Chemistry of the Phenoxathiins and Isosterically Related Heterocycles. XVIII (1). The Synthesis, ^{1}H- and ^{13}C-NMR Spectroscopy of Benzo[*b*]-1,4,9-triazaphenoxathiin

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The first synthesis of a triazaphenoxathiin system, benzo[*b*]-1,4,9-triazaphenoxathiin, is reported. Attempts directed toward the total assignment of the ^{13}C-nmr spectrum of the title compound failed to produce an unequivocal assignment. The carbons of the benzo-portion of the molecule could not be unequivocally assigned at 25.2 MHz but were subgrouped into permutable pairs of resonances on the basis of relaxation times, a result of the antisotropic reorientation of the molecule. Further attempts to complete the ^{13}C-nmr assignment at 100 MHz by selective on-resonance decouplings in the 400 MHz ^{1}H-nmr spectrum were also unsuccessful because of similarities in the chemical shifts of the benzo-protons. Complete ^{1}H-nmr chemical shifts and homo-nuclear spin-coupling constants were obtained using the PANIC program.

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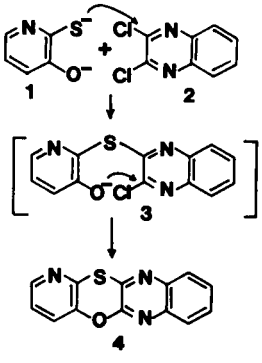
Annular aza-substitutions have been reported in both the phenothiazine and the phenoxazine ring systems and have subsequently led to our previous studies on the effects of annular aza-substitution in the isosterically related phenoxathiin ring system. Thus, the synthesis of the 1-azaphenoxathiin (3) ring system and that of various benzo-substituted analogs (4-7) have been reported. More recently, the syntheses of the 2-azaphenoxathiin (8) and 3-azaphenoxathiin (9) ring systems have been described as have the synthesis of the 1,7- and 1,9- diazaphenoxathiin systems (10,11). There has however been no reported synthesis of a triazaphenoxathiin analog and we therefore wish to report the synthesis of benzo[*b*]-1,4,9-triazaphenoxathiin (**4**) and the results of our ^{1}H- and ^{13}C-nmr studies on this interesting heterocyclic system.

Synthesis of benzo[*b*]-1,4,9-triazaphenoxathiin (**4**) was conducted (Scheme I) using the general procedure employed by Okafor for the synthesis of the isosterically related benzo[*b*]-1,4,9-triazaphenoxazine (12) and benzo[*b*]-1,4,9-triazaphenothiazine (13) systems. The reaction was conducted by the preliminary condensation of the disodium salt of 2-mercapto-3-pyridinol (**1**) in *N,N*-dimethylformamide with 2,3-dichloroquinoxaline (**2**) at room temperature to afford the intermediate phenolate sulfide (**3**). Completion of the cyclization was subsequently achieved by bringing the reaction mixture to reflux to give **4** in a 62% isolated yield.

SCHEME I



Examination of the ^{1}H-decoupled ^{13}C-nmr spectrum of **4** (shown in Figure 1) showed thirteen clearly resolved resonances which could be readily sorted into subgroups comprised of protonated and non-protonated carbons (14). Cursory examination of the spectrum allows the assignment of only one resonance, C10, this assignment based solely on chemical shift arguments (3,11). Assignments of

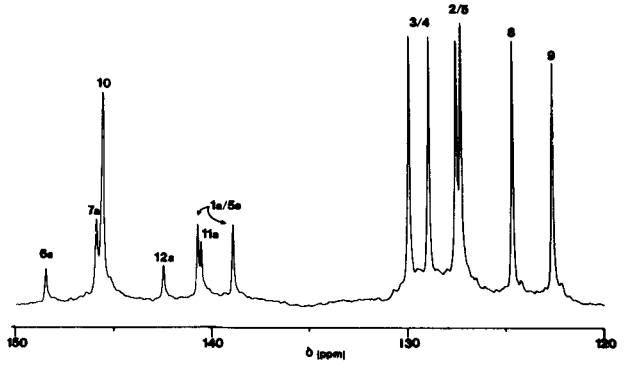


Figure I. ^{1}H-decoupled ^{13}C-nmr spectrum of benzo-[*b*]-1,4,9-triazaphenoxathiin (**4**) in deuteriochloroform at 25.2 MHz.

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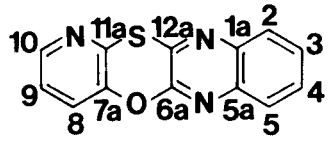

the remaining two resonances contained in the pyridyl portion of the molecule was achieved by coherent on-resonance doucoupling with assignment of the resonances at 122.65 and 124.22 δ to C8 and C9 respectively. Assignment of the remaining protonated resonances necessitated a more complicated approach which relies on spin-lattice (T_1) relaxation times as discussed below. In contrast, assignments were made for the non-protonated resonances based on ^1H- ^{13}C spin-coupling constants.

Table I

25 MHz ^{13}C-NMR Chemical Shift Assignments and T_1 Relaxation Times for Benzo[*b*]-1,4,9-triazaphenoxathiin (**4**) in Deuteriochloroform at 33°

Carbon	δ (ppm)	T_1 (sec)
6a	148.48	– –
7a	145.94	– –
10	145.65	1.68
12a	142.50	– –
1a/5a (a)	140.75	– –
11a	140.56	– –
1a/5a (a)	138.96	– –
3/4 (a)	129.99	1.63
3/4 (a)	128.97	1.56
2/5 (a)	127.55	2.16
2/5 (a)	127.32	2.10
8	124.65	2.17
9	122.62	1.53

(a) pairs of permutable assignments.

Table II

^1H-NMR Chemical Shift Assignments and Homonuclear Spin-coupling Constants for Benzo[*b*]-1,4,9-triazaphenoxathiin (**4**) in Deuteriochloroform at 400 MHz

Signal	(ppm)	*ortho*	*meta*	*para*
H10	9.22	$J_{H_{10}H_9}$ = 4.71	$J_{H_{10}H_8}$ = 1.40	– – – –
H2	8.47	$J_{H_2H_3}$ = 8.31	$J_{H_2H_4}$ = 1.46	$J_{H_2H_5}$ = −0.59
H5	8.33	$J_{H_5H_4}$ = 8.49	$J_{H_5H_3}$ = 1.27	$J_{H_5H_2}$ = −0.59
H3	8.00	$J_{H_3H_4}$ = 8.31	$J_{H_3H_5}$ = 1.27	– – – –
		$J_{H_3H_2}$ = 7.11	– – – –	– – – –
H4	7.96	$J_{H_4H_3}$ = 7.11	$J_{H_4H_2}$ = 1.46	– – – –
		$J_{H_4H_5}$ = 8.49	– – – –	– – – –
H8	7.50	$J_{H_8H_9}$ = 8.18	$J_{H_8H_{10}}$ = 1.40	– – – –
H9	7.02	$J_{H_9H_8}$ = 8.18	– – – –	– – – –
		$J_{H_9H_{10}}$ = 4.71	– – – –	– – – –

Based on the observed anisotropic reorientation for the pyrrolo[3,2,1-*kl*]phenothiazine system (14), it seemed logical to assume that **4** would reorient in a similar fashion. From this assumption, it was clear that protonated carbon resonances should be sub-divisible into two groups if anisotropic reorientation did indeed occur. One group would be comprised of those carbons which possessed C-H bond vectors oriented approximately 90° to the axis of anisotropic reorientation while the other would consist of carbons with C-H bond vectors oriented at an angle of approximately 30° to the axis of rotation. More specifically, resonances corresponding to C2, C5 and C8 would fall into the former group while resonances for C3, C4, C9 and C10 would compose the latter. Examination of the spin-lattice (T_1) relaxation times for **4**, using the inversion recovery method (15,16), substantiated this hypothesis, three resonances exhibit somewhat longer relaxation times (avg. = 2.14 sec) while four exhibit somewhat shorter relaxation times (avg. = 1.60 sec). Utilizing the assigned resonances from the pyridyl portion of the molecule as a starting point, the resonances for C9 and C10 were observed to be in the group with the shorter relaxation times while the resonance assigned to C8 was contained among the more slowly relaxing resonances. Thus, it was possible to assign the C2 and C5 to the resonances observed at 127.55 and 127.32 δ while C3 and C4 were consequently assigned to the resonances observed at 129.99 and 128.97 δ. No further descrimination was possible within these pairings at this point.

Although the benzo[*b*]-1,4,9-triazophenoxathiin ring system (**4**) was expected to undergo anisotropic reorientation from the outset of this study, it is of interest to speculate on the potential role of structure in the control of the tumbling preference ratio, ϱ. While data upon which to base such speculation is limited, an interesting system with which **4**, can be compared is pyrrolo[3,2,1-*kl*]phenothiazine (**5**) (14). In the case of the latter, the [*kl*] fusion of the pyrrole ring to the phenothiazine skeleton would be expected to give the carbon skeleton somewhat greater resistance to reorientation about the long axis than would be expected for a linear tetracycle such as **4**. While such comparisons must be made with considerable caution, this supposition is experimentally supported by the tumbling preference ratios. Thus, pyrrolo[3,2,1-*kl*]phenothiazine (**5**) exhibits a tumbling preference ratio, ϱ = 1.60, while benzo[*b*]-1,4,9-triazaphenoxathiin (**4**) exhibits a somewhat greater tendency to undergo anisotropic reorientation, ϱ = 2.25. Based on this observation, it would be of considerable interest to compare the two aforementioned compounds, **4** and **5**, with linearly fused pentacycles, which should exhibit even greater tendencies to reorient anisotropically or conversely, to compare then with a system such as a dibenz[*h,j*]-1-azaphenoxathiin which should exhibit a lower tendency toward anisotropic reorientation than even pyrrolo[3,2,1-*kl*]phenothiazine (**5**).

Assignment of the non-protonated carbon resonances of

4 utilized ^1H-^{13}C spin-coupling constants and permitted the assignment of four of the six resonances of this group in an uneuqivocal fashion. The resonances corresponding to C12a and C6a were readily assigned as a result of the complete absence of long range couplings to the signals observed at 142.50 and 148.48 δ (3). Discrimination of C11a, C1a and C5a, which exhibit similar chemical shifts, utilizes the large three bond coupling through the nitrogen, $^3J_{C_{11a}H_{10}}$, thereby permitting the assignment of C11a to the resonance observed at 140.56 δ. The remaining pair of non-protonated resonances, C1a and C5a, could not be assigned on the basis of spin-coupling constants. This pair of permutable assignments was made to the resonances at 140.75 and 138.96 δ.

A final attempt to complete the assignment of the protonated benzo-carbons involved the acquisition of the 400 MHz ^1H-nmr spectrum of **4**. Despite the substantially improved spectral dispersion obtained from the higher field, the benzo-protons still displayed sufficient second-order character to preclude the use of coherent on-resonance decoupling for carbon resonance assignmnets at 100 MHz. It was however possible to completely interpret the 400 MHz proton spectrum using the PANIC program (17), which gave the assignments and homonuclear spin-coupling constants shown in Table II. Additional work on ^{13}C-nmr assignment techniques for these and related systems are at present underway and will be reported.

EXPERIMENTAL

Melting points were determined in open capillaries on a Thomas-Hoover melting point apparatus and are uncorrected. ^{13}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, an NT-440 Multi Observe Nuclei Accessory and a TT-760 decoupler. All spectra were obtained as deuteriochloroform solutions and chemical shifts are reported in ppm downfield from TMS. Typical operating parameters were: pulse width = 8 μs (flip angle = 45°); pulse delay = 1.0 sec; sweep width = 5 KHz; ^1H-decoupled spectra were obtained using 4K data points with an acquisition time = 0.82 sec while ^1H-^{13}C spin-coupled spectra were obtained with 8K data points and an acquisition time = 1.64 sec. ^1H-nmr spectra were obtained at 100.06 MHz on the same spectrometer or at 400.1 MHz on a Brucker WM-400 spectrometer. Operating parameters were as follows: at 100 MHz, pulse width = 8.0 μs, pulse delay = 0.5 sec, sweep width = 1.2 KHz, digitization was with 8K data points and an acquisition time = 6.82 sec; 400 MHz spectra were obtained with pulse width = 7.0 μs, pulse delay = 0.0 sec, sweep width = 4 KHz, digitization was with 32K data points and an acquisition time = 4.10 seconds. Infrared spectra were recorded on a Perkin-Elmer Model 283 spectrometer as potassium bromide pellets. Mass spectra were recorded on a Heulett-Packard Model 5930 GC/MS system equipped with a Model 5935A data system with introduction of the sample by direct insertion and an ionizing energy of 70 eV.

Benzo[*b*]-1,4,9-triazaphenoxathiin (**4**).

Using the general procedure of Elliott and co-workers (7), 2.4 g (0.1 *M*) sodium hydride as the 99% dry powder was added to 100 ml of freshly distilled, dry *N,N*-dimethylformamide (DMF), the resultant suspension stirred for 30 minutes at 0°. To this suspension was then added 6.4 g (0.05 *M*) of 2-mercapto-3-pyridinol which was dissolved in 20 ml of dry DMF. The solution was stirred for two hours during which time it was allowed to return to room temperature with concomittant evolution of hydrogen. To the resultant solution was then added 9.95 g (0.05 *M*) of 2,3-dichloroquinoxaline, also dissolved in 20 ml of dry DMF. The reaction mixture was then stirred at room temperature for one hour after which it was brought to reflux for 24 hours. After cooling, the dark colored reaction mixture was poured into 400 ml of cold distilled water and then filtered after a residue precipitated from the aqueous solution. The residue was taken up in 250 ml of ethyl acetate which was then back extracted with 2 × 200 ml portions of distilled water, after which the organic layer was dried over anhydrous sodium sulfate. This solution was decolorized with NORIT-A and evaporated to dryness to give a yellow colored semi-crystalline residue which was recrystallized from hot acetone to give **4** as fine yellow needles, mp 195-196.5°, 62% yield. The infrared spectrum gave ν max (cm^{-1}): 3040, 1610, 1580, 1500, 1420, 1350, 1325, 1220, 790, 750. The mass spectrum showed m/z (% relative intensity): 253 (100), 254 (16), 255 (5), 225 (20), 209 (25), 160 (20), 93 (30). The 100 MHz ^1H-nmr spectrum was obtained but was not analyzed, rather, the 400 MHz proton spectrum was obtained and analyzed using PANIC, the individual chemical shifts and coupling constants summarized in Table II. ^{13}C-nmr resonance assignments and spin-lattice (T_1) relaxation times are summarized in Table I.

Anal. Calcd. for $C_{13}H_7N_3OS$: C, 61.66; H, 2.77; N, 16.6. Found: C, 61.69; H, 2.84; N, 16.66.

Spin-lattice (T_1) Relaxation Time Measurements.

Spin-lattice relaxation times for **4** were measured using the inversion-recovery method (15,16) on a sample which was prepared by dissolving 0.253 g of **4** in 3.0 ml of deuteriochloroform. The sample was degassed with a slow stream of zero-grade argon for 15 minutes followed by three freeze-pump-thaw cycles. Fifteen tau (τ) values were utilized in the experiment ranging from 0.00025 sec to 5.0 sec, the values randomized prior to execution and then automatically reordered prior to data reduction. Data reduction was conducted using the Three-Parameter Fitting Program of Kowalewski and co-workers (18), and the relaxation times obtained were taken as being accurate to ± 10%. NOE measurements for all carbons contained in the compound were $\eta \cong 3.0$.

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