Chemistry of the Phenoxathiins and Isosterically Related Heterocycles. XI (1). The Synthesis and ^{13}C-NMR Spectroscopy of 2-Azaphenoxathiin

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The synthesis of the 2-azaphenoxathiin ring system *via* the intermediary 2-azaphenoxathiin 2-oxide is described. Complete assignment of the ^{13}C-nmr spectrum is reported, based on the observed heteronuclear ^{1}H-^{13}C spin-couplings of the system and calculated chemical shifts as assignment criteria. The possible relation of the chemical shift of Cα to the dehidral angle of the system is also discussed.

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We have described the synthesis and ^{13}C-nmr spectroscopy of the 1-azaphenoxathiin ring system (4,5) as well as several benzo-substituted analogs as (6-9) potential CNS active agents. Although originally intended to have spatial conformations similar to the psychoactive phenothiazines, subsequent studies have shown several 1-azaphenoxathiin analogs to be essentially planar (8), in direct contrast to the phenoxathiin parent ring system (10). More recently we have also shown that a direct correlation exists betwen the ^{13}C-nmr chemical shift of the sulfur bearing carbon on the pyrido-portion of the molecule and the dihedral angle of the system (11). We have thus been interested in the synthesis of additional members of this interesting group of ring systems and now report the synthesis and ^{13}C-nmr spectroscopy of 2-azaphenoxathiin (**6**).

Synthetic elaboration of the 2-azaphenoxathiin ring system (**6**) was achieved by the preliminary synthesis of 3-chloro-4-nitropyridine 1-oxide (**3**) using a modification of the procedure of Talik and Talik (12). Condensation of **3** with the disodium salt of *o*-mercaptophenol prepared according to the procedure of Turley and Martin (13), afforded the intermediate phenolate sulfide (**4**) which was cyclized by bringing the system to reflux, yielding **5**. Reduction of the *N*-oxide function with phosphorus trichloride in refluxing chloroform according to the procedure of Ochiai (14) gave the desired 2-azaphenoxathiin system (**6**), as shown in Scheme I.

Examination of **6** by ^{1}H-nmr clearly showed the H1 and H3 protons flanking the annular nitrogen as well as H4, while in contrast the four benzenoid protons gave rise to a complex multiplet (Figure 1). The decoupled 25.2 MHz ^{13}C-nmr spectrum of **6** was clearly resolved (Figure 2) with

Scheme I

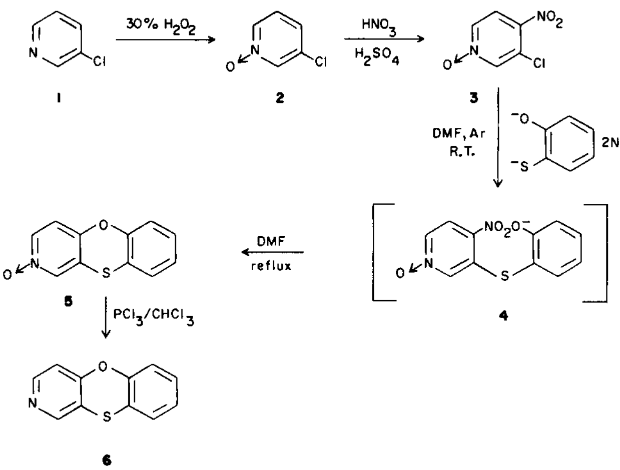
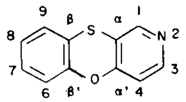


Table I

Calculated *vs.* Observed 25.2 MHz ^{13}C-Nmr Chemical Shifts for 2-Azaphenoxathiin (**6**) in Deuteriochloroform



	Resonance										
	1	3	4	6	7	8	9	α	α'	β	β'
δ ^{13}C Calcd.	149.3	147.2	112.5	117.9	127.1	125.3	128.0	114.6	120.5	158.1	150.3
δ ^{13}C Obs.	148.71	146.53	112.32	117.60	126.81	125.16	127.84	117.25 (a)	117.25 (a)	158.02	149.87
$\Delta\delta$	−2.8	+1.5	−0.2	−0.3	−0.3	−0.1	−0.2	+2.6	−3.3	0.0	−0.4

(a) Degenerate resonances.

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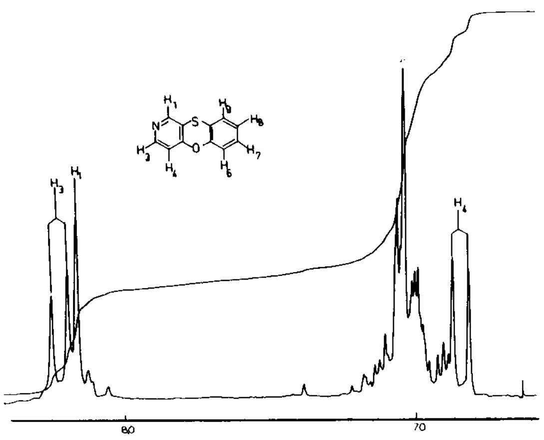

Figure 1. 100 MHz ^{1}H-nmr spectrum of 2-azaphenoxathiin (**6**) in deuteriochloroform.

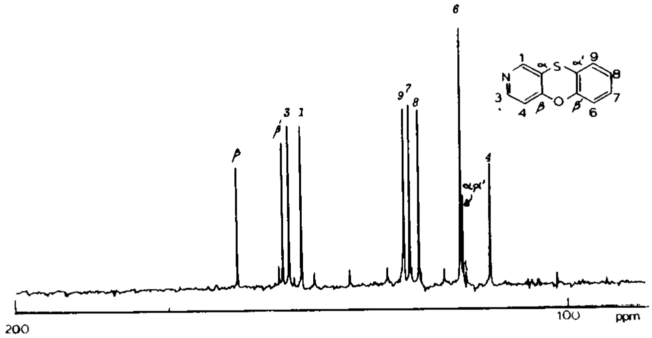

Figure 2. 25.2 MHz ^{13}C-nmr spectrum of 2-azaphenoxathiin (**6**) in deuteriochloroform under full decoupling.

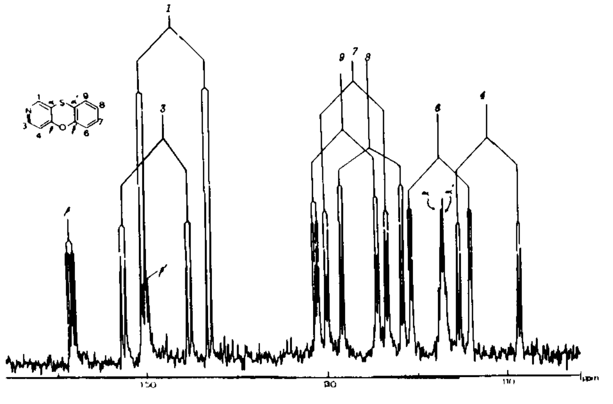

Figure 3. 25.2 MHz ^{13}C-nmr spectrum of 2-azaphenoxathiin (**6**) in deuteriochloroform with gated decoupling.

the exception of the Cα and Cα' resonances which were nearly degenerate with the C6 resonance. Assignment of this spectrum was based on a comparison of the calculated *vs.* observed ^{13}C-chemical shifts and the coupling constant behavior. Chemical shifts were calculated by incrementation of the ^{13}C-nmr chemical shifts of phenoxathiin (15) with additivities for annular nitrogen insertion as was previously described in the total assignment of the 1-azaphenoxathiin ^{13}C-spectrum (4) (Table 1).

Confirmatory discrimination between the resonances for C1 and C3, shown in Figure 2, was based on the consideration of the heteronuclear spin-coupling constants for these two resonances in the Overhauser enhanced spec-

Table II

^{1}H-^{13}C Spin Coupling Constants For 2-Azaphenoxathiin (**6**)

Resonance	$^1J_{CH}$	Coupling Constant $^2J_{CH}$	$^3J_{CH}$
α	———	(a)	(a)
β	———	$^2J_{C_\beta H_4} = 3.92$	$^3J_{C_\beta H_1} = 8.41$ $^3J_{C_\beta H_3} = 8.41$
α'	———	(a)	(a)
β'	———	———	$^3J_{C_{\beta'} H_7} = 8.67$ $^3J_{C_{\beta'} H_9} = 8.67$
1	$^1J_{C_1H_1} = 181.93$	———	$^3J_{C_1H_3} = 13.82$
3	$^1J_{C_3H_3} = 181.20$	$^2J_{C_3H_4} = 1.76$	$^3J_{C_3H_1} = 12.73$
4	$^1J_{C_4H_4} = 166.14$	$^2J_{C_4H_3} = 8.33$	———
6	$^1J_{C_6H_6} = 164.13$	$^2J_{C_6H_2} = 2.92$	$^3J_{C_6H_8} = 5.51$
7	$^1J_{C_7H_7} = 163.57$	$^2J_{C_7H_6} = 2.72$ (b)	$^3J_{C_7H_9} = 7.15$
8	$^1J_{C_8H_8} = 164.16$	———	$^3J_{C_8H_6} = 7.51$
9	$^1J_{C_9H_9} = 163.79$	$^2J_{C_9H_8} = 2.55$	$^3J_{C_9H_7} = 6.67$

(a) Were not unequivocally measurable because of degeneracy. (b) May represent $^2J_{C_7H_8}$ which could be confirmed by spin population transfer (SPT) at a field strength sufficient to give a first order spectrum for the benzenoid protons.

trum acquired under gated decoupling conditions (16) (Figure 3). Primary one bond couplings ($^1J_{CH}$) for C1 and C3 were 181.93 and 181.20 Hz, respectively (Table 2), and in reasonable accord with the value of the corresponding coupling of 177.6 Hz reported for pyridine (17). These couplings, however, did not facilitate the assignment problem. Similarly, the three bond couplings ($^3J_{CH}$), which were augmented by the intervening annular nitrogen, were 13.82 and 12.73 Hz but again were not discriminatory. Unique assignment was, however, possible based on the two bond coupling $^2J_{C_3H_4} = 1.76$ Hz. Although somewhat smaller than the corresponding couplings $^2J_{C_2H_3} = 3.1$ Hz in pyridine and $^2J_{C_6H_5} = 4$ Hz in 3-cyanopyridine (18), the observed two bond coupling did permit the unequivocal assignment which, on the basis of simple chemical shift correlation alone, would have resulted in a premuted pair of assignments.

The remaining ^{1}H-^{13}C heteronuclear spin couplings for **6** were unremarkable and similar to those reported for 1-azaphenoxathiin (4,5). These coupling constants are tabulated in Table 2. One interesting point, however, is the extraction of couplings for Cβ, which in the gated decoupling experiment (16), were obscured by overlap with the downfield limb of the C1 spin multiplet. This difficulty was, however, circumvented by the application of the selective excitation procedure of Freeman (19,20), which we have previously applied to several phenoxathiin systems including 1,3-dinitrophenoxathiin (13) and 1-azaphenoxathiin (5). Thus, the selectively excited and gated decoupled subspectrum for Cβ was observed as an apparent triplet, $^3J_{CH} = {}^3J_{CH} = 8.67$ Hz, thereby providing the complete heteronuclear spin coupling constants for this system (21).

EXPERIMENTAL

All solvents employed were reagent quality or better. The *o*-mercaptophenol was obtained from Parish Chemical Co., Provo, Utah. Melting points were obtained in open capillary tubes in a Thomas Hoover Melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 283 spectrophotometer as potassium bromide pellets. ^{1}H-nmr spectra were recorded on a Varian XL-100 spectrometer equipped with a Nicolet Technology TT-100 data system and an NT-440 frequency synthesizer, the spectrometer operating at a frequency of 100.060 MHz in the Fourier transform mode. The following fixed operating parameters were used for the proton spectral acquisition: pulse width, 10 μs; pulse delay, 100 s; sweep width, 1.5 KHz; acquisition time, 2.7279 seconds; data size 16K.

^{13}C-nmr spectra were recorded on the same instrument at 25.2 MHz in the Fourier transform mode, also incorporating a TT-760 decoupler which was set at 15 watts, broad band noise decoupling centered at δ 7.0 in the ^{1}H-spectral window. The instrument was modified to execute the selective excitation procedures as previously described (5) with the exception that the Varian V-4311 attenuator previously employed was replaced by a Kay variable attenuator. Operating parameters were: pulse width, 5 μs; pulse delay, 5.00 s; sweep width, 5 kHz; acquisition time 0.8192 s (4k); data size 4k (decoupled)/8k (coupled); selective excitation was executed using 100 pulses in the excitation sequence at 18db attenuation. Low resolution mass spectra were obtained on a Hewlett-Packard Model 5930 GCMS sytem with a model 5933A data system at an ionizing energy of 70 eV and a source temperature of 250°. Sample introduction was by direct probe.

Synthesis of 3-Chloro-4-nitropyridine 1-Oxide (**3**).

The synthesis of 3-chloro-4-nitropyridine 1-oxide was conducted by the preliminary oxidation of 3-chloropyridine to the corresponding *N*-oxide (**2**). To 15 g. (0.13 mole) of 3-chloropyridine in 75 ml. of acetic anhydride maintained below 20°, 75 ml. of 30% hydrogen peroxide was slowly added. After the addition, the reaction mixture was stirred at room temperature for 5 hours and then at 60-65° for 30 hours. The reaction mixture was allowed to cool and was then poured into 100 ml. of distilled water. Removal of the solvent, *in vacuo*, gave 9 g. (53% yield) of **2** as a reddish oil which was immediately nitrated without further purification in a mixture of 25 ml. of concentrated sulfuric acid, 10 ml. of 30% fuming sulfuric acid and 60 ml. of concentrated nitric acid by refluxing for 2 hours. After cooling, the mixture was poured into 200 ml. of ice water, brought to *p*H 9 with ammonium bicarbonate and then extracted with dichloromethane (4 × 50 ml.), which was washed with water, dried over anhydrous sodium sulfate and then concentrated to give 7.9 g. (35%), m.p. 113-114°; ms: m/e (%RI) 175(100); 177(33); ir: ν max cm^{-1} 1600, 1560, 1500, 1460, 1350, 1310 and 1060.

Synthesis of 2-Azaphenoxathiin (**6**).

The synthesis of **6** was conducted by dissolving 1.5 g. (0.008 mole) of **3** in 30 ml. of stirred, dry, distilled DMF to which was then added 1.61 g. (0.009 mole) of the disodium salt of *o*-mercaptophenol (13). The mixture was stirred at room temperature for 4 hours and then brought to reflux overnight. After cooling, the solution was poured into 50 ml. of distilled water and extracted with ethyl acetate (8 × 10 ml.). The combined ethyl acetate extracts were back extracted with distilled water (5 × 20 ml.) and then dried over anhydrous sodium sulfate. The solvent was removed to yield **5** as an oily residue (ms: m/e 217, 200), which was dissolved without further purification in 25 ml. of chloroform. Phosphorus trichloride (2 ml.) was added and the mixture brought to reflux for 2 hours (14). After cooling, the solution was cautiously poured into 50 ml. of distilled water and neutralized with 30% sodium hydroxide. The chloroform layer was separated, dried over anhydrous sodium sulfate and chromatographed over silica gel eluted with cyclohexane acetone (3:1) ($R_f = 0.31$). Crystallization of the fractions containing **6** (by tlc) from this solvent system gave 0.20 g. (20% yield) as colorless plates, m.p. 35-37°; ir: ν max cm^{-1} 1460, 1440, 1400, 1270, 1250, 1200, 880, 810; ms: m/e (%RI) 201 (100), 202 (12), 203 (5), 168 (10), 91 (11); uv (95% ethanol): λ (log ϵ) 240 (4.38), 285 (3.29) ^{1}H-nmr (deuteriochloroform): δ 8.18 (d, H3, J = 5.45 Hz), 8.15 (s, H1), 7.04 (m, 4H benzenoid), 6.83 (d, H4, J = 5.45) (see Figure 1). The ^{13}C-nmr of **6** decoupled is shown in Figure 2, while the gated decoupled spectrum is shown in Figure 3. Chemical shift data and coupling constants from Figures 2 and 3 are summarized in Table 1 and 2, respectively.

Anal. Calcd. for $C_{11}H_7NOS$: C, 65.67; H, 3.48; N, 6.96. Found: C, 65.50; H, 3.70; N, 7.00.

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(11) A linear correlation has been established between the dihedral angle and ^{13}C-nmr chemical shift of Cα, with a correlation coefficient r = 0.96, which is described in the paper referred to in (1) above. Further studies are presently underway to determine the fit of the 2-azaphenoxathiin system to this relationship, and will be forth coming.

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(21) The Cα and Cα' resonances represent an exception. Because of their degenerate chemical shifts, these resonances are not amenable to selective excitation and thus ^{1}H-^{13}C coupling constants cannot be measured unequivocally. At higher spectrometer operating frequencies this problem could be overcome using this technique, provided some separation of the resonances is observed.