Chemistry of the Phenoxathiins I. Synthesis of 1-Azaphenoxathiin Analogs as Potential New CNS Depressant Agents

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The condensation of the disodium salt of 2-mercapto-3-pyridinol with various *ortho*-nitrohalobenzenes to yield a group of previously unreported 1-azaphenoxathiins is described. The synthetic pathway and the substituent location on the products is unequivocably demonstrated by Fourier Transform ^{13}C-nmr. Preliminary pharmacologic evaluation of the title compounds as potential CNS depressant agents is also reported.

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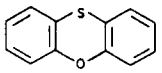
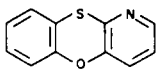
The phenothiazine ring system has been extensively studied and many such compounds have now become firmly established in medical practice (2-4). A number of interesting changes in the properties of the phenothiazines have been observed on aza-substitution of the ring system, and in view of the activity of prothipendyl, the 1-azaphenothiazine analog of promazine (5-7), a wide variety of aza-substituted phenothiazines are now being prepared and examined for pharmacologic properties (8-13). Further interesting structure modifications, in the form of replacement of the heteroatoms of the central ring, have given the phenoxazines (14-16) and the phenoselenazines (17-19), both of which exhibit appreciable pharmacologic activity.



I



II

The phenoxathiin system (I), which appears to have the potential for CNS activity (20), has thus far not provided a CNS agent. Further, although the phenoxathiins have been extensively reviewed (21), there have been no reports of simple azaphenoxathiins. In view of

Scheme I

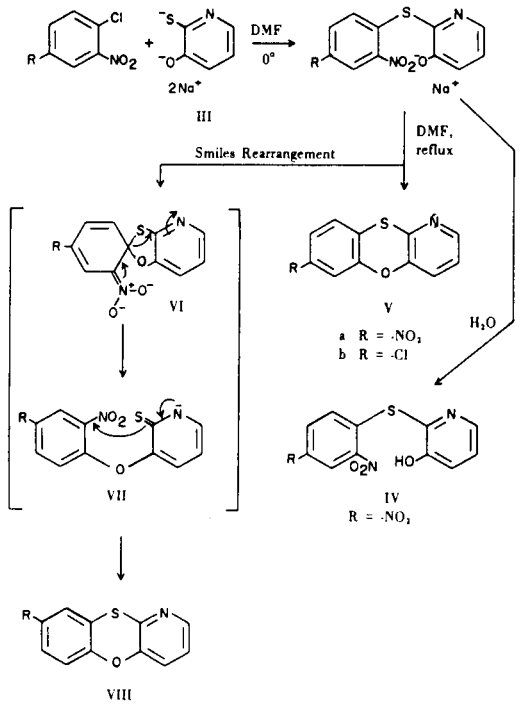
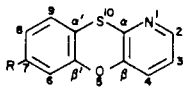


Table I

Observed and Calculated ^{13}C-nmr Shifts of 7-Nitro and 7-Chloro-1-azaphenoxathiins in Deuteriochloroform



		α	β	α′	β′	2	3	4	6	7	8	9	R	Substituent Location
Va	OBS	141.0	146.7	128.6	149.7	145.6	123.1	124.2	112.5	147.2	119.6	126.9	-NO_2	7
	CALC	141.9	147.9	125.7	149.9	143.3	123.4	125.5	112.9	147.5	119.5	127.5	-NO_2	7
	CALC	141.9	147.9	120.8	157.8	143.3	123.4	125.5	118.6	122.7	144.3	121.9	-NO_2	8
Vb	OBS	143.3	147.5	118.0 (a)	150.6	145.2	122.4	123.7	117.8 (a)	133.2	124.9	127.5	-Cl	7
	CALC	141.9	146.7	123.0	150.1	145.6	123.1	124.2	117.7	133.3	124.8	129.0	-Cl	7
	CALC	141.9	146.7	122.4	147.0	145.6	123.4	125.5	117.6	127.6	130.6	128.1	-Cl	8

(a) Cound not be unequivocably assigned

the interesting alterations of pharmacologic activity on aza-substitution in the phenothiazine series, we have now synthesized and tested several aza-analogs of the phenoxathiin series to investigate the effects of aza-substitution on potential CNS-depressant activity. The compounds prepared in this study are represented by the general structure (II).

The synthesis of these 1-azaphenoxathiin analogs was conducted through the condensation of the disodium salt of 2-mercapto-3-pyridinol (III) with the desired *ortho*-nitrohalobenzene derivative in a modification of the method of Mauthner (22), shown in Scheme I. The first phase of the condensation was conducted in *N,N*-dimethylformamide at 0° to afford the intermediate sulfide which, without isolation, on subsequent heating afforded the desired 1-azaphenoxathiins (V). Although it was anticipated that a Smiles rearrangement might occur during this synthesis (10,12,23,24), structure proof of the major products obtained in each reaction showed this not to be the predominant pathway.

Final structure confirmation of the compounds was achieved through the use of ^{13}C-nmr spectroscopy, unequivocably establishing the location of the substituent on the ring in each case. Assignment of the spectra on the basis of calculated versus observed chemical shifts (25), using the chemical shifts of phenoxathiin (I) as a model (26), is shown in Table I.

Preliminary pharmacologic evaluation of the compounds in mice show that these 1-azaphenoxathiin analogs produced a significant decrease in spontaneous motor activity within 30 minutes. It has also been observed that these compounds produce a significant decrease in body temperature of 2.5 to 3.1° at the doses examined which is characteristic of the phenothiazine-type tricyclic agents. Further pharmacologic screening is presently being conducted and will be forthcoming.

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 spectrophotometer 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 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 9-10 μsec. pulse delay 8 and 12 sec., sweep width 5 kHz. Mass spectra were obtained on a Hitachi-Perkin Elmer Model RMU-67 Spectrometer at an electron energy of 70eV.

Disodium Salt of 2-Mercapto-3-pyridinol (III).

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 general method of Kornblum (27). The resultant solution was refluxed for 48 hours, the methanol removed *in vacuo*, and the resultant light brown powder washed three times with dry distilled cyclohexane, dried under vacuum, and used without further purification m.p. >300°.

2(3-Hydroxypyridyl)-2,4-dinitrophenylsulfide (IV).

To a solution of 0.61 g. (0.003 mole) of 1-chloro-2,4-dinitrobenzene in 30 ml. of dry distilled *N,N*-dimethylformamide, under dry argon purge at 0°, was added 0.50 g. (0.003 mole) of III with constant stirring. The mixture was allowed to stir for 2 hours and was then poured over 25 g. of ice in 50 ml. of distilled water. The aqueous solution was extracted three times with 100 ml. portions of chloroform, the extracts combined and extracted with three 100 ml. portions of distilled water, and finally dried over anhydrous sodium sulfate powder. The chloroform solution was then concentrated to give 0.13 g. Of IV as yellow needles, m.p. 196-197° (15% yield); ir: ν max, 3400, 3100, 1600, 1565, 1505, 1450, 1345, 1305, 1240, 1200, 1130, 1080, 830, 800, 730 cm^{-1}; ^{1}H-nmr (d_6-acetone): 9.0, d, (1H); 8.30, m (2H); 7.50, m, (3H). MS: m/e (relative intensity %), 293 (9), 292 (6), 247 (100), 201 (96), 183 (35), 137 (18).

Anal. Calcd. for $C_{11}H_7N_3O_5S$: C, 45.05, H, 2.38, N, 14.33. Found, C, 44.92, H, 2.41, N, 14.27.

7-Nitro-1-azaphenoxathiin (Va).

To a solution of 2.5 g. (0.012 mole) of 1-chloro-2,4-dinitrobenzene in 30 ml. of dry distilled *N,N*-dimethylformamide at 0° under dry argon purge, was added 2.052 g. (0.012 mole) of III. The mixture was stirred for 4 hours at 0° and then brought to reflux for 48 hours without prior isolation of the sulfide intermediate. Following completion of the reflux, the reaction mixture was allowed to cool and then poured over 25 g. of ice in 50 ml. of distilled water. The aqueous solution was extracted with three 100 ml. portions of ether which were combined and extracted with three 100 ml. portions of distilled water. The ether layer was then dried over anhydrous sodium sulfate and concentrated. The resultant oil which did not crystallize was chromatographed over a 1 kg. silica gel column eluted with cyclohexane ethylacetate (4:1) to yield crude Va. The crude material was recrystallized from absolute ethanol to give 0.55 g. (20% yield) of Va as fine yellow needles, m.p. 166-167°; ir: ν max, 1600, 1510, 1420, 1345, 1280, 1225, 870, 805, 790 cm^{-1}; ^{1}H-nmr (deuteriochloroform): 8.05, dd, (1H); 7.85, m, (2H), 7.10, m, (3H); MS: m/e (relative intensity %); 246 (100), 200 (58), 172 (38); ^{13}C-nmr data see Table I.

Anal. Calcd. for $C_{11}H_6N_2O_3S$: C, 53.66, H, 2.44, N, 11.38. Found: C, 53.76, H, 2.39, N, 11.37.

7-Chloro-1-azaphenoxathiin (Vb).

To a solution of 1.123 g. (0.0056 mole) of 1-nitro-2,5-dichlorobenzene in 30 ml. of dry distilled *N,N*-dimethylformamide at 0° under dry argon purge, was added 1.00 g. (0.0056 mole) of III. The mixture was allowed to stir for 4 hours at 0° and was then brought to reflux for 48 hours. At the end of this period, the mixture was allowed to cool and was then poured over 25 g. of ice in 50 ml. of distilled water. The resultant aqueous solution was extracted with three 100 ml. portions of ether which were combined and extracted with three 100 ml. portions of distilled water. The ether solution was dried over anhydrous sodium sulfate powder and then concentrated to an oil and recrystallized from absolute ethanol to give a 0.26 g. (19% yield) of Vb as fine golden needles, m.p. 122-124°; ir: ν max, 2900, 1600, 1560, 1470, 1410, 1280, 1210, 1195, 1100, 920, 850, 825, 795 cm^{-1}; ^{1}H-nmr (deuteriochloroform): 9.05, dd, (1H), 7.8, m, (5H); MS:

m/e (relative intensity %) 235 (100), 200 (44), 149 (65), 81(54). ^{13}C-nmr (deuteriochloroform): examination of the spectrum of Vb using the parameters specified in the experimental section failed to resolve the position of carbon α'. However, by decreasing the pulse width to 4.000 μsec. and maintaining the pulse delay at 10.000 sec., it was possible to resolve the farthest upfield signal into two closely overlapping signals at 117.85 and 118.03 δ. Attempts to make unequivocal assignment of one of these to the quaternary carbon were unsuccessful because of the proximity of the signals. See also Table I.

Anal. Calcd. for $C_{11}H_6ClNOS$: C, 56.17, H, 2.55, N, 5.96. Found: C, 55.96, H, 2.60, N, 6.01.

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