# Chemistry of the Phenoxathiins and Isosterically Related Heterocycles. IX. (1) The Effects of *N*-Oxidation on the $^{13}$C-Nmr Chemical Shifts and Coupling Constants of the 1-Azaphenoxathiin System



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Received September 17, 1979

The synthesis of 1-azaphenoxathiin *N*-oxide is described. Total assignment of the $^{13}$C-nmr spectrum and the effects of the *N*-oxide moiety on the chemical shifts and $^{1}$H-$^{13}$C spin couplings constants are described and compared to the parent 1-azaphenoxathiin system. The potential for the use of *N*-oxidation induced changes in $^{13}$C-nmr chemical shifts and $^{1}$H-$^{13}$C coupling constants as an assignment criterion is also discussed.

*J. Heterocyclic Chem.*, 17, 429 (1980).

The synthesis, $^{13}$C-nmr chemical shift assignment (2) and the $^{1}$H-$^{13}$C spin-coupling constants (2,3) of the 1-azaphenoxathiin ring system have been reported. $^{13}$C-nmr chemical shift assignments for several substituted 1-azaphenoxathiin derivatives have also been reported (4-6). Two assumptions are implicit in this work: first, that all resonances of the parent heterocycle have been assigned correctly; second, that the additivity constants routinely used for benzenoid systems and simple pyridines are equally as applicable to tricyclic systems containing heteroatoms bridging benzene and pyridine rings. To examine the $^{13}$C-nmr signal assignments of the parent ring system (2) more rigorously and to further evaluate the utility of additivity parameter considerations, we now report the synthesis of 1-azaphenoxathiin *N*-oxide (**5**), and the assignment and comparison of its $^{13}$C-nmr chemical shifts and $^{1}$H-$^{13}$C spin-coupling constants with the data previously reported for 1-azaphenoxathiin (2,3).

The synthesis of **5** was conducted by initial preparation of 2,3-dichloropyridine *N*-oxide (**2**) according to the general procedure of Talik and Talik (7). Following isolation, **2** was reacted immediately without further purification with the disodium salt of *o*-mercaptophenol (**3**) (8). The initial phase of the condensation was conducted at room temperature under an argon atmosphere. It is presumed that the reaction proceeded *via* the phenolate sulfide intermediate **4** based on previous studies (2,4). Completion of the condensation was carried out by refluxing overnight followed by a normal isolation (4).

Unequivocal confirmation of the identity of the product of this reaction as **5** was obtained by $^{13}$C-nmr spectroscopy. Empirical calculation of the $^{13}$C-nmr chemical shifts of **5** was based on the assigned spectrum of 1-azaphenoxathiin (2) incremented with the additivity parameters for pyridine *N*-oxide (9). (See Table I)

It should also be noted, however, that a second isomeric ring system could also have formed during the reaction. Because of the well known alteration of susceptibility to nucleophilic displacement on *N*-oxidation, the possibility of initial nucleophilic attack at the 3-position of **2** could not be completely eliminated. (See Scheme I, Pathway B) Cyclization of this intermediate phenolate sulfide **6** would be expected to result in the formation of the as yet unknown 4-azaphenoxathiin *N*-oxide (**7**). $^{13}$C-nmr chemical shifts were calculated for **7**, for discriminatory purposes, from phenoxathiin (11) incremented for the replacement of the carbon atom at the 4-position by an annular nitrogen (2,12) and then for *N*-oxidation (9). Discrimination between the two isomeric systems was based largely on the comparison of the observed chemical shifts of the non-protonated resonances with the calculated shifts of **5** and **7** shown in Table I.

The chemical shifts of the $\beta$ and $\beta'$ carbons, observed at $\delta$ = 148.99 and 148.12 respectively, are clearly in much better accord with the calculated shifts of these carbons in **5** than for **7**, which would require the $\beta$ resonance to be in

SCHEME I

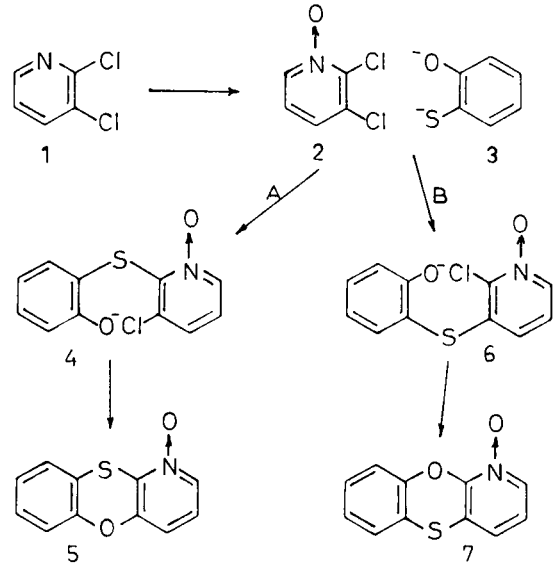


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Table I

Calculated *vs.* Observed Chemical Shifts of 1-Azaphenoxathiin *N*-Oxide (**5**) and Calculated Chemical Shifts of 4-Azaphenoxathiin *N*-Oxide (**7**).

| | $\alpha$ | $\beta$ | $\alpha'$ | $\beta'$ | 1 | 2 | 3 | 4 | 6 | 7 | 8 | 9 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Calcd. **5** | 132.2 | 149.9 | 119.0 | 150.0 | — | 133.4 | 124.2 | 114.0 | 117.4 | 126.9 | 123.6 | 127.7 |
| Obs. **5** | 136.04 | 148.99 | 116.05 | 148.12 | — | 133.90 | 125.16(a) | 113.04 | 117.41 | 127.35 | 121.09(a) | 128.56 |
| *N*-oxidation additivities | +3.8 | +1.1 | −3.0 | −1.9 | — | +0.5 | +1.0 | −1.0 | 0.0 | +0.5 | +2.5 | +0.9 |
| Pyridine *N*-oxide additivity | -11.9 | +2.0 | — | — | — | -11.3 | +2.0 | -10.7 | — | — | — | — |
| Calcd. **7** | 115.1 | 172.9 | 119.0 | 150.0 | 134.6 | 118.8 | 147.9 | — | 117.4 | 126.9 | 123.6 | 127.7 |

(a) Resonances may be permuted.

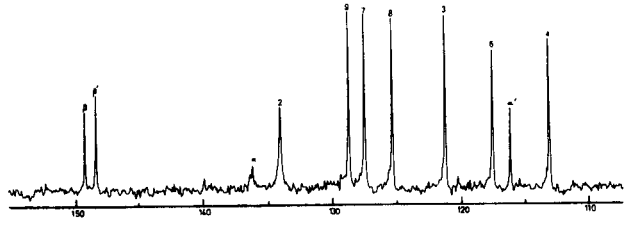

Figure 1. 25.2 MHz $^{13}$C-nmr spectrum of the aromatic region of **5** in deuteriochloroform.

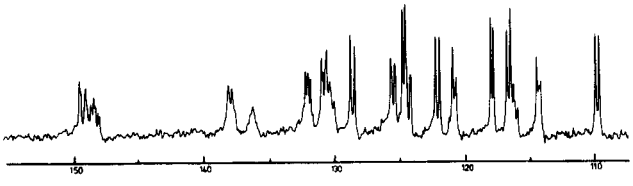

Figure 2. 25.2 MHz $^{13}$C-nmr spectrum of the aromatic region of **5** with full $^{1}$H-$^{13}$C spinspin coupling acquired under gated decoupling conditions.

the vicinity of $\delta$ = 172.9. A second discriminatory feature was the observed chemical shifts of the $\alpha$ and $\alpha'$ carbons. From Table I, the key feature of this pair of non-protonated resonances is the downfield shift predicted for $\alpha$ ($\delta$ = 132.2) in **5** while for **7** both the $\alpha$ and $\alpha'$ resonances would be located upfiled at $\delta$ = 115.1 and 119.0 respectively.

A final pair of key resonances utilized as discriminatory features were the anticipated chemical shifts at C-4 and C-6 for **5** at $\delta$ = 114.0 and 117.4 respectively. Resonances observed at $\delta$ = 113.04 and 117.41 were clearly assignable to the 4 and 6-positions based on the arguments developed above for the non-protonated resonances.

Assignment of the remaining resonances was straight forward with the exception of the resonances at $\delta$ = 121.09 and 125.16 which would be assigned to C-3 or C-8. Final assignment was made with the resonance observed at $\delta$ = 125.16 assigned to C-3 based on the resultant calculated *N*-oxidation additivity of +3.0 ppm (13) which is consistant with the additivity increment observed for pyridine *N*-oxide (9). Had the resonance at $\delta$ = 121.09 been assigned to C-3, the additivity calculated would be −0.9 ppm which is totally inconsistant with previously reported behavior (9,14).

Proton-coupled $^{13}$C-nmr spectra were also acquired using the gated decoupling technique of Freeman and Hill (15). Comparison of the coupling patterns for the $\beta$ and $\beta'$ resonances readily allowed the assignment of $\beta$ as the downfield of the two resonances. This assignment is based on the recognition of the importance of the three bond couplings ($^{3}J_{CH}$). Thus, C$\beta$ has only one three bond coupling possible $^{3}J_{C\beta H3}$ = 11.73 Hz (Table II) while C$\beta'$ has two. Further, it should also be noted that the magnitude of this coupling is significantly larger than the corresponding coupling (8.6 Hz) observed for the parent 1-azaphenoxathiin system (2).

Coupling at C$\beta'$ was also observed to be substantially more complex in **5** than in the parent 1-azaphenoxathiin system (2). Both three bond couplings, $^{3}J_{C\beta'H7}$ and $^{3}J_{C\beta'H9}$, were observable and had different relative magnitudes which are tentatively assigned values of 12.53 and 9.09 Hz respectively. The assignment of the larger coupling to $^{3}J_{C\beta'H7}$ is based on the observed coupling $^{3}J_{C\beta'H3}$ discussed above. A third and smaller coupling, $^{2}J_{C\beta'H6}$ = 2.60 Hz was also observed for the $\beta'$ resonance. The overall coupling behavior observable for $\beta'$ was more reminiscent of the corresponding resonance in the 1,3-dinitrophenoxathiin (7) than the corresponding resonance for 1-azaphenoxathiin (2).

Considerable differences in the coupling behavior of the C$_\alpha$-resonance was also observed between **5** and the parent ring system. Thus, although the $\alpha'$ resonance showed a well resolved doublet of doublets (dd) arising as a result of the $^{3}J_{C\alpha'H6}$ and $^{3}J_{C\alpha'H8}$ spin couplings, the proton coupled resonance for the former was severely broadened and not at all well resolved. While a rigorously definitive explanation cannot presently be offered, it is suggested that the *N*-oxidation substantially decreases the effectiveness of the $^{14}$N-$^{13}$C dipolar relaxation process (16). A consequence anticipated for this behavior would be a greater susceptability to $^{14}$N-quadrupolar line broadening

Table II

$^{1}H$-$^{13}C$ Spin-coupling Constants of 1-Azaphenoxathiin *N*-Oxide (**5**).

| Resonance | Coupling (Hz) $^{1}J_{CH}$ | $^{2}J_{CH}$ | $^{3}J_{CH}$ |
|---|---|---|---|
| $\alpha$ | — | — | —(a) |
| $\beta$ | — | $^{2}J_{C_\beta H_4}$ = 2.70 | $^{3}J_{C_\beta H_3}$ = 11.73 |
| $\alpha'$ | — | — | $^{3}J_{C_{\alpha'} H_6}$ = 7.82 |
| | | | $^{3}J_{C_{\alpha'} H_8}$ = 5.46 |
| $\beta'$ | — | $^{2}J_{C_{\beta'} H_6}$ = 2.60 | $^{3}J_{C_{\beta'} H_7}$ = 12.53 |
| | | | $^{3}J_{C_{\beta'} H_9}$ = 9.09 |
| 2 | $^{1}J_{C_2H_2}$ = 195.27 | — | $^{3}J_{C_2H_4}$ = 7.84 |
| 3 | $^{1}J_{C_3H_3}$ = 164.29 | $^{2}J_{C_3H_2}$ = 7.89 | — |
| 4 | $^{1}J_{C_4H_4}$ = 171.23 | — | $^{3}J_{C_4H_2}$ = 7.08 |
| 6 | $^{1}J_{C_6H_6}$ = 162.28 | — | $^{3}J_{C_6H_8}$ = 6.53 |
| 7 | $^{1}J_{C_7H_7}$ = 162.20 | $^{2}J_{C_7H_6}$ = 1.99 | $^{3}J_{C_7H_9}$ = 7.80 |
| 8 | $^{1}J_{C_8H_8}$ = 164.29 | — | $^{3}J_{C_8H_6}$ = 7.89 |
| 9 | $^{1}J_{C_9H_9}$ = 163.84 | $^{2}J_{C_8H_8}$ = 1.86 | $^{3}J_{C_9H_7}$ = 7.68 |

(a) $^{3}J_{CH}$ couplings were not observed due to $^{14}N$ quadrupolar broadening.

thereby accounting for the observed behavior for this resonance.

Heteronuclear spin-couplings associated with the 2- and 4-positions of **5** were also significantly altered by *N*-oxidation. While the one bond coupling, $^{1}J_{C_2H_2}$, was observed to be 180.9 Hz for 1-azaphenoxathiin (2), which is good agreement with that observed for the corresponding coupling of pyridine (17), the same coupling in **5** was 195.27 Hz. Similarly, there was also an increase in the magnitude of the one bond coupling, $^{1}J_{C_4H_4}$ at the 4-position from 163.7 Hz to 171.23 Hz. In direct contrast, the three bond couplings for these positions, $^{3}J_{C_2H_4}$ = 7.84 and $^{3}J_{C_4H_2}$ = 7.08, were essentially unchanged from the couplings observed for the 1-azaphenoxathiin system of 7.3 Hz and 8.4 Hz respectively. Spin-coupling behavior was also substantially unaltered at the 3-position of **5**. Based on these observations, it is suggested that *N*-oxidation, through its predictable effects on chemical shift and the observed effects on coupling constants, might serve as a useful assignment criterion for the $^{13}C$-nmr spectra of complex heteroaromatic systems, particularly when used in conjunction with selective excitation techniques (3,8,18,19). Further studies on the effects of *N*-oxidation on relaxation phenomena and the application of the modulatory effects of *N*-oxidation on heteronuclear spin-coupling constants as an assignment criterion are presently underway in these laboratories. Results of these studies will be forthcoming.

## EXPERIMENTAL

Melting points were determined in open capillary tubes on a Thomas-Hoover melting point apparatus and are reported uncorrected. Infra-red spectra were obtained on a Perkin-Elmer Model 283 spectrophotometer as potassium bromide pellets. $^{1}H$-nmr spectra were recorded in deuteriochloroform on a Varian Associates Model XL-100 spectrometer operating at 100.060 MHz in the Fourier transform mode. The spectrometer was equipped with a Nicolet TT-100 data system and a Model NT-440 frequency synthesizer. Typical instrument parameters for $^{1}H$-spectral acquisition were: pulse width = 10 μsec; pulse delay, 1.00 sec; acquisition time 6.82393 sec; sweep width 1200 Hz; apodization = −0.1 sec; data size = 8K data points. $^{13}C$-nmr spectra were recorded in deuteriochloroform on the same spectrometer system at 25.158 MHz in the pulsed Fourier transform mode. Additional instrumentation in the form of a TT-760 decoupler set at 100.061400 MHz with a power level of 15 watts was also employed for these experiments. Typical instrument parameters were: pulse width 6.0 μsec (30°); pulse delay = 5.0 sec; acquisition time = 0.8192 sec; sweep width 5 KHz; apodization = 1.0 sec; data size = 4K data points/decoupled, 8K data points/coupled.

Synthesis of 1-Azaphenoxathiin *N*-Oxide (**5**).

To 2.00 g. (0.0136 mole) of 2,3-dichloropyridine dissolved in 10 ml. of acetic anhydride at 0° was slowly added 10 ml. of 30% hydrogen peroxide over a period of 30 minutes, according to the general procedure of Talik and Talik (7). The ice bath was then removed and the reaction stirred at room temperature for 5 hours, followed by stirring at 60-65° for an additional 30 hours. After allowing the reaction mixture to cool, 10 ml. of distilled water was added and the solvent mixture removed under reduced pressure to give a reddish orange crystalline material which was dissolved without further characterization or purification in 25 ml. of anhydrous *N,N*-dimethylformamide. The reaction mixture was purged with dry argon for 30 minutes after which 2.31 g. (0.0136 mole) of the disodium salt of *o*-mercaptophenol (8) was added. Darkening of the solution occurred immediately after addition. The reaction mixture was stirred at room temperature for 4 hours and then at reflux overnight. After

cooling, the dark reaction mixture was poured into 100 ml. of cold distilled water and then extracted with 3 × 50 ml. portions of ethyl acetate. The ethyl acetate fractions were combined, dried over anhydrous sodium sulfate and then concentrated under reduced pressure. Crystallization occurred and a reddish brown needle-like crystalline material was isolated, 0.407 g. (14% yield), m.p. 183-184°; ms: M+ (% relative intensity) 217 (100), 218 (14.27), 219 (6.58), 201 (30.35), 169 (19.42), 157 (9.54), 108 (12.89); $^1$H-nmr (deuteriochloroform): $\delta$ $H_2$ = 7.85 ($J_{H_2H_3}$ = 6.3 Hz, $J_{H_2H_4}$ = 1.2 Hz); $\delta$ $H_3$ = 6.87 ($J_{H_3H_2}$ = 6.3 Hz, $J_{H_3H_4}$ = 8.4 Hz); $\delta$ $H_4$ = 6.70 ($J_{H_4H_3}$ = 8.4 Hz, $J_{H_4H_2}$ = 1.2 Hz); $\delta$ = 6.99 (4H, m); $^{13}$C-nmr see Tables I and II also Figures I and II.

*Anal.* Calcd. for $C_{11}H_7NO_2S$: C, 60.83; H, 3.23; N, 6.45. Found: C, 60.97; H, 3.51; N, 6.39.

Acknowledgement.

The author would like to express his thanks to Bonnie Copeland for the preparation of this manuscript.

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(13) *N*-Oxidation additivites were calculated from the observed shift between 1-azaphenoxathiin and the observed data for 1-azaphenoxathiin *N*-oxide. Downfield shifts are denoted (relative to 1-azaphenoxathiin) as (+) while upfield shifts are denoted (−).

(14) Although magnitudes of additivities varied with the nature of the substituent on either 2- or 3-substituted pyridine *N*-oxides reported in reference 9, there were, none-the-less, no additivities reported for the 5-position which is equivalent to the 3-position of the 1-azaphenoxathiin system which were upfield. On this basis, the assignment is made and serves as further confirmatory evidence for the correct assignment of the resonances of the parent 1-azaphenoxathiin ring system made in reference 2.

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