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The synthesis of 1-azaphenoxathiin, the parent ring system of a recently reported class of novel CNS agents is described. The ^{13}C-nmr spectrum and its assignment are also reported as a model for structure confirmation studies.

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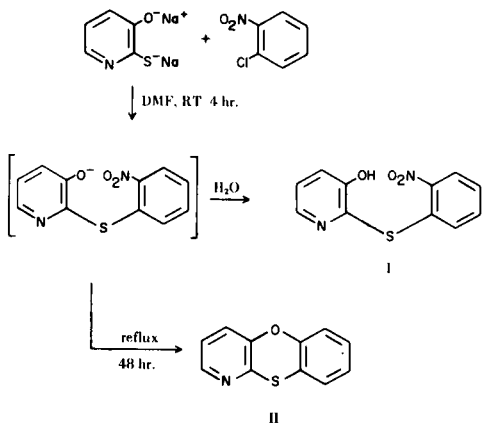
The synthesis of the parent ring systems of several azaphenothiazines (2-6) and azaphenoxazines (7-10) have been reported. We recently reported the synthesis of several 7-substituted-1-azaphenoxathiins (11) as potential novel CNS agents and would now like to report the synthesis of the corresponding parent, 1-azaphenoxathiin (II), system.

Synthesis of this system was conducted through the condensation of the disodium salt of 2-mercapto-3-pyridinol (11) with *ortho*-chloronitrobenzene, as shown in Scheme I. Previous reports have relied on highly substituted systems bearing more than one electron withdrawing group to activate the system to displacement with only two reports appearing which have utilized simple *ortho* halonitro derivatives (9,10). As in these reports, the synthesis of 1-azaphenoxathiin proceeds smoothly to give the desired product even in the absence of a highly activated substrate.

Scheme I



I

II

When the disodium salt of 2-mercapto-3-pyridinol was added to a stirred solution of *ortho*-chloronitrobenzene in DMF at room temperature, there was an immediate darkening of the reaction mixture. Subsequent examination of the reaction mixture by mass spectrometry after quenching with water and extraction of the aqueous/DMF solution with chloroform showed a molecular ion at m/e = 248 corresponding to the intermediate sulfide (I), which was not otherwise isolated. When the reaction mixture was brought to reflux, the cyclization proceeded smoothly to give II.

Following the isolation of II from the reaction mixture, it was subjected to spectral analysis by ir, mass spectrometry and ^{1}H-nmr as well as ^{13}C-nmr. The ^{13}C-nmr spectrum was obtained and assigned to provide a more adequate model for future assignment of substituted 1-azaphenoxathiins, than the present phenoxathiin ^{13}C-nmr model (12) used in a recent study (11). The decoupled 25.2 MHz spectrum of II is shown in Figure 1A, while the completely coupled spectrum is shown in Figure 1B. Assignment of the signals was made on the basis of calculated chemical shifts (13,14), based on phenoxathiin (12). The assigned values were confirmed by careful examination of the coupled ^{13}C-nmr spectrum of II, an expansion of which is shown in Figure 2. The complete calculated and assigned observed chemical shift values as well as the observed coupling constants for II are shown in Table I.

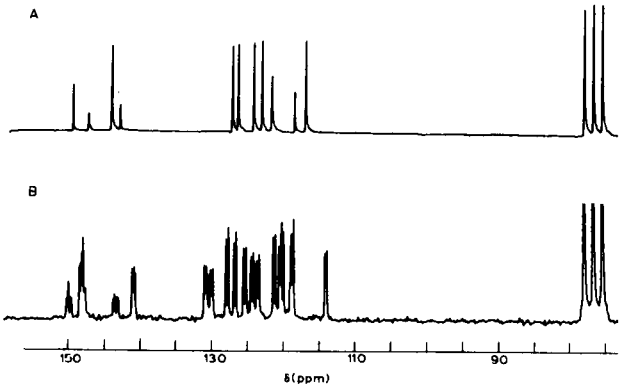


Figure 1. 25.2 MHz ^{13}C-nmr spectrum of 1-Azaphenoxathiin, aromatic region in deuteriochloroform, A. decoupled spectrum, B. coupled spectrum.

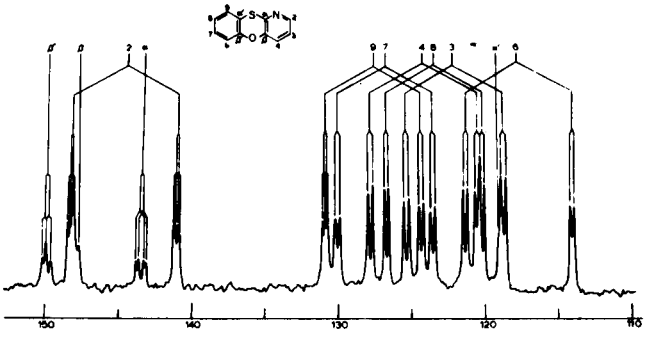
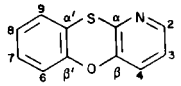


Figure 2. 25.2 MHz ^{13}C-nmr spectrum of 1-Azaphenoxathiin (II), expansion of coupled spectrum.

Table I

Calculated and Observed 25.2 MHz ^{13}C-nmr Chemical Shifts of 1-Azaphenoxathiin (II) in Deuteriochloroform



Signal	Calculated	Assigned	J_{CH} (Hz)	J_{CCCH} (Hz)
α	140.9	143.5	--	13.3
β	146.7	147.9	--	8.6
α′	121.3	119.0	--	(a)
β′	148.8	150.0	--	8.3
2	145.6	144.7	180.9	7.3
3	123.2	122.2	165.9	8.6 (c)
4	124.2	124.7 (b)	184.1	8.4
6	117.3	117.4	182.2	7.1
7	127.2	126.9	162.5	8.3
8	124.4	123.6 (b)	164.7	7.5
9	127.7	127.7	164.2	7.4

(a) Could not be measured due to signal overlap. (b) Assignment based on coupled spectrum. (c) Represents J_{CCH} (Hz).

EXPERIMENTAL

Melting points were determined in capillary tubes in a Thomas-Hoover apparatus and are uncorrected. Infrared spectra were obtained on a Perkin Elmer Model 700 spectrometer as potassium bromide pellets. ^{1}H-nmr spectra were recorded on a Varian Associates Model EM-360 spectrometer and chemical shifts are reported in parts per million (δ) downfield from TMS. ^{13}C-nmr spectra were obtained on a Varian Associates Model XL-100 fourier transform spectrometer operating at 25.2 MHz, equipped with a Nicolet Model TT-100 data system and a NT-440 frequency synthesizer. ^{13}C-nmr spectra were run in deuteriochloroform and chemical shifts are reported in parts per million (δ) downfield from TMS. Typical fixed instrument parameters were pulse width 4 μsec, pulse delay 10.00 seconds sweep width 5 k Hz. Mass spectra were obtained on a Hewlett-Packard Model 5930 GCMS system equipped with a model 5933A data system at an electron engery of 70 eV.

Disodium Salt of 2-Mercapto-3-pyridinol.

To a solution of 0.078 mole of sodium methoxide in 200 ml. of absolute methanol was added 5.00 g. (0.039 mole) of 2-mercapto-3-pyridinol as in the procedure of Martin (11). The resultant salt obtained by this procedure was used without further purification.

1-Azaphenoxathiin (II).

To 0.921 g. (0.0059 mole) of *ortho*-chloronitrobenzene in 30 ml. of dry distilled DMF under dry argon purge was added, with stirring, 1.000 g. (0.0059 mole) of the disodium salt of 2-mercapto-3-pyridinol over a period of thirty minutes. The reaction was stirred at room temperature for 4 hours, darkening immediately after the first addition of the salt to a reddish brown. A sample of this solution was removed for mass spectroscopic examination and the balance of the reaction mixture brought to reflux for 48 hours. Following reflux, the solution was cooled and poured over about 50 g. of ice, the resultant aqueous solution then being extracted with ether (3 x 200 ml.), the ether extracts combined and dried over anhydrous magnesium sulfate. The ether solution was then concentrated to an oil and recrystallized from petroluem ether/ethyl acetate to give 0.330 g. of reddish orange plates m.p. 66-68° (28% yield); ir: ν max 3400, 1480, 1440, 1420, 1280, 1225, 805, 755 cm^{-1}; ^{1}H-nmr (deuteriochloroform): 8.20 (1H, dd) 7.15 (6H, m); ms: m/e (% relative intensity) 203 (5.3), 201 (100), 169 (11.1), 157 (18.7); ^{13}C-nmr see Table 1.

Anal. Calcd. for $C_{11}H_7NOS$: C, 65.55; H, 3.40; N, 6.80. Found: C, 65.70; H, 3.53 N, 7.05.

Acknowledgement.

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