Novel Heterocyclic Systems. Part 26 [1]. The Synthesis and ^{13}C-NMR Assignment of 1,8-Diazaphenoxathiin

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Although the syntheses of numerous diazaphenoxathiins have been reported, only two dipyrido[1,4]-oxathiin systems are thus far known, *viz.* the 1,7- and 1,9-diazaphenoxathiins. The synthesis of a third, 1,8-diazaphenoxathiin *via* the condensation of the dianion of 3-hydroxypyridine-2(1*H*)-thione with 4-nitro-3-chloropyridine 1-oxide is now described. A minor quantity of 1,7-diazaphenoxathiin was obtained as a by-product of the reaction. Complete assignment of the ^{13}C-nmr spectrum was achieved and this conclusively differentiates the 1,8-compound from the 1,7-isomer.

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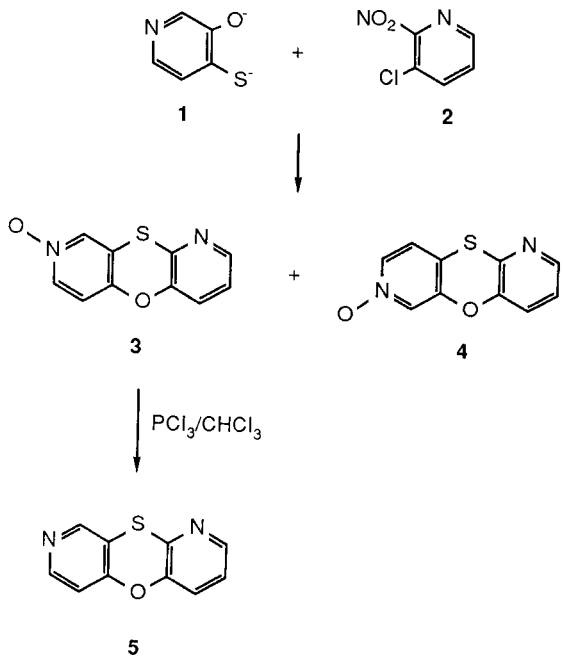
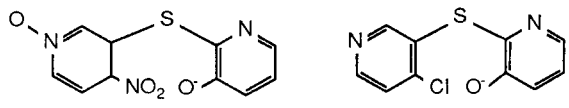
Syntheses of examples of all four of the monoazaphenoxathiins have been described [2-4] as have those of a number of diazaphenoxathiin systems [5-10]. However, of the ten possible dipyrido[1,4]oxathiin systems, examples of only two are thus far known, *viz.* the 1,9- ([1,4]oxathiino-[3,2-*b*:5,6-*b'*]dipyridine) [5,6] and the 1,7- ([1,4]oxathiino-[2,3-*c*:5,6-*b'*]dipyridine) [6] isomers. Thus, we were interested in the preparation of other members of the series and now report the preparation of the parent 1,8-diazaphenoxathiin ([1,4]oxathiino[3,2-*c*:5,6-*b'*]dipyridine) (**5**) (see Scheme I).

Scheme I



1 2 3 4 5



6 7

Preparation of **5** employed the condensation of the dianion of 3-hydroxypyridine-2(1*H*)-thione (**1**) with 3-chloro-4-nitropyridine 1-oxide (**2**) prepared by the method of Talik and Talik [11] followed by reduction. Presumably, the condensation proceeds *via* the initial displacement of chloride by the thiolate anion to give the sulfide intermediate followed by cyclization with displacement of the nitro group during reflux. By this procedure, 1,8-diazaphenoxathiin 8-oxide (**3**) was obtained in 75% yield; a minor product which was tentatively identified as 1,7-diazaphenoxathiin 7-oxide (**4**) on the basis of mass spectral and proton nmr data was obtained in 7% yield. The minor isomer, **4**, can be accounted for through either a Smiles rearrangement of the intermediate phenolate sulfide, **6**, or alternatively by a competing initial attack at the 4-nitro substituent to afford **7** as a minor intermediate.

No formation of minor isomers was observed during the syntheses of the 1,9- and 1,7-diazaphenoxathiins [5,6,8]. However, in those syntheses the electrophilic substrates were 2-chloro- and 4-chloro-3-nitropyridine, respectively, rather than a 3-chloro substituted pyridine 1-oxide as in the present case. Thus, the competitive displacement of the two leaving groups in **2** is much more likely than for the other reagents. Also, Smiles rearrangements are very unusual in phenoxathiin syntheses [9]. For these reasons, we favor the contention that the minor isomer arises through the less efficient initial attack of the thiolate anion at the 4-position rather than through a Smiles rear-

rangement.

Following its isolation by flash column chromatography, 1,8-diazaphenoxathiin 8-oxide (**3**) was reduced to the parent 1,8-diazaphenoxathiin (**5**) in 87% yield using phosphorus trichloride in chloroform according to the method of Ochiai [12].

In their electron impact mass spectra, both **3** and **4** gave molecular ions at m/z = 218 (100%) with a major characteristic fragment ion at m/z = 202 (93% for **3**, 90% for **4**), probably corresponding to the loss of their respective *N*-oxide functions. After reduction, the parent 1,8-diazaphenoxathiin (**5**) gave a molecular ion at m/z = 202 (100%) with characteristic fragment ions corresponding to loss of HCN and CS at m/z = 175 (37%) and 158 (10%), respectively.

Final characterization of the 1,8-diazaphenoxathiin system (**5**) was based upon assignment of its ^{13}C-nmr spectrum. Complete chemical shift assignments for **3** and **5** are contained in Table I along with those for 1,7-diazaphenoxathiin (**8**) [6]. Several key resonances allow the unequivocal differentiation of the 1,7- and 1,8-diazaphenoxathiins. For example, additivity effects of the annular nitrogen atom shift the C5a resonance of **5** 8.6 ppm downfield of its location in the ^{13}C-nmr spectrum of **8**. Correspondingly, the C6 resonance of **5** is shifted upfield of the characteristic C6 chemical shift of the parent phenoxathiin system (117.4 ppm) [13]. Finally, the C9a quaternary carbon resonance of **5** is shifted considerably upfield for the corresponding position of **8**. The wider spread of chemical shift values observed for **5** could not be accounted for by interchange of structures **5** and **8** even if the resonance assignments were altered. Thus, the structures are unequivocally established. The balance of the ^{13}C-nmr assignments for **3** and **5** which were made on the basis of chemical shift additivity considerations were largely unremarkable.

In conclusion, the 1,8-diazaphenoxathiin (**5**) ring system has been synthesized and its structure rigorously confirmed by ^{13}C-nmr spectroscopy.

EXPERIMENTAL

Melting points were obtained on a Gallenkamp microscope heating stage and are uncorrected. Infrared spectra were obtained from potassium bromide discs using a Pye-Unicam SP1050 spectrophotometer. Proton nmr spectra were recorded in deuteriochloroform using a Varian HA-100 spectrometer operating in the CW mode. The ^{13}C-nmr spectra were recorded on a Varian XL-100-12 spectrometer operating in the Fourier transform mode at 25.158 MHz. All chemical shifts are reported in ppm downfield of tetramethylsilane.

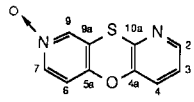
Synthesis of 1,8-Diazaphenoxathiin 8-Oxide (**3**).

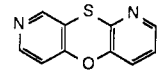
A solution of 0.508 g (0.0040 mole) of 3-hydroxypyridine-2(1*H*)-thione [14] in 20 ml of freshly distilled *N,N*-dimethylformamide (DMF) was added to a suspension of 0.216 g (0.0090 mole) of sodium hydride in 10 ml of dry, distilled DMF over a period of fifteen minutes. After two hours, the stirred suspension was cooled to 0° and maintained thus while 0.696 g (0.0040 mole) of 3-chloro-4-nitropyridine 1-oxide [11] was added in a further 20 ml of DMF over a period of fifteen minutes. The stirred reaction was allowed to warm to room temperature overnight and was then brought to reflux temperature for six hours. After cooling, the reaction mixture was poured into 100 ml of ice-water and extracted with 5 x 20 ml portions of chloroform. The combined chloroform extracts were back extracted with 2 x 50 ml portions of aqueous sodium carbonate solution, washed with 2 x 50 ml portions of distilled water and then dried over anhydrous magnesium sulfate. Removal of the chloroform *in vacuo* left an oily residue which was shown to contain a major and minor component by tlc (silica, 3% methanol in chloroform). Flash column chromatography afforded 0.648 g (75% yield of crystalline **3**, mp 91-91.5°; ms: m/z (% relative intensity) 218 (100, M$^+$), 203 (25), 202 (93), 175 (44), 82 (37), 39 (42); ^{1}H-nmr (100 MHz, deuteriochloroform): δ 8.17 (H9, d, J = 2 Hz), 8.10 (H2, dd, J = 5, 2 Hz), 8.01 (H7, dd, J = 7, 2 Hz), 7.31 (H4, dd, J = 8, 2 Hz), 7.16 (H3, dd, J = 8, 5 Hz), 7.05 (H6, d, J = 7 Hz). The structure was confirmed as **3** on the basis of the ^{13}C-nmr assignment (see Table I).

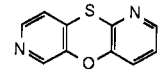
Anal. Calcd. for $C_{10}H_6N_2O_2S$: C, 55.04; H, 2.75; N, 12.85. Found: C, 55.19; H, 2.81; N, 12.41.

Table I

Comparison of the ^{13}C-NMR Chemical Shift Data for 1,8-Diazaphenoxathiin 8-Oxide (**3**), 1,8-Diazaphenoxathiin (**5**) and 1,7-Diazaphenoxathiin (**8**)







Position	3	5	8
2	147.31	145.71	145.14
3	125.10 [a]	122.77	122.87
4	126.00 [a]	124.07	123.96
4a	147.73	146.70	146.05
5a	151.05	156.12	147.50
6	115.88	112.28	145.24
7	137.68	147.63	
8			138.34
9	140.13	149.68	120.79
9a	121.95	116.75	129.78
10a	140.45	141.88	140.70

[a] May be permuted

The minor isomeric product isolated from the reaction mixture was tentatively identified as 1,7-diazaphenoxathiin 7-oxide (**4**) on the basis of its electron impact mass spectrum: m/z (% relative intensity) = 218 (100, M$^+$), 203 (27), 202 (90), 175 (46), 82 (41), 39 (88); and ^{1}H-nmr data (100 MHz, deuteriochloroform): 8.15 (H2, dd, J = 4, 2 Hz), 7.90 (H6, d, J = 2 Hz), 7.85 (H8, dd, J = 4, 2 Hz), 7.10 (H3, H4, m, 2H), 6.9 (H9, d, J = 4 Hz).

Synthesis of 1,8-Diazaphenoxathiin (**5**).

To a solution of 1,8-diazaphenoxathiin 8-oxide (**3**), 0.153 g (0.0007 mole) in 25 ml of dry, distilled chloroform, 2 ml of phosphorus trichloride was cautiously added. The solution was refluxed for four hours and then cooled. Distilled water (50 ml) was added to the reaction mixture which was then neutralized with 5% sodium hydroxide. The chloroform

layer was decanted, dried over anhydrous magnesium sulfate and concentrated to give the crude product as an oil which subsequently crystallized. The crude product was recrystallized from anhydrous diethyl ether to give a white crystalline material, 0.123 g (87% yield), mp 146-147°; ms: m/z (% relative intensity): 203 (12), 202 (100, M^+), 175 (37), 158 (10), 82 (14), 39 (21); ^{1}H-nmr (100 MHz, deuteriochloroform): 8.24 (H7, d), 8.18 (H9, bs), 8.10 (H2, dd, J = 5, 2 Hz), 7.2-6.9 (H3, H4, m, 2H), 6.75 (H6, d, J = 6 Hz); ^{13}C-nmr (deuteriochloroform) see Table I.

Anal. Calcd. for $C_{10}H_6N_2OS$: C, 59.41; H, 2.97; N, 13.86. Found: C, 59.05; H, 2.96; N, 14.00.

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REFERENCES AND NOTES

[1] For Part **25** in this series, see: I. K. Morris, K. Smith and R. J. Bass, manuscript in preparation. The current work also represents Part XXXIV in the series, "Chemistry of the Phenoxathiins and Isosterically Related Heterocycles".

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