6,7,9-Trimethyl-4-azaphenoxathiin: First Reported Synthesis of an Analog of the 4-Azaphenoxathiin Ring System

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The reaction of 2-chloro-3-thiocyanatopyridine with a substituted spiroepoxycyclohexadienone, which served as a masked phenol with reversed polarity, led to the first reported synthesis of an analog of the 4-azaphenoxathiin ring system. Confirmation of the structure was obtained from the assignment of the ^{13}C-nmr spectrum.

In view of the considerable interest in the synthesis of annular aza-substituted tricyclic ring systems, as evidenced by the numerous examples of azaphenothiazines and azaphenoxazines in the literature (4), it is rather surprising that the first synthesis of an azaphenoxathiin, specifically 1-azaphenoxathiin (5,6), appeared only in 1977. It was synthesized *via* the reaction of 2-mercapto-3-pyridinol with 2-chloronitrobenzene in the initial report and has also since been synthesized *via* the reaction of 2,3-dichloropyridine with *o*-hydroxythiophenol. Similarly, 4-chloro-3-nitropyridine was reacted to afford the 3-azaphenoxathiin ring system (7). Due to the marked absence of a Smiles rearrangement in the phenoxathiin series, the 4-aza- and 2-azaphenoxathiin systems, respectively, were not obtained as by-products of these reactions. In order to obtain the 2-azaphenoxathiin system, 3-chloro-4-nitropyridine 1-oxide was reacted with *o*-hydroxythiophenol to afford 2-azaphenoxathiin 2-oxide which was then reduced to the parent system with phosphorus trichloride in chloroform (8). Similar attempts at the synthesis of the 4-azaphenoxathiin ring system using 2,3-dichloropyridine 1-oxide (9), however, were uniformly unsuccessful, leading instead to 1-azaphenoxathiin 1-oxide. Other approaches to the synthesis of the 4-azaphenoxathiin system (10) have also proven unsuccessful. However, we now wish to report the synthesis of 6,7,9-trimethyl-4-azaphenoxathiin (6), which is the first known example of this ring system to be prepared.

Recent reports of the utilization of a series of spiroepoxycyclohexadienones as masked phenols with reversed polarity (11-13), and in particular the application of these reagents in the synthesis of highly substituted phenoxathiins (12), suggested a possible approach to the 4-aza-
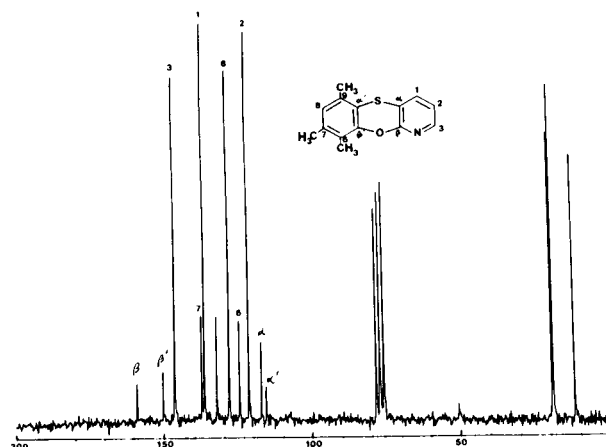

Figure 1. ^{1}H-Decoupled ^{13}C-nmr spectrum of 6,7,9-trimethyl-4-azaphenoxathiin (6) in deuteriochloroform.

phenoxathiin system. The necessary co-reactant in this case potassium 2-chloropyridine-3-thiolate (2) which is available *via* the basic hydrolysis of 2-chloro-3-thiocyanatopyridine (1) (14) in aqueous media.

The reaction was carried out using 3,5,6-trimethyl-2-spiroepoxycyclohexa-3,5-dienone (3) as shown in Scheme I, and is envisioned to procede through the attack of the thiolate on the spiro-carbon of 3 to afford 4 as a transient intermediate (12). Subsequent collapse of this intermediate with concurrent rearomatization and expulsion of formaldehyde gives the phenolate sulfide, 5. At this point in the reaction, the composition of the isolated products is dependent upon the length of the reaction time. When short reaction times are employed, considerable quantities
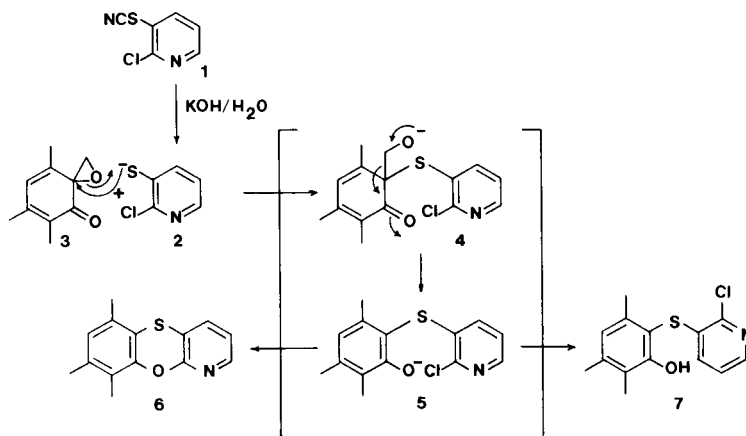
of uncyclized phenol **7** accompany the trimethyl-4-aza-phenoxathiin (**6**). By increasing the duration of the reaction, however, the phenoxathiin may be obtained to the exclusion of the uncyclized phenol.

Proof of the structure of **6** as the desired 4-azaphenoxa-thiin analog was obtained by the assignment of the [1]H-decoupled ^{13}C-nmr spectrum of the compound which is shown in Figure 1. The aromatic region of the spectrum contains eleven resonances, seven of which can be attributed to quaternary carbons on the basis of relaxation time considerations (15), while the remaining four are clearly due to the protonated carbons. In addition, the spectrum also contains the necessary three methyl resonances upfield. Observed ^{13}C-nmr chemical shift data are compared in Table I with values calculated by incrementing the assigned phenoxathiin chemical shift data for the insertion of the annular nitrogen (7) and for the addition of the appropriately positioned methyl groups. With the exception of the $C\beta$ resonance, there is reasonable correspondence between the calculated and observed chemical shifts.

In the case of the $C\beta$ resonance, however, the observed resonance is -12.9 ppm from its calculated position. Since the correct assignment of the $C\beta$ resonance is critical to the unequivocal proof of structure, the [1]H- [13]C spin-coupled spectrum of the molecule was also obtained (Figure 2). Thus, $C\beta$ in a 4-azaphenoxathiin is expected to exhibit a pair of three bond couplings, $^{3}JC_{\beta}H3$ and $^{3}JC_{\beta}H1$, the former with a magnitude of 11-13 Hz and the latter in the range of 6-8 Hz (16). In contrast, if the system had somehow rearranged during synthesis, for example to a 2-azaphenoxathiin, a considerably different coupling pattern would be observed. In particular, the $C\beta$ resonance of 2-azaphenoxathiin has already been observed to give the following couplings (8): $^{2}JC_{\beta}H4 = 3.9$ Hz; $^{3}JC_{\beta}H3 = 8.4$ Hz; $^{3}JC_{\beta}H1 = 8.4$ Hz. Thus, the observation of a large three bond coupling through the annular nitrogen would firmly establish the identity of **6** as a 4-aza-
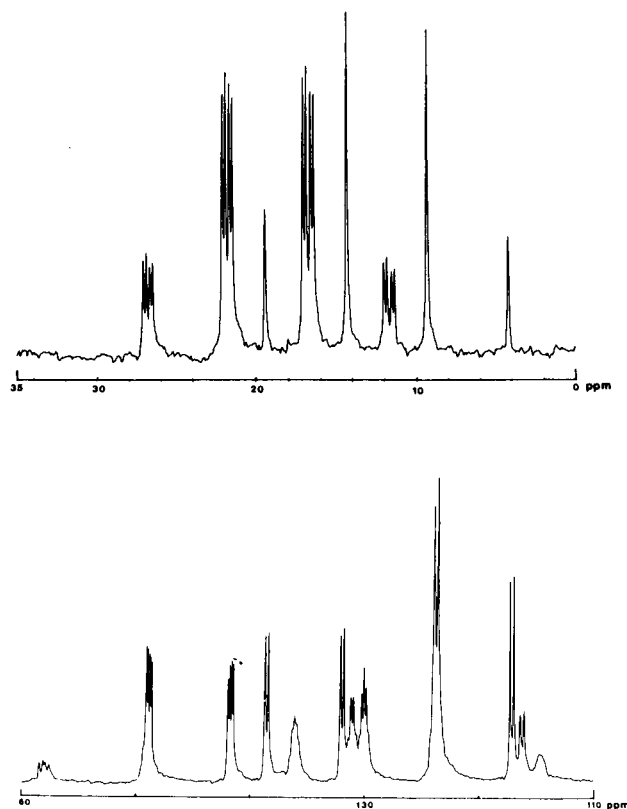

Figure 2.   [1]H- [13]C Spin-coupled spectrum of 6,7,9-tri-methyl-4-azaphenoxathiin (**6**) aquired under gated decoupling conditions.

phenoxathiin. Expansion of the $C\beta$ portion of the coupled spectrum (Figure 3) clearly showed two spin-couplings to this carbon. The larger of the two couplings is attributed to the three bond coupling through the annular nitrogen, $^{3}JC_{\beta}H3 = 12.4$ Hz, and the smaller to the coupling to H1, $^{3}JC_{\beta}H1 = 7.5$ Hz. On this basis, the location of the nitro-

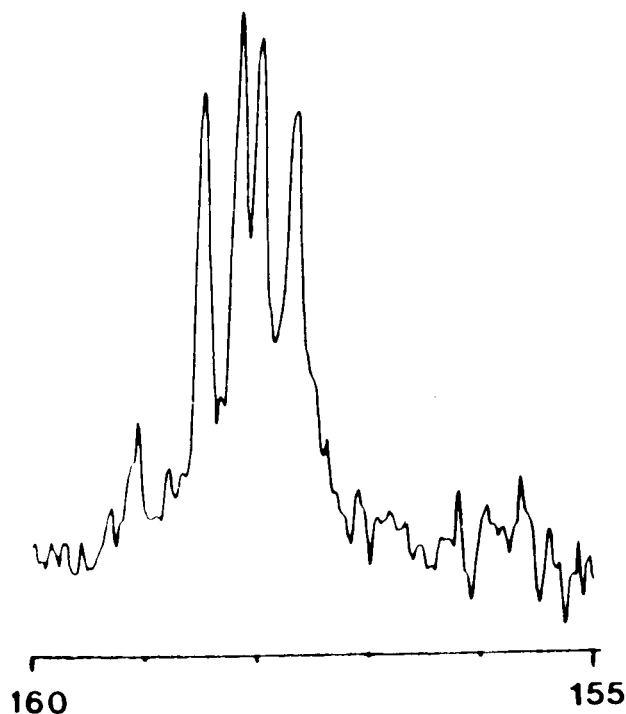gen is unequivocally established and confirms the identity of the ring system as a 4-azaphenoxathiin.

Figure 3. Expansion of the ^{1}H- ^{13}C spin-coupled spectrum in the region from δ 160-155 to show detail of the Cβ resonance.

Table I

Calculated vs. Observed ^{13}C-NMR Chemical Shifts of 6,7,9-Trimethyl-4-azaphenoxathiin (6) in Deuteriochloroform

Carbon	δ ^{13}C$_{calcd}$	δ ^{13}C$_{obs}$	Δδ
α	115.5	116.34	+0.8
β	171.0	158.12	−12.9
α'	117.8	114.82	−3.0
β'	150.8	149.38	−1.4
1	135.3	135.36	+0.1
2	120.0	120.52	+0.5
3	148.2	145.36	−2.8
6	124.5	123.67	−0.8
7	137.3	136.28	−1.0
8	126.0	127.03	+0.1
9	134.1	131.23	−2.9
6-CH$_3$	—	11.78	—
7-CH$_3$	—	19.46 (a)	—
9-CH$_3$	—	19.01 (a)	—

(a) Assignments may be permuted.

In an effort to determine the potential source of the discrepancy between the calculated and observed chemical shifts for the Cβ resonance, the ^{13}C-nmr spectrum of 2-phenoxypyridine was also obtained. The observed resonance for C2 was also found to be considerably upfield of the chemical shift calculated by incrementing the ^{13}C-nmr chemical shifts for diphenyl ether for the annular aza-insertion, C2 resonating in this case at δ = 163.10. This parallels the situation for Cβ in 6 so it appears that the observed disparity is due to an electronic effect arising from the proximity of the annular nitrogen and the oxygen substituent.

It has previously been shown that the linear relationship exists between the ^{13}C-nmr chemical of the Cα carbon atom in phenoxathiin derivatives and the molecular dihedral angle of the compounds (17). If compound 6 were also to conform to this relationship, its Cα chemical shift would indicate that it is folded to a slightly greater extent than the phenoxathiin parent ring system. In this event, annular nitrogen substitution at the 2- or 4-position would cause greater folding of the molecule whereas substitution at the 1- or 3-position would cause flattening (11,18). We are currently attempting the synthesis of the parent 4-aza-phenoxathiin ring system to obtain further information on this phenomenon.

EXPERIMENTAL

Melting points were obtained in open capillary tubes on a Thomas-Hoover melting point aparatus and are reported uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 283 spectrophotometer as potassium bromide pellets. The ^{13}C-nmr spectra were obtained on a Varian XL-100 spectrometer operating at 25.158 MHz in the Fourier transform mode. The spectrometer was equipped with a Nicolet 1180 data system interfaced through a Model 293-A' pulse programmer. The spectrometer was also equipped with a Model TT-760 decoupler, with decoupling centered at δ 4.0 in the ^{1}H-spectral window with sufficient power such that $\gamma H_2/2\pi$ = 2.9 KHz. Spectra were obtained using the following aquisition conditions: pulse width = 12 μsec (90° pulse = 21 μsec); interpulse delay = 5 sec; spectral width = ±2500 Hz from the carrier; decoupled spectra were obtained using 8K data points and an acquisition time = 0.82 sec while ^{1}H-^{13}C sin-coupled spectra were obtained with 16K data points and an acquisition time = 1.64 sec; apodization = 1.0 sec.

6,7,9-Trimethyl-4-azaphenoxathiin (6).

To a well stirred solution of potassium hydroxide (0.800 g, 0.014 mole) in 30 ml of distilled water was added 2-chloro-3-thiocyanatopyridine (0.500 g, 2.9 mmoles) (14). The resultant solution was refluxed for two hours, cooled and filtered to remove any insoluble materials. To the resultant stirred filtrate was added 3,5,6-trimethyl-2-spiroepoxycyclo-hexa-3,5-dienone (0.481 g, 2.9 mmoles) which was prepared according to the procedure of Cacioli (11,12), dissolved in 40 ml of ethanol. The resultant aqueous ethanol solution was refluxed for 40 hours, allowed to cool and the ethanol removed under reduced pressure. The remaining aqueous suspension was extracted with ethyl acetate (3 × 150 ml), the extracts combined and back extracted with distilled water (2 × 100 ml). The resultant ethyl acetate solution was then dried over anhydrous sodium sulfate and concentrated to yield a light yellow oil.

This oil was chromatographed on silica using a linear gradient solvent system which was varied from pure heptane to a mixture of heptane:ethyl

acetate (3:7). The product, 6,7,9-trimethyl-4-azaphenoxathiin (6) was eluted as the first band from the column to give 0.34 g (48% yield), which was crystallized as white needles from methanol, mp 80-81°; ms: m/z (% relative intensity) 243 (100) (molecular ion, M⁺), 244 (13.8), 245 (5.2), 246 (0.6), 228 (12.7), 211 (13.8), 210 (65.2), 198 (6.5), 184 (8.9), 167 (10.4), 154 (4.6), 121 (14.1), 115 (8.9); ir: ν (cm⁻¹) 3070, 3040, 2970, 2920, 1580, 1425, 1395, 1310, 1260, 1235, 1095, 805, 745.

Anal. Calcd. for $C_{14}H_{13}NOS$: C, 69.14; H, 5.35; N, 5.76. Found: C, 69.01; H, 5.40; N, 5.70.

The ¹³C-nmr spectra of 6 are shown in Figures 1-3, and the calculated *vs.* observed chemical shift data are given in Table I.

Conduct of the reaction for shorter periods of time than the 40 hours specified above gave an additional product on column chromatography over silica which was identified as the half-cyclized phenosulfide, 7, mp 148-151°. No yield was calculated as the quantity of compound isolated was a function of reaction time, with none isolated under the conditions specified above. The mass spectrum of this compound gave a molecular ion, M⁺ = 279, with a characteristic M + 2 ion corresponding to the ³⁷Cl isotope peak: 279 (100) (molecular ion, M⁺), 280 (18.7), 281 (37), 282 (6.5), 283 (2.1), 244 (21.7), 229 (7.1), 210 (7.2), 167 (5.8), 164 (5.9). The infrared gave ν (cm⁻¹): 3400, 3050, 2980, 2950, 1610, 1570, 1550, 1460, 1440, 1390 (strong), 1335, 1245, 1220, 1135, 1100, 1050, 860, 815, 805, 735, 590.

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