

Chemistry of the Phenoxathiins and Isosterically Related Heterocycles.
 XIX. (1). The Crystal and Molecular Structure of 1-*N,N*-Dimethylamino-2,3-diazaphenoxathiin: An Interesting Product Isolated from the Reaction of *o*-Mercaptophenol with 3,4,5-Trichloropyridazine in *N,N*-Dimethylformamide

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Received April 30, 1981

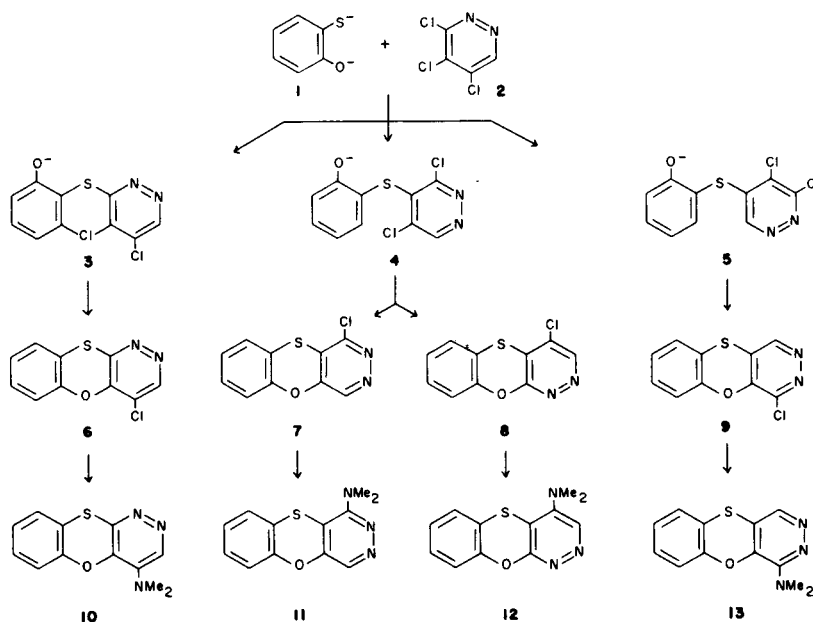
The isolation of 1-*N,N*-dimethylamino-2,3-diazaphenoxathiin and its molecular structure as determined by X-ray crystallography are described. The existence of a potential non-bonded interaction between the lone pair of electrons of the dimethylamino group nitrogen and sulfur atom are also discussed.

J. Heterocyclic Chem., **18**, 1173 (1981).

The interrelation between the ^{13}C -nmr chemical shifts of the sulfur bearing carbon ($\text{C}\alpha$) and the molecular dihedral angle in a series of phenoxathiin analogs has been recently described (3). In an extension of these studies, we have also recently reported the synthesis and structure of 1-methoxy-3,4-diazaphenoxathiin (4), the first investigation into the potential cumulation of effects due to annular substitution of a second nitrogen atom. In efforts to further understanding of the nucleophilic reactions undergone by the pyridazine system, we now report the results of our study of the reaction of 3,4,5-trichloropyridazine (1) with the disodium salt of *o*-mercaptophenol (2) in *N,N*-dimethylformamide. Rather interestingly, a *N,N*-dimethylamino diazaphenoxathiin was isolated as a byproduct of this reaction and forms the basis of this report.

Nucleophilic displacement of halogens from tri-substituted pyridazines has been investigated by several authors. Itai and Kamiya (5) have shown that treatment of 1 with one mole of sodium methoxide results exclusively in the formation of 5-methoxy-3,4-dichloropyridazine. Analogous results are obtained with 3,4,6-trichloropyridazine, the isolated product arising as a result of displacement of the 4-chloro substituent (6). In addition to these studies, it has also been shown in a sequential reaction (5) that 3,5-dimethoxy-4-chloropyridazine is formed on the reaction of 5-methoxy-3,4-dichloropyridazine with methoxide. In contrast, reaction of 1 with two moles of methoxide results in both the formation of 3,5-dimethoxy- and 4,5-dimethoxypyridazines (5). Based on these results, we thus anticipated that the initial attack

Scheme 1



of the thiophenolate anion would occur at the 5-position of **1** to afford **5** as the intermediate in this reaction (see Scheme I). The other reaction intermediates, **3** and **4**, were not considered to be probable, but could not be completely ruled out. Subsequent cyclization of **5** was anticipated to provide 4-chloro-2,3-diazaphenoxathiin (**9**) as the product of the reaction.

The reaction of **1** and **2** was conducted in freshly distilled dry *N,N*-dimethylformamide (DMF) as previously described (4,7) at room temperature, after which the reaction was brought to reflux to complete the cyclization of the intermediate phenolate sulfide, which was presumably **5** in this case. Examination of the mass spectrum of the crude reaction mixture isolate showed a relatively intense ion at $m/z = 245$ (45% relative intensity). Assuming a monosubstituted diazaphenoxathiin ring system, this mass was consistent with the presence of an *N,N*-dimethylamino group attached to the ring system rather than the anticipated chlorine atom. On this basis, we elected to isolate the compound and to unequivocally obtain a structure for the product. Similar products containing an *N,N*-dimethylamino group have been reported previously (7-11) in nucleophilic reactions in DMF where an activated halogen was present.

Following an acid extraction of the ethyl acetate solution of the crude reaction product, the solution was neutralized, back extracted with ethyl acetate and dried over sodium sulfate. The mass spectrum of the product thus isolated (Figure 1) gave the same ion at $m/z = 245$ (45%) which was presumed to be the parent ion and fragment ions at $m/z = 230$ (25%; $M^+ - CH_3$) and $m/z = 216$ (68%; $M^+ - NCH_3$) which were consistent with the proposed *N,N*-dimethylamino-diazaphenoxathiin structure.

The isolated crude material was chromatographed over silica gel and recrystallized from acetone:hexane to give 0.012 g of pale yellow crystals, mp 114-115°.

The structure of the dimethylamino compound isolated in the reaction was unequivocally shown to be the 1-*N,N*-dimethylamino-2,3-diazaphenoxathiin (**11**) from a single crystal X-ray diffraction study. Rather interestingly, the structure of the compound precludes the intermediacy of **5** in the reaction in the absence of a Smiles rearrangement. Instead, **11** must necessarily have been formed from **4** which can be envisioned to cyclize to give **7** followed by reaction with *N,N*-dimethylformamide to give the isolated product. Further studies into the precise nature of the reaction and its potential mechanism are at present underway and will be described in a future report.

Bond lengths and angles for **11** are shown in Figure 2 and 3 respectively. Final positional and thermal parameters for the non-hydrogen atoms are given in Table Ia, while data for the hydrogens are given in Table Ib. The diazaphenoxathiin nucleus was nearly planar with the exception of one of the methyl carbons of the dimethylamino group. Table II gives the least squares planes passing through (a) the fused three ring system, (b) the benzene ring and (c) the pyridazine ring, together with the deviations of the individual atoms from the calculated planes. The dihedral angle between the benzene and pyridazine rings of the molecule is 174.01°. In view of the ^{13}C -nmr chemical shift additivity associated with the annular nitrogens in the 2- and 3-positions, the observed dihedral angle is rather surprising as the chemical shift of the $C\alpha$ carbons of the unsubstituted parent 2,3-diazaphenoxathiin ring system is calculated to be $\delta^{13}C\alpha = 125.5$ (12), which would correspond to a dihedral angle $\phi = 152.2^\circ$ based

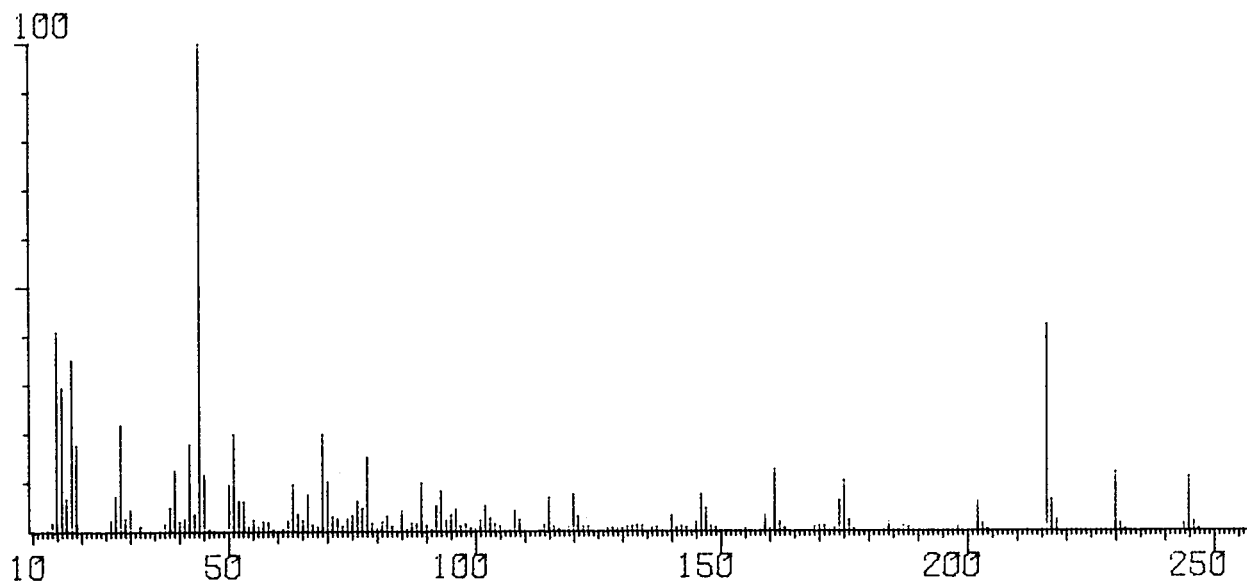


Figure 1. Low resolution mass spectrum of 1-*N,N*-dimethylamino-2,3-diazaphenoxathiin (**11**) at 70 eV.

Table I

(a) Final Positional and Thermal Parameters of Non-hydrogen Atoms. All U's are X10**.

Atom	X	Y	Z	U11	U22	U33	U12	U13	U23
S1	.4165(1)	.1218(0)	.5318(1)	46(0)	29(0)	68(0)	1(0)	-17(0)	-2(0)
C2	.6429(3)	.1119(2)	.7518(3)	59(1)	39(1)	57(1)	2(1)	-12(1)	3(1)
C3	.7497(3)	.1510(2)	.8580(3)	73(2)	52(1)	73(2)	1(1)	-29(1)	9(1)
C4	.7651(3)	.2582(2)	.8798(3)	62(1)	57(1)	61(2)	-12(1)	-21(1)	3(1)
C5	.6743(2)	.3256(2)	.7933(2)	52(1)	42(1)	50(1)	-9(1)	-5(1)	-1(1)
O6	.4842(2)	.3609(1)	.6052(2)	65(1)	32(1)	90(1)	-3(1)	-35(1)	-2(1)
C7	.3063(2)	.4187(2)	.4170(3)	60(1)	33(1)	54(1)	0(1)	-0(1)	2(1)
N8	.2004(2)	.4085(1)	.3052(2)	67(1)	40(1)	52(1)	5(1)	-5(1)	8(1)
N9	.1496(2)	.3121(1)	.2679(2)	52(1)	44(1)	42(1)	3(1)	-3(1)	7(1)
C10	.2083(2)	.2277(1)	.3412(2)	36(1)	40(1)	31(1)	-1(1)	6(1)	2(1)
C11	.5505(2)	.1784(2)	.6641(2)	35(1)	36(1)	38(1)	-1(1)	1(1)	-0(1)
C12	.5681(2)	.2858(2)	.6866(2)	40(1)	35(1)	44(1)	-1(1)	0(1)	3(1)
C13	.3731(2)	.3344(2)	.4961(2)	43(1)	34(1)	47(1)	1(1)	-2(1)	-1(1)
C14	.3278(2)	.2344(1)	.4572(2)	36(1)	31(1)	37(1)	0(1)	4(1)	2(1)
N15	.1532(2)	.1304(1)	.2934(2)	40(1)	43(1)	33(1)	-7(1)	-0(1)	2(1)
C16	.0508(3)	.1299(2)	.1531(3)	53(1)	62(2)	37(1)	-10(1)	-6(1)	0(1)
C17	.1097(3)	.0618(2)	.4058(3)	53(1)	52(1)	49(1)	-16(1)	1(1)	8(1)

*The anisotropic thermal parameters are of the form $\exp[-2\pi^2(U_{11}h^2a^{*2} + U_{22}k^2b^{*2} + U_{33}l^2c^{*2} + 2U_{12}hka^*b^* + 2U_{13}hla^*c^* + 2U_{23}kfb^*c^*)]$

(b) Final Positional and Thermal Parameters of Hydrogen. All U's are X10*

Atom	X	Y	Z	U
HC2	.633(3)	.039(2)	.738(3)	.062(7)
HC3	.806(3)	.105(2)	.915(3)	.081(7)
HC4	.840(3)	.291(2)	.956(3)	.079(7)
HC5	.681(3)	.401(2)	.806(3)	.068(11)
HC7	.339(2)	.488(2)	.441(3)	.062(12)
H1C16	-.034(3)	.163(2)	.166(3)	.059(9)
H2C16	.085(2)	.165(2)	.078(3)	.058(7)
H3C16	.029(3)	.058(2)	.122(3)	.062(9)
H1C17	.114(3)	-.010(3)	.377(3)	.095(8)
H2C17	.014(4)	.069(3)	.400(4)	.127(8)
H3C17	.157(3)	.072(2)	.505(3)	.079(7)

on regression analysis using the data from our recently reported communication (3). This calculation does not, however, incorporate the effects of the dimethylamino group on C α , and no convenient means at present exists for predicting this shift additivity. Furthermore, because of the very limited quantity of material available, there was no convenient means for obtaining the necessary decoupled and coupled spectra upon which to base an unequivocal ¹³C-nmr spectral assignment of 11.

A final point of particular interest was the orientation of the *N,N*-dimethylamino group relative to the sulfur atom. Specifically, the nitrogen atom is located 3.042(2) Å, from the sulfur atom, which is considerably less than the sum of the van der Waal's radii of 3.35 Å. The orientation of the nitrogen with respect to the S-C₁₁ bond (See Figure 2), which corresponds to an angle of 153.5° formed by atoms N---S---C₁₁, is consistent with the results of a study of non-bonded contacts with divalent sulfur made by Rosenfield,

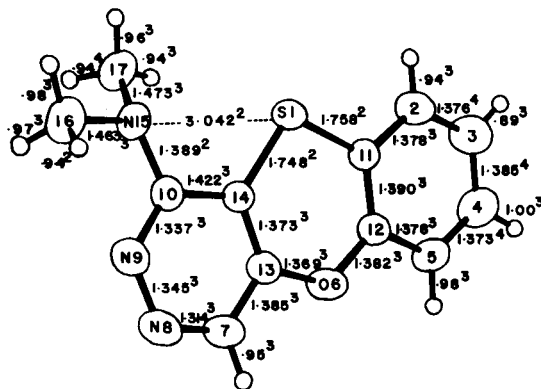
Figure 2. Bond lengths of 1-*N,N*-dimethylamino-2,3-diazaphenoxathiin.

Table II

Least Squares Planes and Deviations of Atoms from the Planes

(a) Plane defined by the fused three ring system

$$0.7349X - 0.0065Y - 0.6781Z + 0.9311 = 0$$

C ₂	0.054	C ₇	0.050	S ₁	0.029
C ₃	0.045	N ₈	0.105	O ₆	-0.040
C ₄	-0.014	N ₉	0.018	N ₁₅	-0.128
C ₅	-0.042	C ₁₀	-0.088	C ₁₆	0.161
C ₁₁	0.023	C ₁₃	-0.042	C ₁₇	-0.268
C ₁₂	-0.023	C ₁₄	-0.076		

(b) Plane defined by the benzene ring

$$0.7338X + 0.0299Y - 0.6787Z + 0.8322 = 0$$

C ₂	-0.002	C ₅	0.001	S ₁	-0.019
C ₃	0.005	C ₁₁	-0.001	O ₂	0.002
C ₄	-0.004	C ₁₂	0.002		

(c) Plane defined by the pyridazine ring

C ₇	-0.011	C ₁₀	-0.019	S ₁	0.247
N ₈	0.018	C ₁₃	-0.011	O ₆	0.003
N ₉	-0.002	C ₁₄	0.025	N ₁₅	0.005

Parthasarathy and Dunitz (13) in which it was found that nucleophiles tend to approach sulfur along the extension of one of the bonds to the sulfur. This suggests that the nitrogen atom is interacting with the LUMO of the sulfur, a σ^* (S-C₁₁) orbital.

Figure 4 is the stereopacking diagram viewed along the *c*-axis. The molecules pack in layers inclined slightly to the *ab* plane with no unusually close intermolecular contacts. Thus, it must be presumed that the control of the dihedral angle in this system is either by virtue of the chemical shift additivity due to the *N,N*-dimethylamino group at the 1-position, or in some fashion through the interaction between the sulfur and the dimethylamino group nitrogen.

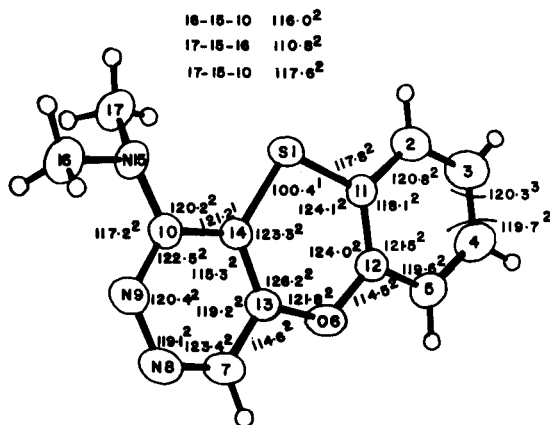


Figure 3. Bond angles of 1-*N,N*-dimethylamino-2,3-diazaphenoxathiin.

Further studies into the effects of this type of interaction in related systems have already been reported (12) and still other studies are at present underway in these laboratories.

X-Ray Data Collection and Structure Determination.

A crystal of the title compound, C₁₇H₁₁N₃OS (fw 245.32), having dimensions 0.30 × 0.35 × 0.40 mm was selected for investigation. Systematic absences were unique for the monoclinic space group P2₁/c. Unit cell dimensions, obtained by least squares refinement using Bragg angles (Mo, K α , $\lambda = 0.791069 \text{ \AA}$) of 27 reflections ($25^\circ < 2\theta < 30^\circ$) are: *a* = 9,891(3), *b* = 12,740(3), *c* = 9,092(6), $\beta = 101.46(3)^\circ$, *Z* = 4, volume = 1122.9 \AA^3 , $\rho(\text{calcd}) = 1.451 \text{ g cm}^{-3}$, $\mu = 2.91 \text{ cm}^{-1}$. Intensity data were collected at room temperature on a P2₁ Syntex diffractometer by the ω -scan mode utilizing Mo K α radiation monochromatized by a graphite crystal. Scans of 1.0° were used with scan rates which vary from 2.0 to $5.0^\circ \text{ min}^{-1}$ depending directly upon the number of counts obtained in a short preliminary count of the peak. Background counts were taken at both ends of the scan with ω displaced $\pm 1.0^\circ$ from the K α peak; the time of each background measurement was one-half the scan time. A total of 2579 unique reflections were measured in the range $4^\circ < 2\theta < 55^\circ$; 1971 reflections had intensities greater than $3\sigma(I)$. The intensities of four standard reflections, measured after every 96 reflections, showed no significant variation during data collection. Lorentz and polarization corrections were applied, but no absorption corrections were made. Standard deviations of the intensities, $\sigma(I)$, and of the structure amplitudes, $\sigma(F)$, were derived directly from counting statistics and an "ignorance factor" *p* of 0.040 (15).

The structure was solved by direct methods using MULTAN (16) to calculate phases for 200 $|E|$ values greater than 1.81. The E-map obtained from the phase set with the largest combined figure-of-merit, 2.00, revealed all the non-hydrogen atoms except for two carbon atoms of the phenyl ring. The 1791 observed reflections were used

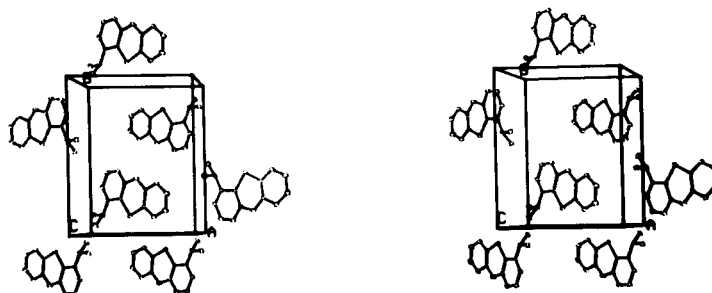
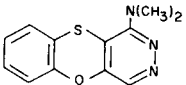
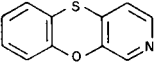
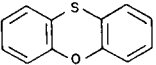
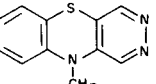
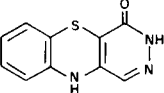
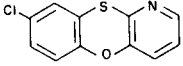
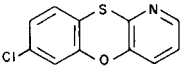


Figure 4. Stereo view of crystal packing of 1-*N,N*-dimethylamino-2,3-diazaphenoxathiin looking down the *c*-axis of the crystal lattice.

Table III

Comparison of some Structural Parameters of 1-*N,N*-Dimethylamino-2,3-diazaphenoxathiin and Related Compounds

Chemical Structure	C - S	C - O (N)	C - S - C	C - O(N) - C	Dihedral angle
	1.748(2) 1.758(2)	1.369(3) 1.382(3)	100.4(1)°	121.8(2)°	174.01°
 (20)	1.749(1) 1.764(1)	1.377(2) 1.389(2)	100.3(1)°	121.2(1)°	167.07°
 (21)	1.753(43) 1.751(43)	1.401(54) 1.386(52)	97.68(3)°	117.63(5)°	138.4°
 (22)	1.789(4) 1.763(4)	1.423(2) 1.408(3)	100.2(2)°	120.6(3)°	146.4°
 (23)	1.769(4)	1.394(4)	100.5(4)°	125.4(7)°	175.6°
 (24)	1.761(3)	1.385(2)	100.8(1)°	123.3(1)°	175.73°
 (24)	1.757(2)	1.370(3)	100.47(9)°	122.2(2)°	176.78°

for the full matrix least squares refinement of the structure, in which the function minimized was $\Sigma W(|F_o| - |F_c|)^2$ where $w = 1/\sigma^2(F_o)$. The initial refinement of non-hydrogen atoms using individual isotropic temperature factors resulted in a conventional $R = \Sigma ||F_o| - |F_c|| / \Sigma |F_o|$ of 0.179. Alternate Fourier maps and least-squares cycles yielded the coordinates of all hydrogen atoms. Refinement of non-hydrogen atoms with anisotropic temperature factors and hydrogen atoms with isotropic temperature factors was terminated at a conventional R of 0.039 and weighted R of 0.048 ($R_w = (\Sigma w(|F_o| - |F_c|)^2 / \Sigma w |F_o|^2)^{1/2}$). The hydrogen atoms refined normally with thermal parameters which ranged from 4.5 to 10.0 Å². All parameter shifts during the final cycle were less than 0.09σ and the largest peak in the final difference map was 0.17 e Å⁻³, located near the sulfur atom. The final atomic positional and thermal parameters are given in Table I. The atomic scattering factors for S, O, N, and C were those of Cromer and Waber (17) for H, the scattering factors of Stewart, Davidson, and Simpson (18) were used. Mathematical and computational details are noted elsewhere (19).

Supplementary Material Available.

A listing of the observed and calculated structure amplitudes from the final cycle of least-square refinement is available. Ordering information is given on any current masthead page.

Acknowledgement.

The authors would like to acknowledge the support of Merck, Sharp and Dohme through their University Grants Program, which supported the synthetic aspects of this work and one of the authors, S.H.S., would like to thank the Robert A. Welch Foundation which supported the crystallographic portion of this work through Grant No F-019. Lastly, the authors would also like to express their thanks to Cathy Meier for the preparation of this manuscript.

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account any interaction between the pyridazine nitrogens in these calculations. For a discussion of the possible nature of this effect, the interested reader is referred to a discussion of this point which is contained in reference 4.

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