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The Structure of 6,7,9-Trimethyl-4-azaphenoxathiin, $C_{14}H_{13}NOS$

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Abstract. $M_r = 243{\cdot}33$, $P4/mnc$, $a = 18{\cdot}495\,(3)$, $c = 6{\cdot}8054\,(10)$ Å, $V = 2327{\cdot}9\,(6)$ Å^3, $Z = 8$, $D_x = 1{\cdot}388$ g cm^{-3}, Mo $K\alpha$ radiation, $\lambda = 0{\cdot}71069$ Å, $\mu = 2{\cdot}57$ cm^{-1}, $F(000) = 1024$, $T = 163$ K, $R = 0{\cdot}036$ for 1356 reflections. The molecule is planar as required by symmetry. The S—C and O—C bonds are asymmetric with the shorter bonds to the aza-substituted ring. The molecules are stacked perpendicular to **c** with the phenyl ring of one molecule above the pyridine ring of the neighboring molecule. A comparison of dihedral angles in azaphenoxathiin and related compounds is made.

Introduction. The structural determination of the title compound was undertaken as part of a series of investigations of the geometry of phenoxathiins and isosterically related heterocycles as determined by X-ray diffraction methods and the correlation of these results with their solution-state ^{13}C NMR spectra (Womack, Turley, Martin, Kimura & Simonsen, 1981; Caldwell, Martin, Simonsen, Inners & Willcott, 1981; Puig-Torres, Martin, Smith, Cacioli & Reiss, 1982). During the course of this study it was observed that a linear relationship existed between the ^{13}C NMR chemical shift of the sulfur-bearing carbon atom [C(10a)] and the dihedral angle of the molecule (defined as the angle between the planes of the aromatic rings) for several phenoxathiins (Caldwell, Turley & Martin, 1980). The geometry of this class of compounds is of interest because for certain members of the isosteric phenothiazine series changes in pharmacologic activity are associated with changes in the dihedral angle of the molecule (Caldwell *et al.*, 1980).

Experimental. Synthesis and ^{13}C NMR spectra of title compound as previously reported (Puig-Torres *et al.*, 1982). Rectangular prismatic crystal of dimensions $0{\cdot}36 \times 0{\cdot}37 \times 0{\cdot}51$ mm obtained by sublimation. Data collected at 163 K, Syntex $P2_1$ diffractometer, graphite monochromator. Unit-cell parameters obtained by least-squares refinement of setting angles of 30 reflections, 2θ 24·2–25·8°. No correction for absorption. 1836 unique reflections, ω-scan technique, 2θ 4–60° ($h = 0$–18, $k = 0$–26, $l = 0$–9, $h \leq k$), 1° scan range, scan rate 2–5° min^{-1}. Intensities of 4 reflections (006, 903, 093, $2\bar{1}\bar{2}$) measured every 96 reflections to monitor instrument and crystal stability. Data analyzed as described by Henslee & Davis (1975) resulting in a decay correction of <0·01. Data reduction as described by Riley & Davis (1976). 480 reflections had $F \leq 6(\sigma_F)$ and were considered unobserved. Structure solved using *MULTAN*78 (Main, Hull, Lessinger, Germain, Declercq & Woolfson, 1978) which afforded positions of S and N atoms and five C atoms of the phenyl ring. All other non-H atoms located from subsequent electron density maps. After several cycles of full-matrix least-squares refinement {function minimized $\sum[w(|F_o| - |F_c|)]^2$, where $w = (\sigma_F)^{-2}$} with anisotropic thermal parameters for all non-H atoms, positions for H atoms obtained from a difference map. H atoms refined isotropically. 002 reflection had large negative ΔF and appeared to be suffering from extinction, so it was removed from further refinement. Final $R = 0{\cdot}036$ for 136 parameters with $wR = 0{\cdot}044$ and $S = 1{\cdot}46$. Max. $\Delta/\sigma = 0{\cdot}01$ for final refinement cycle. Max. and min. peaks in final difference map 0·37 and −0·31 e Å^{-3}, respectively. Least-squares planes program supplied by Cordes (1983); other computer programs are listed in reference 11 of Gadol & Davis (1982).* Atomic scattering factors from *International Tables for X-ray Crystallography* (1974).

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* Tables of anisotropic thermal parameters for the non-H atoms, bond distances and angles for the H atoms and observed and calculated structure factor amplitudes have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 39402 (12 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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Although the intensity statistics indicated a centrosymmetric structure, the space group was initially assumed to be *P*4*nc* on the basis of the ^{13}C NMR results which indicated that the molecule had a dihedral angle of 145 (3)° [from data of Caldwell *et al.* (1980) modified by inclusion of 147·71 (9)° for the dihedral angle of phenoxathiin (Kimura, 1981)]. In the centrosymmetric space group the molecule would be required to lie on a mirror plane. However, during refinement in *P*4*nc* the *z* coordinates and the U_{13} and the U_{23} parameters for several atoms oscillated. Therefore, refinement was begun in *P*4/*mnc* with the *z* coordinates of all but six methyl H's lying in the *ab* plane and the U_{13} and U_{23} parameters of all non-H atoms fixed at zero as required by symmetry. Although the choice of the noncentrosymmetric space group could not be eliminated on the basis of statistical tests (Hamilton, 1965) the results using the centrosymmetric model are reported here because of the intensity statistics, the satisfactory convergence of the centrosymmetric model upon refinement and because there are no significant differences in geometry between the two refined models. The dihedral angle, for example, is required to be 180° in space group *P*4/*mnc* and was found to be 179·85 (10)° for refined coordinates in space group *P*4*nc*.

Discussion. A view of the molecule with the atom labeling scheme is shown in Fig. 1. Atomic positional and thermal parameters are listed in Table 1. Bond distances and angles for the non-H atoms are listed in Table 2.

The bond angles around the C atoms of the central ring system are significantly greater than 120°, which is largely due to the relatively small bond angle at S and to the differences in the S—C bond distances compared with the O—C distances. This is commonly observed for phenoxathiins. The S—C and O—C bond lengths show some asymmetry with the bonds to the ring with the aza substituent being slightly shorter, which is probably due to electronic effects arising from the aza substitution.

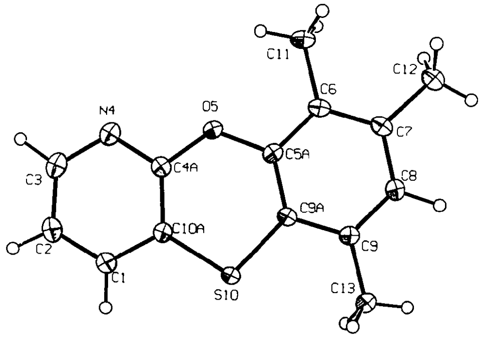


Fig. 1. View of molecule showing atom-labeling scheme. Ellipsoids are scaled to the 50% probability level.

Table 1. *Positional parameters with equivalent isotropic thermal parameters for the non-hydrogen atoms and isotropic thermal parameters for the hydrogen atoms of* 6,7,9-*trimethyl*-4-*azaphenoxathiin*

	x	*y*	*z**	U_{eq}/U_{iso}(Å^2)†
S(10)	0·45173 (3)	0·10447 (3)	0	0·0194 (2)
C(10a)	0·47067 (11)	0·19704 (11)	0	0·0176 (6)
C(1)	0·54247 (12)	0·21954 (12)	0	0·0229 (6)
C(2)	0·55895 (13)	0·29262 (13)	0	0·0268 (7)
C(3)	0·50205 (14)	0·34103 (13)	0	0·0276 (7)
N(4)	0·43192 (11)	0·32104 (10)	0	0·0232 (6)
C(4a)	0·41775 (12)	0·25146 (12)	0	0·0189 (6)
O(5)	0·34478 (9)	0·23801 (8)	0	0·0231 (5)
C(5a)	0·31532 (11)	0·16864 (11)	0	0·0174 (5)
C(6)	0·23975 (12)	0·16668 (12)	0	0·0184 (6)
C(7)	0·20506 (11)	0·09937 (12)	0	0·0193 (6)
C(8)	0·24651 (12)	0·03682 (12)	0	0·0194 (6)
C(9)	0·32152 (11)	0·03818 (12)	0	0·0174 (5)
C(9a)	0·35653 (11)	0·10542 (11)	0	0·0163 (6)
C(11)	0·19625 (13)	0·23570 (13)	0	0·0260 (7)
C(12)	0·12382 (13)	0·09452 (14)	0	0·0263 (7)
C(13)	0·36465 (13)	−0·03103 (12)	0	0·0226 (7)
H(C1)	0·581 (2)	0·184 (2)	0	0·030 (7)
H(C2)	0·607 (2)	0·311 (2)	0	0·035 (8)
H(C3)	0·5097 (14)	0·3933 (14)	0	0·024 (7)
H(C8)	0·2231 (13)	−0·0130 (14)	0	0·020 (6)
H(C11)*A*	0·1652 (11)	0·2389 (12)	0·112 (3)	0·051 (6)
H(C11)*B*	0·223 (2)	0·278 (2)	0	0·025 (7)
H(C12)*A*	0·1029 (9)	0·1198 (10)	0·118 (3)	0·032 (5)
H(C12)*B*	0·110 (2)	0·045 (2)	0	0·047 (9)
H(C13)*A*	0·3969 (9)	−0·0348 (10)	−0·116 (3)	0·031 (5)
H(C13)*B*	0·335 (2)	−0·070 (2)	0	0·039 (8)

* Required by symmetry to be zero for most atoms.

† For non-hydrogen atoms, the *U* value is U_{eq}, calculated as

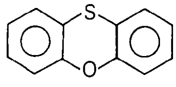
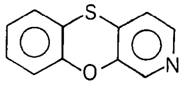
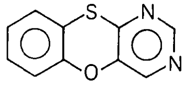
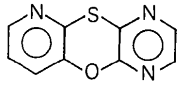
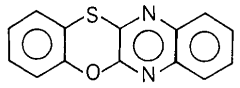
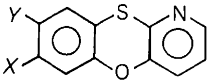
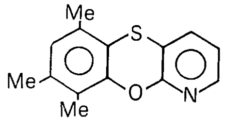
$$U_{eq} = \tfrac{1}{3}\textstyle\sum_i\sum_j U_{ij}a_i^*a_j^*A_{ij},$$

where A_{ij} is the dot product of the *i*th and *j*th direct-space unit-cell vectors.

Table 2. *Bond distances* (Å) *and angles* (°) *for the non-hydrogen atoms of* 6,7,9-*trimethyl*-4-*azaphenoxathiin*

1	2	3	1—2	1—2—3
C(10a)	S(10)	C(9a)	1·747 (2)	101·00 (10)
C(9a)	S(10)		1·761 (2)	
C(1)	C(10a)	C(4a)	1·391 (3)	116·8 (2)
C(1)	C(10a)	S(10)		119·0 (2)
C(4a)	C(10a)	S(10)	1·404 (3)	124·2 (2)
C(2)	C(1)	C(10a)	1·386 (3)	120·1 (2)
C(3)	C(2)	C(1)	1·382 (4)	117·7 (2)
N(4)	C(3)	C(2)	1·349 (3)	123·7 (2)
C(4a)	N(4)	C(3)	1·313 (3)	117·4 (2)
O(5)	C(4a)	C(10a)	1·372 (3)	123·8 (2)
O(5)	C(4a)	N(4)		111·9 (2)
C(10a)	C(4a)	N(4)		124·3 (2)
C(5a)	O(5)	C(4a)	1·394 (3)	123·5 (2)
C(6)	C(5a)	C(9a)	1·398 (3)	121·6 (2)
C(6)	C(5a)	O(5)		114·5 (2)
C(9a)	C(5a)	O(5)	1·396 (3)	123·9 (2)
C(7)	C(6)	C(11)	1·400 (3)	120·5 (2)
C(7)	C(6)	C(5a)		118·7 (2)
C(11)	C(6)	C(5a)	1·509 (3)	120·7 (2)
C(8)	C(7)	C(12)	1·388 (3)	120·1 (2)
C(8)	C(7)	C(6)		119·2 (2)
C(12)	C(7)	C(6)	1·505 (3)	120·7 (2)
C(9)	C(8)	C(7)	1·388 (3)	122·5 (2)
C(9a)	C(9)	C(13)	1·402 (3)	120·6 (2)
C(9a)	C(9)	C(8)		118·5 (2)
C(13)	C(9)	C(8)	1·508 (3)	120·9 (2)
S(10)	C(9a)	C(5a)		123·7 (2)
S(10)	C(9a)	C(9)		116·9 (2)
C(5a)	C(9a)	C(9)		119·4 (2)

Table 3. *Comparison of dihedral angles for phenoxathiin and related compounds*

Compound	Dihedral angle (angle between planes of aromatic rings) and reference
 Phenoxathiin	147·71 (9)° Kimura (1981)
 3-Azaphenoxathiin	167·1° Caldwell, Martin, Simonsen, Inners & Willcott (1981)
 1,3-Diazaphenoxathiin	165·46 (8)° Larson (1983)
 1,4,9-Triazaphenoxathiin	172·47 (8)° Larson (1983)
 Benzo[*b*][1,4]diazaphenoxathiin (two molecules per asymmetric unit)	167·84 (12)° 176·36 (13)° Hoffschwelle, Simonsen & Martin (1981)
 (1) $X = \mathrm{Cl}$, $Y = \mathrm{H}$ (2) $X = \mathrm{H}$, $Y = \mathrm{Cl}$ 7-Chloro and 8-chloro-1-azaphenoxathiin	(1) 176·8° (2) 175·7° Martin, Korp, Turley & Bernal (1978)
 6,7,9-Trimethyl-4-azaphenoxathiin	180° This work

There is no evidence from the bond angles around C(6) and C(9) that this asymmetry is due to steric interactions between the methyl groups and the S and O atoms. The effect of aza ring substitution in phenoxathiins appears to cause an increase in the dihedral angle of the compound regardless of the position of substitution. Examples of aza-substituted phenoxathiins with their dihedral angles are found in Table 3. The dihedral angle of phenoxathiins is generally more sensitive to changes in substituents than are the analogous thianthrenes. For example, 1-azathianthrene has a dihedral angle of 132·13 (6)° which is only slightly greater than the 128·28 (7)° found for thianthrene (Larson, Simonsen, Martin, Smith & Puig-Torres, 1984) while the 1-azaphenoxathiins show much greater changes compared to phenoxathiin (Table 3). Benzo[*b*][1,4]diazathianthrene (Lynch, 1983) has a dihedral angle of 136·83 (10)°, an increase of only 7·55° relative to thianthrene, whereas benzo[*b*][1,4]-diazaphenoxathiin, with two molecules per asymmetric unit, has increases of 20·13 and 28·65°, respectively, relative to phenoxathiin.

Although there are no unusually close intermolecular contacts, it has been observed that crystal packing forces can affect the dihedral angles in phenoxathiins and similar types of compounds (Chu, 1975; Chu & Mangion, 1975; Chu & Yang, 1977; Lynch, Larson, Simonsen & Thomas, 1984; Hoffschwelle, Simonsen & Martin, 1981; Phelps & Cordes, 1974). The molecules are stacked one on top of another in layers perpendicular to the *c* axis and arranged so that the phenyl ring of one molecule lies over the pyridine ring of another molecule in order to minimize intermolecular methyl-group interactions. The extent to which packing forces influence the dihedral angle in this instance and whether such forces are responsible for the apparent difference between the geometry in the solid state and in solution is unknown.

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Structures of Morphine Methyl Iodide Monohydrate, $(C_{18}H_{22}NO_3)^+.I^-.H_2O$, and Di(morphine) Dihydrogensulfate Pentahydrate, $2(C_{17}H_{20}NO_3)^+.SO_4^{2-}.5H_2O$*

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Abstract. Morphine methyl iodide monohydrate: $M_r = 445\cdot3$, orthorhombic, $P2_12_12_1$, $a = 9\cdot574$ (1), $b = 10\cdot614$ (2), $c = 17\cdot549$ (4) Å, $V = 1783\cdot3$ (6) Å^3, $Z = 4$, $D_x = 1\cdot658$ g cm^{-3}, Mo $K\alpha$, $\lambda = 0\cdot71069$ Å, $\mu = 17\cdot95$ cm^{-1}, $F(000) = 896$, room temperature, final $R = 6\cdot1$% for 2575 reflections. Morphine methyl iodide displays methyl bonding to nitrogen and an extensive hydrogen-bonding network involving a phenolic hydrogen with an oxygen of the monohydrate. (Morphine)$_2$ H_2SO_4 pentahydrate; asymmetric unit $(C_{17}H_{19}NO_3)$-$\frac{1}{2}H_2SO_4.2\frac{1}{2}H_2O$, orthorhombic, $P22_12_1$, $M_r = 379\cdot4$, $a = 8\cdot463$ (3), $b = 6\cdot825$ (2), $c = 30\cdot71$ (1) Å, $V = 1774$ (1) Å^3, $Z = 4$, $D_x = 1\cdot420$ g cm^{-3}, Mo $K\alpha$, $\lambda = 0\cdot71069$ Å, $\mu = 1\cdot58$ cm^{-1}, $F(000) = 808$, room temperature, final $R = 6\cdot2$% for 1754 reflections. (Morphine)$_2H_2SO_4$ pentahydrate shows similar detail in the framework structure but the hydrogen bonding involves OH and NH hydrogen atoms and sulfate oxygen atoms.

Introduction. The molecular chirality of the opium alkaloids has been exploited in the development of analytical procedures for their determination using circular dichroism (CD) spectropolarimetry. Spectra have been obtained for morphine in three different matrices, namely pressed in KBr pellets (Bowen & Purdie, 1980), dissolved in cholesteric liquid crystals (Bowen, Crone, Hermann & Purdie, 1980) and in aqueous media (Crone & Purdie, 1981). The third is the only quantitative procedure.

The CD spectra of morphine free base and its salts are similar in all the supporting media except the solid state. In this matrix only the spectra of the salts bear a qualitative resemblance to the spectra observed in aqueous solution. Typically two Cotton bands are observed over the wavelength range 230–350 nm. These have been attributed to the electronic transitions ^1L_a (positive maximum at 248 nm) and ^1L_b (negative maximum at 286 nm). For the ^1L_b transition an inversion to a weak positive Cotton band is observed for morphine free base in a KBr pellet.

In order to interpret these obvious changes in chirality in the solid state, single-crystal X-ray structures have been determined at room temperature for morphine methyl iodide monohydrate (I) and (morphine)$_2H_2SO_4$ pentahydrate (II). These results may be compared with previously published data for morphine free base (Bye, 1976).

Experimental. Crystals of (I) and (II) [$0\cdot1 \times 0\cdot2 \times 0\cdot2$ (I); $0\cdot2 \times 0\cdot2 \times 0\cdot4$ (II)] sealed in a capillary and mounted on Syntex *P*3 automated diffractometer. Unit-cell dimensions determined by least-squares refinement of the best angular positions for 15 independent reflections ($2\theta > 15°$) during normal alignment procedures. Data sets [(I) 8044 points, h 0–12, k 0–12, l 0–17; (II) 4268 points h 0–15, k 0–15, l 0–20] collected using variable scan rate, θ–2θ scan mode and scan width 1·2° below $K\alpha_1$ and 1·2° above $K\alpha_2$ to max. 2θ of 116°. Backgrounds measured at each side of the scan for combined time equal to total scan time. Systematic absences (I) $h00$, $h \neq 2n$; $0k0$, $k \neq 2n$, $00l$, $l \neq 2n$; (II) $0k0$, $k \neq 2n$, $00l$, $l \neq 2n$. Intensities of three standard reflections remeasured after every 97 reflections, <8% variation, no corrections for decomposition. Data corrected for Lorentz, polarization and background effects. After removal of redundant and space-group forbidden data, 2575 (I), 1754 (II) reflections considered observed [$I > 3\cdot0\sigma(I)$]. Structures solved by direct methods using *MULTAN*80 (Main *et al.*, 1980). Refinement of scale factor, positional and anisotropic thermal parameters for all nonhydrogen atoms with *XRAY* (Stewart, 1978).

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* 17-Methylmorphinium iodide and di(17H^+-morphinium) sulfate.

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