

XV. (1) Synthesis of 1-Nitrophenoxathiin and the Relation of the  $^{13}\text{C}$ -Nmr Chemical Shift of the  $\alpha$ -Carbon to the Dihedral Angle

James C. Turley and Gary E. Martin\*

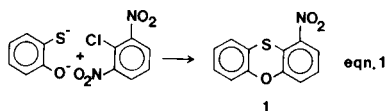
Department of Medicinal Chemistry and Pharmacognosy,  
College of Pharmacy, University of Houston, Houston, Texas 77004  
Received September 13, 1980

The synthesis of the previously unreported 1-nitrophenoxathiin is described. The  $^{13}\text{C}$ -nmr spectrum of the title compound is assigned based on chemical shift additivites and  $^1\text{H}$ - $^{13}\text{C}$  spin-coupling constants. From the observed  $^{13}\text{C}$ -nmr chemical shift of the  $\alpha$ -carbon the title compound was predicted to have a molecular dihedral angle,  $\varnothing = 143.3^\circ$ , based on a recently described interrelation between the  $\alpha$ -carbon  $^{13}\text{C}$ -nmr chemical shift and the dihedral angle. Independent measurement of the dihedral angle in a crystallographic study has shown that there are two independent molecules contained in the assymetric unit which possess dihedral angles,  $\varnothing = 145.7$  and  $163.4^\circ$ , the former in excellent agreement with the angle predicted by the assigned  $^{13}\text{C}$ -nmr data.

*J. Heterocyclic Chem.*, **18**, 431 (1981).

Since the initial synthesis of an analog of the phenoxathiin ring system by Mauthner (2), various nitro derivatives have been prepared both by direct condensation of suitable nitro-bearing precursors and by nitration of the parent phenoxathiin ring system (3). We have recently reported the synthesis and correction of the substitution pattern of 1,3-dinitrophenoxathiin through the use of  $^{13}\text{C}$ -nmr spectroscopy (4). During the course of this work, we observed that there was a significant interaction between the 1-nitro group and the sulfur atom which produced changes in the  $^{13}\text{C}$ -nmr chemical shifts of the molecule analogous to those observed for 9-nitro-1-azaphenoxathiin (5). More recently, we have also reported the interrelation between the  $^{13}\text{C}$ -nmr chemical shift of the  $\alpha$  carbon in a series of phenoxathiin analogs and the molecular dihedral angles as determined by single crystal X-ray diffraction studies (6). In an extension of this work, we now report the synthesis of 1-nitrophenoxathiin, the assignment of the  $^{13}\text{C}$ -nmr spectrum of this compound and the correlation of the  $\alpha$  carbon chemical shift with the crystallographically determined dihedral angle.

The synthesis of 1-nitrophenoxathiin was conducted by the condensation of the disodium salt of *o*-mercaptophenol with chloro-2,6-dinitrobenzene to afford the desired product as shown in equation 1. Since there have been no observations of Smiles rearrangements in the synthesis of numerous highly similar systems (7-10), the occurrence of such a reaction, which would lead to the ultimate formation of 4-nitrophenoxathiin, was not considered a viable possibility in this case.

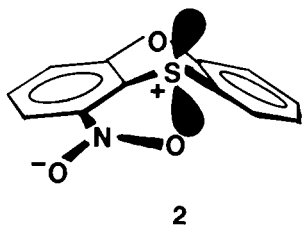


Calculated  $^{13}\text{C}$ -nmr chemical shifts for **1** were obtained by incrementation of the  $^{13}\text{C}$ -nmr chemical shifts of phenoxathiin (11) for the substitution of a nitro group (12) at the 1-position. The interaction of the nitro group with the sulfur atom and its consequent effect on the  $^{13}\text{C}$ -nmr spectrum of **1** was also taken into account as was previously described for 9-nitro-1-azaphenoxathiin (5). Assignment of the spectrum was based on correlation of the calculated *vs.* the observed  $^{13}\text{C}$ -nmr spectrum.

From the outset of this study, based on previous work it was quite logical to assume that **1**, as a result of the sulfur-nitro group interaction, would assume a pseudo-tetracyclic character as shown by **2**. A facet of this study which could not however be predicted at the outset was the effect of the sulfur-nitro interaction on the molecular dihedral angle. While the 1-azaphenoxathiins are essentially planar (13), with the dihedral angle being largely controlled by the annular aza-substituent (6), there was no over-riding influence to prevent the sulfur-nitro interaction from markedly altering the shape of the system. However, based on the observed  $^{13}\text{C}$ -nmr chemical shift,  $\delta^{13}\text{C}\alpha = 120.38$ , we calculate, using regression analysis and the data previously reported (6), a dihedral angle  $\theta = 143.3^\circ$  for **1**, indicating that the sulfur-nitro interaction has only a minor effect on the dihedral angle. For comparison, phenoxathiin (14) possesses a dihedral angle of  $\theta = 138.0^\circ$ . Confirmation of this conclusion was provided by an X-ray crystal structure of **1** which showed two independent molecules in the unit cell possessing dihedral angles,  $\theta = 145.7^\circ$  and  $163.4^\circ$  at  $-130^\circ$  (15).

It should also be noted that in the crystal, the more folded molecule ( $\theta = 145.7^\circ$ ) exhibits a weak sulfur-nitro group interaction, the absence of which may account for the relatively small difference between the dihedral angles of **1** and the parent phenoxathiin system. In contrast, the

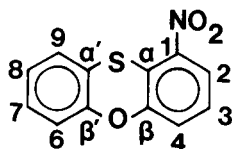
more flattened molecule exhibits a much stronger sulfur-nitro interaction. In conclusion, while the  $^{13}\text{C}$ -nmr data is in accord with the dihedral angle of the former, no readily apparent explanation is available to account for the second molecule observed in the crystal.



2

Table I

Calculated vs.  $^{13}\text{C}$ -Nmr Chemical Shifts for  
1-Nitrophenoxathiin (I) in Hexadeuteriodimethyl Sulfoxide at 33°



1

Carbon	$\delta$ $^{13}\text{C}$ Calculated	$\delta$ $^{13}\text{C}$ Observed	$\Delta\delta$ (a)
$\alpha$	122.1 (b)	120.38	-1.7
$\beta$	152.8	151.76	-1.0
$\alpha'$	119.9	117.95	-1.9
$\beta'$	151.9	150.89	-1.0
1	147.4	144.98	-2.4
2	119.9	121.49	+1.6
3	127.4	127.61	+0.2
4	123.3	123.10	-0.2
6	117.5	117.36	-0.1
7	126.5	126.88	+0.4
8	124.4	125.42	+1.2
9	127.4	129.11	+1.7

(a) Positive values denote a downfield shift of the observed resonance relative to the calculated chemical shift. (b) The calculated chemical shift of this resonance was adjusted for the sulfur-nitro interaction as previously described (5).

## EXPERIMENTAL

All  $^{13}\text{C}$ -nmr spectra were obtained on a Varian XL-100-15 spectrometer operating at 25.2 MHz in the Fourier transform mode and Equipped with a Nicolet TT-100 data system, a TT-760 decoupler and an NT-440 frequency synthesizer. Typical instrument parameters were as follows: spectral width, 5 KHz; pulse width 8.0  $\mu\text{s}$  (38° tip angle); interpulse delay, 4.0 seconds; acquisition time, 0.8192 seconds (4K decoupled spectrum) or 1.6834 seconds (8K coupled spectrum). All infrared spectra were obtained as potassium bromide pellets on a Perkin-Elmer model 283 spectrophotometer and mass spectra were obtained by direct probe insertion with a source temperature of 250° and an ionizing voltage of 70 eV in a Hewlett-Packard Model 5930 GC/MS system equipped with a Model 5933 data system. Melting points were obtained in open capillaries in a Thomas-Hoover melting point apparatus and are

uncorrected. Elemental analyses were performed by Micro-Analysis, Atlanta, Ga.

## Synthesis of 1-Nitrophenoxathiin (I).

Chloro-2,6-dinitrobenzene (1.0 g., 0.0049 mole) was dissolved in 30 ml. of dry distilled *N,N*-dimethylformamide under a dry argon purge. To this solution was then added the disodium salt of *o*-mercaptophenol (0.833 g., 0.0049 mole), which was prepared by the procedure of Turley and Martin (4). The reaction mixture was then allowed to stir at room temperature for 4 hours after which it was brought to reflux overnight. The reaction mixture was then quenched with distilled water and the resultant semi-crystalline residue collected by Buchner filtration. The reddish semi-crystalline material was then dissolved in chloroform, washed with distilled water to remove any remaining DMF and dried over anhydrous sodium sulfate. The dried solution was concentrated to yield 0.335 g. (27.5% yield) of I as reddish orange crystals, m.p. 125.5-127°. The infrared spectrum of I showed absorptions ( $\text{cm}^{-1}$ ): 1610, 1590, 1515, 1475, 1440, 1335, 1300, 1290, 810, 795, 757 and 732. The mass spectrum showed a parent ion,  $\text{M}^+$ , at  $m/z = 245$  (54%) and a characteristic ion for  $\text{M}^+ - \text{NO}_2$  at  $m/z = 199$  (22%). The  $^1\text{H}$ -nmr showed resonance at  $\delta = 8.11$ , dd, 1H,  $J = 5.9, 3.8$  Hz, H2 and a complex multiplet centered at approximately 7.4 and integrating for the remaining six protons.

Anal. Calcd. for  $\text{C}_{12}\text{H}_7\text{NO}_3\text{S}$ : C, 58.78; H, 2.86; N, 5.71. Found: C, 58.50; H, 2.92; N, 5.58.

## Acknowledgment.

The authors would like to acknowledge the assistance of the University of Houston Research Grants Program, which was served as a stimulus for the present work through Grant K-94 to JCT. We would also like to express our sincere thanks to Laurie Battarbee for the preparation of this manuscript.

## REFERENCES AND NOTES

- (1) For the previous paper in this series, see R. T. Gampe, Jr., G. E. Martin, A. C. Pinto and R. A. Hollins, Chemistry of the Phenoxathiins and Isosterically Related Heterocycles. XIV, *J. Heterocyclic Chem.*, **18**, 155 (1981).
- (2) F. Mauthner, *Chem. Ber.*, **38**, 1411 (1905).
- (3) The interested reader is referred to the review of D. S. Breslow and H. Skolnik, "Multi-Sulfur and Sulfur and Oxygen Five and Six-Membered Heterocycles", Part II, Wiley-Interscience, New York, N.Y., 1966, pp. 864-997.
- (4) J. C. Turley and G. E. Martin, *Spec. Letters*, **11**, 681 (1978).
- (5) G. E. Martin and J. C. Turley, *J. Heterocyclic Chem.*, **15**, 609 (1978).
- (6) S. R. Caldwell, J. C. Turley and G. E. Martin, *ibid.*, **17**, 1145 (1980).
- (7) G. E. Martin, J. C. Turley and L. Williams, *ibid.*, **14**, 1249 (1977).
- (8) G. E. Martin, J. C. Turley, L. Williams, M. L. Steenberg and J. P. Buckley, *ibid.*, **14**, 1069 (1977).
- (9) S. R. Caldwell and G. E. Martin, *ibid.*, **17**, 989 (1980).
- (10) S. R. Caldwell, J. C. Turley and G. E. Martin, *ibid.*, **17**, 1153 (1980).
- (11) L. R. Isenbrand, R. K. Jensen and L. Petrakis, *J. Magn. Reson.*, **12**, 143 (1973).
- (12) F. W. Wehrli and T. Wirthlin, "Interpretation of Carbon-13 NMR Spectra," Heyden, New York, N.Y., 1976, p. 37.
- (13) G. E. Martin, J. C. Turley, J. D. Korp and I. Bernal, *J. Heterocyclic Chem.*, **15**, 721 (1978).
- (14) S. Hosoya, *Acta Crystallogr.*, **20**, 429 (1966).
- (15) M. B. Hossain, C. A. Dwiggin, D. van der Helm, P. K. Sen Gupta, J. C. Turley and G. E. Martin, *ibid.*, submitted.