bond and the carbonyls. The C(2)–C(3) bond length is that expected for a simple unconjugated double bond. This suggests that conjugation of the carbonyl with the oxirane system is energetically more favourable than with the C(2)–C(3) double bond.

Hoffmann (1970) predicted that  $\pi$ -accepting substituents would make cyclopropane rings unsymmetrical by shortening the bond distal to the substituents and lengthening the vicinal bonds. The effect has been observed in Allen's (1980) study of cyclopropanes, but not in his 1982 study of  $C_2X$  compounds. The reason may be related to the differences in hybridization between cyclopropane and oxirane. The *s* character of the C–C bonds is greater (27.0% vs 20.5%) and the *p* character of the C–O bonds is enhanced (92.0% vs 79.5%) in oxirane relative to cyclopropane. In phyllostine, the C–C bond is only marginally longer than Allen's (1982) value for an

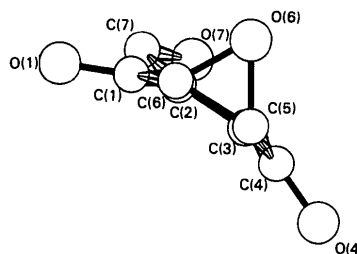


Fig. 2. Phyllostine viewed perpendicular to the oxirane ring showing the boat-shaped six-membered ring. Hydrogens have been omitted for clarity.

'average' oxirane ring, although the C—O bonds appear to have been shortened by about 0.013 Å. It may be fortuitous that this is the value that would have been expected on the basis of the cyclopropane work. A similar effect has been observed in two related compounds (Kerr, to be published).

The molecules are linked in pairs by intermolecular hydrogen bonds in which O(7) acts as both donor and acceptor with O...O 2.655 (4) Å, H...O 1.88 (4) Å and  $\angle$ O—H...O 157 (2)°. However, the NMR spectrum in deuterio-acetone (Sekiguchi & Gaucher, 1978) shows coupling between the protons on C(7) and C(3). This has been interpreted as strong evidence for an intramolecular hydrogen bond to O(1) in solution. There are four additional intermolecular O...H contacts between 2.56 (3) and 2.64 (3) Å.

The most significant intramolecular interactions involve the hydroxymethyl side chain: C(7)...O(1) 2.844, O(7)...C(3) 2.788 (3) Å. The epoxy oxygen makes short contacts of 2.911 (3) and 2.915 (3) Å with atoms C(2) and C(3), respectively.

Examination of Fig. 1 yields the impression that phyllostine may be librating about an axis corresponding to the smallest moment of inertia. This is borne out by rigid-body analysis (Table 3). The mean-square amplitudes of libration are 20.0, 10.4 and 3.5 deg<sup>2</sup> in the three principal directions while the translational component is more nearly isotropic with eigenvalues of 0.0302, 0.0235 and 0.0178 Å<sup>2</sup> (after symmetrizing S). The corrected bond lengths for the oxirane ring are

close to the gas-phase values of 1.470 Å (C—C) and 1.434 Å (C—O) observed by Hirose (1974).

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## Methoxypromazine at 120 K\*

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**Abstract.** C<sub>18</sub>H<sub>22</sub>N<sub>2</sub>OS, *M<sub>r</sub>* = 314.5, monoclinic, *P*2<sub>1</sub>/*n*, *a* = 7.462 (2), *b* = 17.223 (6), *c* = 12.745 (3) Å,  $\beta$  =

96.18 (2)°, *V* = 1628.3 (8) Å<sup>3</sup>, *Z* = 4, *D<sub>m</sub>* = 1.29 (1), *D<sub>x</sub>* = 1.28 (1) Mg m<sup>-3</sup>,  $\lambda$ (Cu K $\alpha$ ) = 1.5418 Å,  $\mu$  = 0.173 mm<sup>-1</sup>, *F*(000) = 672, *T* = 120 K, *R* = 0.067, 2484 contributing reflections. The 3-(dimethylamino)propyl side chain is located with respect to the

\* The Structures of (Dimethylaminopropyl)phenothiazine Drugs and Their Metabolites. IV. Part III: Hough, Wold & Dahl (1985).