Chemistry of the Phenoxathiins and Isosterically Related Heterocycles. XII. Synthesis of Diazaphenoxathiin Analogs: 1,9-Diazaphenoxathiin and 1,7-Diazaphenoxathiin

Steven R. Caldwell (1), James C. Turley and Gary E. Martin (2)

Department of Medicinal Chemistry and Pharmacognosy, College of Pharmacy, University of Houston, Houston, Texas 77004

Received February 8, 1980

The synthesis of the first diazaphenoxathiins, 1,9-diazaphenoxathiin and 1,7-diazaphenoxathiin, are described. Complete assignments are made for the ^{13}C-nmr spectra of these compounds based on additivity correlation and ^{1}H-^{13}C spin-coupling constants. The isolation and confirmation of the structure of 2-[2′(-3′-nitropyridylthio)]-3-[2″-(3″-nitropyridyloxy)] pyridine using ^{13}C-nmr and appropriate model compounds is also discussed. A preliminary evaluation of spontaneous motor depression in mice showed a substantial difference between the observed activities of the two diazaphenoxathiins reported. The possibility of the observed difference being associated with the relative positions of the annular aza-substitutions is discussed.

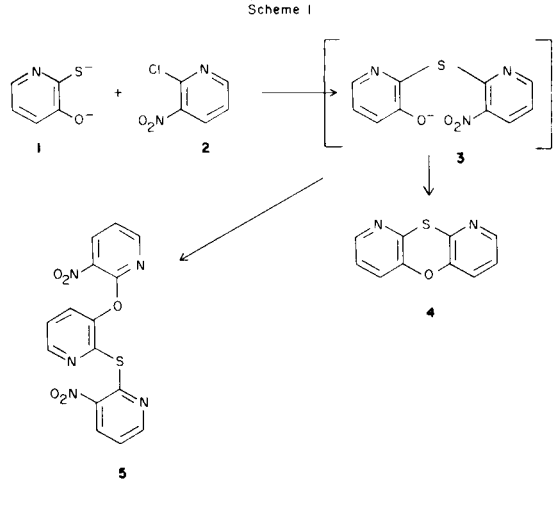
J. Heterocyclic Chem., **17**, 1153 (1980).

Synthesis of chlorpromazine (3), the prototypical antipsychotic agent, and the subsequent description of its unique pharmacologic properties (4-6) has spurred the synthesis of vast numbers of tricyclic heterocycles in the search for new compounds possessing similar and related activities. In particular, numerous analogs of the phenothiazine nucleus have been synthesized which contain annular nitrogen substitutions and which include all of the mono-azaphenothiazines and many of the possible diaza- and triazaphenothiazines (7-11). Similar studies have also been conducted with several isosterically related groups of heterocycles including the azaphenoxazines (12-15) and most recently the azaphenoxathiins (16-22). To date, however, no reports have appeared in the literature which have described the synthesis of any of the diazaphenoxathiin analogs. As a part of our ongoing studies of the chemistry and spectroscopic properties of phenoxathiin and isosterically related analogs, we now report the synthesis of two interesting diazaphenoxathiin analogs: 1,9-diazaphenoxathiin (**4**) and 1,7-diazaphenoxathiin (**14**) which, despite their close structural similarity, exhibit surprising differences in a preliminary screen of spontaneous motor depressant activity.

The synthesis of both **4** and **14** was based on condensation of the disodium salt of 2-mercapto-3-pyridinol (**1**) which was prepared by the well established procedure of Martin, *et al.* (16). Condensation of **1** with 2-chloro-3-nitropyridine (**2**), shown in Scheme I, was presumed to proceed through the phenolate sulfide intermediate (**3**) which was not isolated, subsequent cyclization of **3** affording the desired 1,9-diazaphenoxathiin (**4**) in a 79% yield.

It is of interest to compare the isolated yield of **4** with the related synthesis of the 1-azaphenoxathiin ring system (17), which gave only a 26% yield of the desired heterocycle. The responsible factor for the apparant disparity of the synthetic yields is the relative activation of the chloro-substituent. Thus, the 2-chloro substituent of **2** is activated toward nucleophilic displacement by both the pyridine nitrogen and the nitro group, providing an overall activation which is probably analogous to that for a 2-halopyrimidine. In contrast, the displacement of halogen from *o*-chloronitrobenzene, the requisite starting material for the synthesis of 1-azaphenoxathiin, is activated only by the single nitro group which, not surprisingly, is much less effective. A further consequence of the enhanced susceptibility of the 2-chloro substituent of **2** toward nucleophilic displacement is seen in the isolation of a by-product of the reaction which has been identified as 2-[2′-(3′-nitropyridylthio)]-3-[2″-(3″-nitropyridyloxy)]pyridine (**5**). Indeed, the 2-chloro substituent is so highly activated toward nucleophilic displacement that when **1** is reacted in the presence of excess quantities of **2** at room temperature for prolonged periods of time, halogen displacement by the phenolate anion, which is much weaker than the thiophenolate anion (23) occurs to a favorable extent.

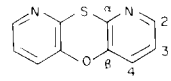
Scheme I



0022-152X/80/061153-10$02.25

Table I

Calculated *vs.* Observed 25.2 MHz ^{13}C-Nmr Chemical Shifts of 1,9-Diazaphenoxathiin (**4**) in Deuteriochloroform



	α	β	2	3	4
δ^{13}C calcd	143.6	147.9	144.7	122.2	124.7
δ^{13}C obs	142.84	146.49	145.08	122.31	123.49

The structure of 1,9-diazaphenoxathiin (**4**) was straightforwardly determined by mass-spectroscopy and ^{1}H-nmr which, because of the high order of symmetry, gave a first order ^{1}H-nmr spectrum which is shown in Figure 1. Similarly, the decoupled ^{13}C-nmr spectrum, shown in Figure 2, was also readily assignable based on the previously assigned spectrum of 1-azaphenoxathiin (17,20). The ^{1}H-^{13}C spin-couplings for **4** were obtained by the gated decoupling technique of Freeman and Hill (24) which also provided readily interpretable results, again because of the inherent molecular symmetry. The spin-couplings obtained were comparable in magnitude and occurrence to those reported for pyridine (25) and the pyridyl-portion of 1-azaphenoxathiin (17,20). No effect on the coupling constants was seen which could have reflected the incorporation of the second pyridyl moiety in place of the benzenoid moiety, leading to the conclusion that the two rings are essentially isolated from one another in an electronic sense. Calculated *vs.* observed ^{13}C-nmr chemical shifts for **4** are shown in Table I while the ^{1}H-coupled ^{13}C-nmr spectrum is shown in Figure 3, the ^{1}H-^{13}C spin-coupling constants summarized in Table II.

Determination of the chemical structure of **5** was somewhat more difficult than for 1,9-diazaphenoxathiin (**4**). Because of the close similarity of the protons attached to the three pyridyl portions of **5**, the 100 MHz ^{1}H-nmr spectrum of **5** was exceedingly complex and only partially resolved. The mass spectrum of **5** was however considerably more diagnostic, containing a parent ion and several characteristic fragment ions which are summarized in Figure 4. Because of the complex and non-definative nature of the ^{1}H-nmr spectrum of **5**, we sought to confirm the structure by a second spectroscopic means and

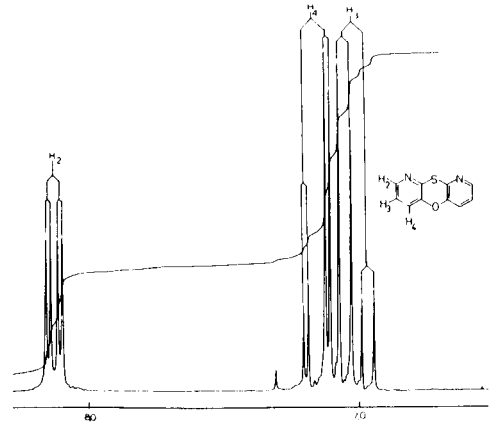


Figure 1. 100.060 MHz ^{1}H-nmr spectrum of 1,9-diazaphenoxathiin in deuteriochloroform.

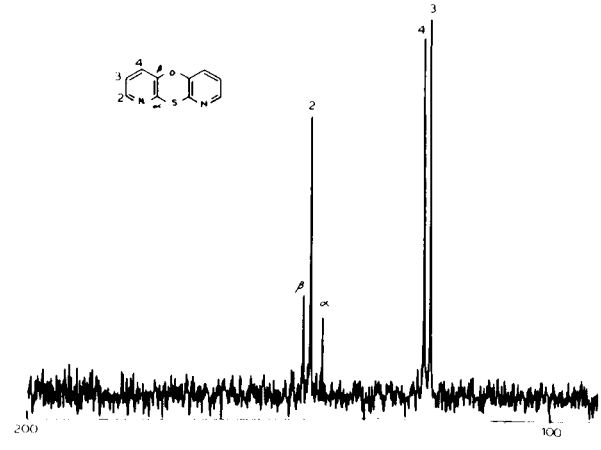
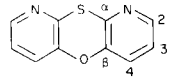


Figure 2. 25.158 MHz decoupled ^{13}C-nmr spectrum of the aromatic region of 1,9-diazaphenoxathiin (**4**) in deuteriochloroform.

Table II

^{1}H-^{13}C Spin Coupling Constants For 1,9-Diazaphenoxathiin (**4**) in Deuteriochloroform



Coupling Constant (Hz)

Resonance	$^1J_{CH}$	$^2J_{CH}$	$^3J_{CH}$
α	———	———	$J_{C_\alpha H_2}$ = 13.33 $J_{C_\alpha H_4}$ = 4.70
β	———	$J_{C_\beta H_4}$ = 2.15	$J_{C_\beta H_3}$ = 7.37
2	$J_{C_2H_2}$ = 181.82	$J_{C_2H_3}$ = 3.55	$J_{C_2H_4}$ = 7.12
3	$J_{C_3H_3}$ = 166.97	$J_{C_3H_2}$ = 9.41	———
4	$J_{C_4H_4}$ = 165.00	———	$J_{C_4H_2}$ = 6.60

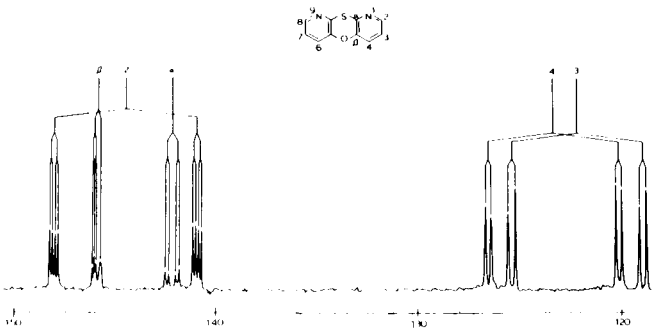


Figure 3. 25.158 MHz ^1H-^{13}C coupled spectrum of 1,9-diazaphenoxathiin (**4**) in deuteriochloroform.

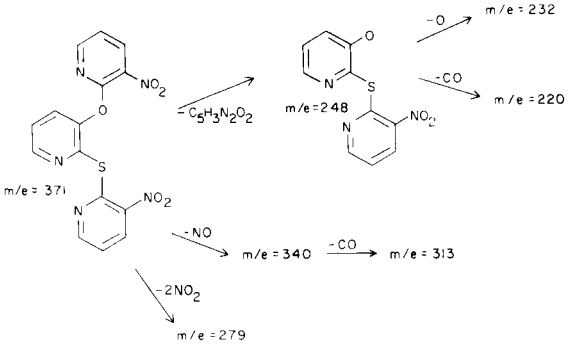


Figure 4. Major mass spectral fragments of 2-[2′-(3′-nitropyridylthio)]-3-[2″-(3″-nitropyridyloxy)]-pyridine (**5**).

resorted to ^{13}C-nmr spectroscopy (Figure 5). Preliminary attempts at assigning the ^{13}C-nmr spectrum of **5** using additivity correlations from simple pyridine derivatives (26-28) were fruitless. As an alternative means of assigning the spectrum, we undertook the synthesis of two model compounds which, because of close structrual similarities, were hoped to provide an adequate basis for the complete assignment of the ^{13}C-nmr spectrum of **5**. Thus, 2-(2′-pyridylthio)-3-nitropyridine (**7**) and 2-(2′-pyridyloxy)-3-nitropyridine (**9**) were synthesized as shown in

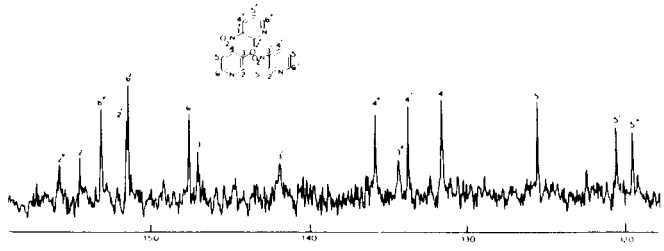
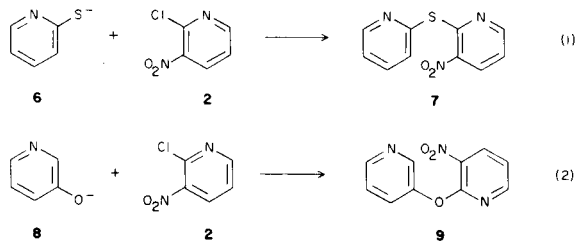


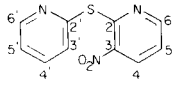
Figure 5. 25.158 MHz decoupled ^{13}C-nmr spectrum of 2-2′-(3′-nitropyridylthio)-3-2″-(3″-nitropyridyloxy)-pyridine (**5**) in deuteriochloroform.



reactions (1) and (2) respectively. The assignment of the ^{13}C-nmr spectrum of **7**, which is shown in Figure 6, was based on the previously reported assignments of 2,2′-dipyridyldisulfide and 2-pyridylphenyl sulfide analogs (18), the additivity effects for a pyridyl 3-nitro substituent (29)

Table III

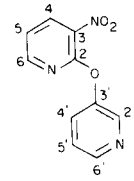
^1H-^{13}C Spin Coupling Constants For 2-(2′-Pyridylthio)-3-nitropyridine (**7**) in Deuteriochloroform



Resonance	Coupling Constant (Hz) $^1J_{CH}$	$^2J_{CH}$	$^3J_{CH}$
2	———	———	$J_{C_2H_4}$ = 7.83 $J_{C_2H_2}$ = 11.79
3	———	———	$J_{C_3H_5}$ = 7.19
4	$J_{C_4H_4}$ = 171.73	$J_{C_4H_5}$ = 2.03	$J_{C_4H_6}$ = 7.22
5	$J_{C_5H_5}$ = 170.12	$J_{C_5H_4}$ = 9.20	———
6	$J_{C_6H_6}$ = 183.01	$J_{C_6H_5}$ = 3.72 (a)	$J_{C_6H_4}$ = 7.47 (a)
2′	———		
3′	$J_{C_3'H_3'}$ = 168.78	———	$J_{C_3'H_5'}$ = 6.72
4′	$J_{C_4'H_4'}$ = 164.79	———	$J_{C_4'H_6'}$ = 6.93
5′	$J_{C_5'H_5'}$ = 165.70	$J_{C_5'H_6'}$ = 8.24 (b)	$J_{C_5'H_3'}$ = 6.23 (b)
6′	$J_{C_6'H_6'}$ = 180.64	$J_{C_6'H_5'}$ = 3.20	$J_{C_6'H_4'}$ = 6.72

(a) Couplings unresolved due to line broadening. (b) Couplings may be reversed.

Table IV
^{1}H-^{13}C Spin-Coupling Constants For 2-(3'-Pyridyloxy)-3-nitropyridine (9) in Deuteriochloroform



Coupling Constant (Hz)

Resonance	$^{1}J_{CH}$	$^{2}J_{CH}$	$^{3}J_{CH}$
2	———	———	$J_{C_2H_4}$ = 6.25 $J_{C_2H_6}$ = 12.21
3	———	———	$J_{C_3H_5}$ = 6.58
4	$J_{C_4H_4}$ = 169.05	$J_{C_4H_5}$ = 2.44	$J_{C_4H_6}$ = 7.18
5	$J_{C_5H_5}$ = 170.66	$J_{C_5H_6}$ = 8.61	———
6	$J_{C_6H_6}$ = 182.01	$J_{C_6H_5}$ = 3.75	$J_{C_6H_4}$ = 8.55
2'	$J_{C_2'H_2'}$ = 182.01	———	$J_{C_2'H_4'}$ = 3.66
3'	———	$J_{C_3'H_2'}$ = 7.97 (a) $J_{C_3'H_4'}$ = 2.90 (a)	$J_{C_3'H_5'}$ = 7.21
4'	$J_{C_4'H_4'}$ = 165.92	———	$J_{C_4'H_2'}$ = 4.72 (b) $J_{C_4'H_6'}$ = 7.14 (b)
5'	$J_{C_5'H_5'}$ = 165.75	$J_{C_5'H_6'}$ = 9.61	———
6	$J_{C_6'H_6'}$ = 179.64	$J_{C_6'H_5'}$ = 2.65	$J_{C_6'H_2'}$ = 11.30 $J_{C_6'H_4'}$ = 6.37

(a) Coupling constants may be reversed. (b) Coupling constants may be reversed.

and the premise that an *ortho* nitropyridylsulfide system would undergo a sulfur nitro interaction analogous to that previously described for 9-nitro-1-azaphenoxathiin (18) and 1,3-dinitrophenoxathiin (30). On these bases, the assignment of the ^{13}C-nmr spectrum of **7** is shown in Figure 7. Spin-coupling constants were determined for **7** and are shown in Table III. Assignments for the ^{13}C-nmr spectrum of **9** (Figure 8) were based on additivity constants for 2- (27) and 3-pyridyl ethers (26) as well as the pyridyl 3-nitro additivity coefficients (29) and are shown in Figure 7 as well. Spin-coupling constants were also determined for **9** and are shown in Table IV.

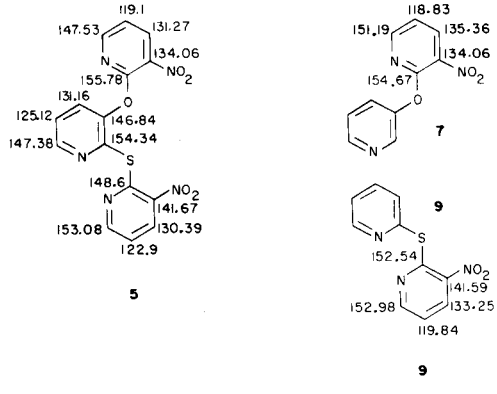


Figure 7. ^{13}C-nmr chemical shift assignments of 2-[2'-(3'-nitropyridylthio)]-3-[2"-(3"-nitropyridyloxy)]-pyridine (**5**), 2-(2'-pyridylthio)-3-nitropyridine (**7**) and 2-(2'-pyridyloxy)-3-nitropyridine (**7**).

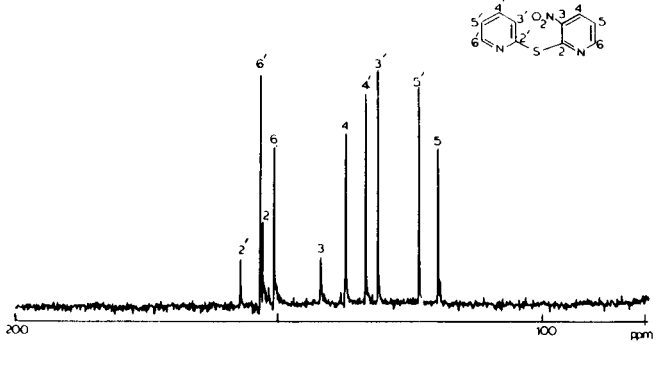


Figure 6. 25.158 MHz decoupled ^{13}C-nmr spectrum of 2-(2'-pyridylthio)-3-nitropyridine (**7**) in deuteriochloroform.

From the assigned spectra of the model compounds, **7** and **9**, the assignment of the two nitro-substituted pyridyl segments of **5** was undertaken, guided by the ^{1}H-^{13}C spin-coupling constants which are summarized in Table V. Reasonable agreement was obtained between the assigned resonances of **7** and **9** and the counterpart carbons of **5**. The assignment of the remaining resonances for the central pyridyl ring were based on additivity considerations and spin-coupling constants, the initial problems in

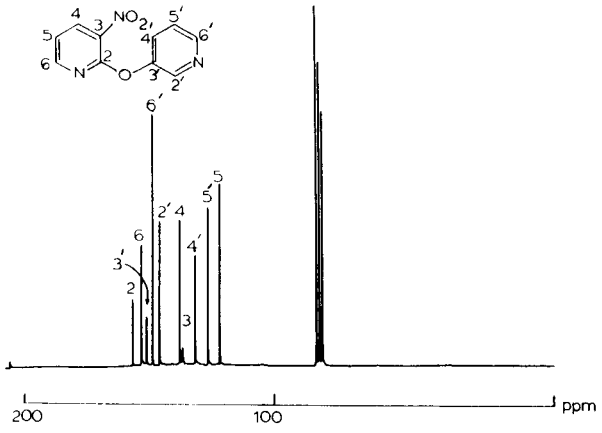


Figure 8. 25.158 MHz decoupled ^{13}C-nmr spectrum of 2-(2′-pyridyloxy)-3-nitropyridine (**9**) in deuteriochloroform.

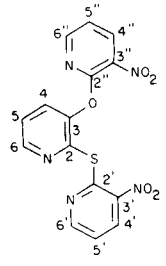
assignment considerably simplified by the preliminary assignment of the other resonances from the model compounds.

The synthesis of 1,7-diazaphenoxathiin (**14**), which is shown in Scheme II, was based on the conversion of 4-hydroxypyridine (**10**) to 4-hydroxy-3-nitropyridine in a mixture of fuming nitric and sulfuric acids, followed by the conversion of the 4-hydroxyl substituent to a 4-chloro substituent with phosphorus pentachloride according to the procedure of Kruger and Mann (31). Condensation of the resultant 4-chloro-3-nitropyridine (**12**) with **1**, again in dry *N,N*-dimethylformamide under an argon atmosphere, presumed to proceed through the phenolate sulfide intermediate (**13**), gave **14** in a 58% yield after cyclization. The lower yield of **14** is consistent with the anticipated reduction in activation associated with the 4-position relative to the 2-position of the pyridine ring.

Characterization of **14** was based on mass spectroscopy and ^{1}H-nmr spectroscopy, the latter giving a readily interpretable spectrum despite the lack of symmetry in the molecule (Figure 9). Analysis and assignment of the ^{13}C-nmr spectrum of **14** was considerably more complex and largely dependant on ^{1}H-^{13}C spin-coupling constants. Preliminary chemical shift calculations for half of the molecule were based on the chemical shifts for the corresponding segment of 1-azaphenoxathiin (17,20) while the remainder were calculated from the annular aza-substitution of phenoxathiin (32) as previously described (22). Despite the use of model compounds, permutations of resonance assignments were still possible and required the consideration of the ^{1}H-^{13}C spin-coupling constants to

Table V

^{1}H-^{13}C Spin-Coupling Constants For 2-[2′-(3′-Nitropyridylthio)]-3-[2″-(3″-nitropyridyloxy)]pyridine (**5**) in Deuteriochloroform



Resonance	Coupling Constant (Hz) $^{1}J_{CH}$	$^{2}J_{CH}$	$^{3}J_{CH}$
2	———	———	$J_{C_2H_4}$ = 4.37 $J_{C_2H_6}$ = 8.53
3	———	———	$J_{C_3H_5}$ = 5.17
4	$J_{C_4H_4}$ = 166.21	———	$J_{C_4H_6}$ = 6.86
5	$J_{C_5H_5}$ = 166.18	$J_{C_5H_6}$ = 9.17	———
6	$J_{C_6H_6}$ = 182.45	$J_{C_6H_5}$ = 3.23	$J_{C_6H_4}$ = 7.63 (a)
2′	———	———	
3′	———	———	$J_{C_3'H_5'}$ = 5.46
4′	$J_{C_4'H_4'}$ = 170.23	$J_{C_4'H_5'}$ = 1.70	$J_{C_4'H_6'}$ = 6.60
5′	$J_{C_5'H_5'}$ = 169.54	$J_{C_5'H_6'}$ = 9.13	———
6′	$J_{C_6'H_6'}$ = 183.60	$J_{C_6'H_5'}$ = 3.74	$J_{C_6'H_4'}$ = 8.56
2″	———	———	$J_{C_2''H_4''}$ = 6.81 $J_{C_2''H_6''}$ = 14.61
3″	———	———	$J_{C_3''H_5''}$ = 8.86
4″	$J_{C_4''H_4''}$ = 169.11	$J_{C_4''H_5''}$ = 2.15	$J_{C_4''H_6''}$ = 7.26
5″	$J_{C_5''H_5''}$ = 169.62	$J_{C_5''H_6''}$ = 8.86	———
6″	$J_{C_6''H_6''}$ = 183.12	$J_{C_6''H_5''}$ = 3.49	$J_{C_6''H_4''}$ = 7.85

(a) Was not resolved due to line broadening.

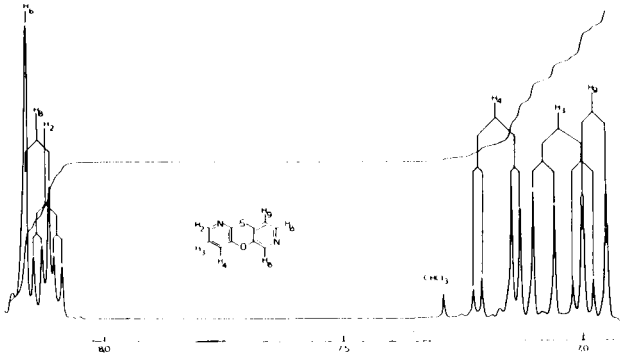


Figure 9. 100.060 MHz ^{1}H-nmr spectrum of the aromatic region of 1,7-diazaphenoxathiin (**14**) in deuteriochloroform.

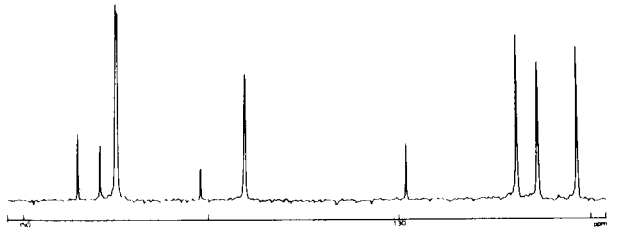
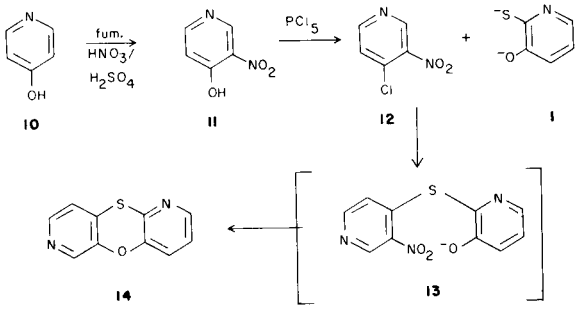


Figure 10. 25.158 MHz decoupled ^{13}C-nmr spectrum of 1,7-diazaphenoxathiin (**14**) in deuteriochloroform.

derive arguments for the unequivocal assignment, especially since some of the chemical shifts were very nearly degenerate, as shown by Figure 10.

Scheme II



The assignment of the ^{13}C-nmr spectrum of **14** was greatly facilitated by the ^{1}H-^{13}C spin-coupling constants obtained from the proton coupled spectrum which is shown in Figure 11. Thus, the protonated carbon resonances of C2, C6 and C8, which flank the two annular nitrogens, wich calculated chemical shifts of δ 145.7, 144.9 and 138.6 respectively, were clearly attributable to the resonances observed at δ 145.24, 145.14 and 138.34. The upfield resonance of this trio, δ 138.34, was clearly and umambiguously assignable to C8. The unequivocal discrimination of the resonances for C2 and C6 was possible only from the coupled spectrum in conjunction with an understanding of the spin-coupling behavior of pyridine (25). On this basis, both C2 and C6 were expected to exhibit a three bond coupling ($^3J_{CH}$), shown in the expansion of the ^{1}H-^{13}C coupled selectively excited subsepctrum for these resonances in Figure 12 (20). A convenient means of discriminating these resonances is however provided by the relative magnitude of the compounds the two resonances exhibit. Thus, C2 will exhibit a three bond coupling to H4, $^3J_{C_2H_4}$ = 7 Hz, while C6 experiences a three bond coupling to H8 modulated through the annular nitrogen $^3J_{C_6H_8}$ = 12-13 Hz. From this consideration, unequivocal assignment of the resonance at δ 145.24 can be made to C6 while the resonance at δ 145.14 is assignable to C2 (^{13}C-nmr chemical shift assignments for **14** are summarized in Table VII while the ^{1}H-^{13}C spin-coupling constants are summarized in Table VIII). Similar arguments can also be developed which readily permit the assignment of the Cβ and Cβ' resonances despite the similar calculated chemical shifts of δ 146.5 and 148.0, respectively, the observed resonances located at δ 147.50 and 146.05. Once again, the discriminatory basis is the coupling constants observed for the resonance, Cβ which is expected to exhibit a single three bond coupling, $^3J_{C_\beta H_3}$ = 8 Hz, while Cβ' was expected to exhibit two couplings of approximately equal magnitude, $^2J_{C_{\beta'}H_6}$ = 8 Hz and $^3J_{C_{\beta'}H_9}$ = 8 Hz. This two bond coupling in this case is characteristic to the pyridine system (25) and is substantially larger than other typical two bond couplings which range from about 1.1 Hz in benzene (34) to as large as $^2J_{C_2H_3}$ = +3.1 Hz for pyridine (25,35). Thus, the resonance observed at δ 147.50 is assignable to Cβ' while the resonance at δ 146.05 is assignable to Cβ. Finally, spin-coupling behavior also provided a means for the discrimation and unequivocal assignment of C3, C4 and

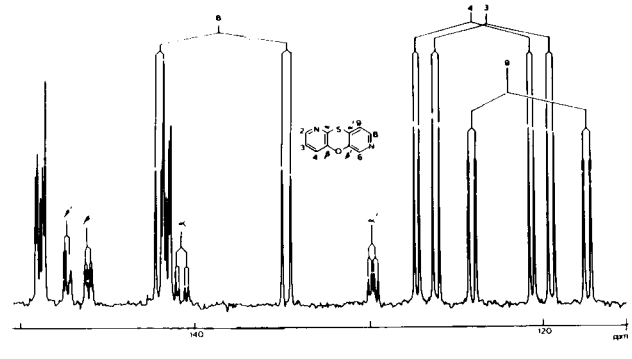
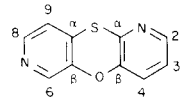


Figure 11. ^{1}H-^{13}C coupled spectrum of 1,7-diazaphenoxathiin (**14**) in deuteriochloroform.

C9, which were initially attributable to the resonances observed at δ 123.96, 122.87 and 120.79. The resonances for C3 and C9 were expected to exhibit large two bond ($^2J_{CH}$) couplings analogous to those of pyridine (25) and

Table VI

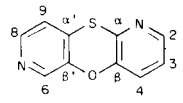
Calculated *vs.* Observed 25.2 MHz ^{13}C-Nmr Chemical Shifts of 1,7-Diazaphenoxathiin (**14**) in Deuteriochloroform



	α	α′	β	β′	2	3	4	6	8	9
δ^{13}C calcd	142.8	130.6	146.5	148.0	145.7	122.3	123.5	144.9	138.6	120.7
δ^{13}C obs	140.70	129.78	146.05	147.50	145.14	122.87	123.96	145.24	138.34	120.79

Table VII

^{1}H-^{13}C Spin-Coupling Constants of 1,7-Diazaphenoxathiin (**14**) in Deuteriochloroform



	Coupling Constant (Hz)			
Resonance	$^{1}J_{CH}$	$^{2}J_{CH}$	$^{3}J_{CH}$	$^{4}J_{CH}$
α	———	———	$J_{C_\alpha H_2}$ = 11.41 $J_{C_\alpha H_4}$ = 5.21	———
α′	———	———	$J_{C_{\alpha'} H_6}$ = 5.25 (a) $J_{C_{\alpha'} H_8}$ = 8.52 (a)	———
β	———	$J_{C_\beta H_4}$ = 2.52 (b)	$J_{C_\beta H_3}$ = 8.38	$J_{C_\beta H_2}$ = 2.39 (b)
β′	———	$J_{C_{\beta'} H_6}$ = 8.56	$J_{C_{\beta'} H_9}$ = 6.60	$J_{C_{\beta'} H_8}$ = 1.70
2	$J_{C_2H_2}$ = 182.00	$J_{C_2H_3}$ = 3.59	$J_{C_2H_4}$ = 6.83	———
3	$J_{C_3H_3}$ = 166.18	$J_{C_3H_2}$ = 9.17	———	———
4	$J_{C_4H_4}$ = 165.54	———	$J_{C_4H_2}$ = 7.18	———
6	$J_{C_6H_6}$ = 181.67	———	$J_{C_6H_8}$ = 11.81	———
8	$J_{C_8H_8}$ = 182.50	———	$J_{C_8H_6}$ = 11.39	———
9	$J_{C_9H_9}$ = 167.01	$J_{C_9H_8}$ = 10.35	———	$J_{C_9H_6}$ = 1.09

(a) Coupling constants may be reversed. (b) Coupling constants may be reversed.

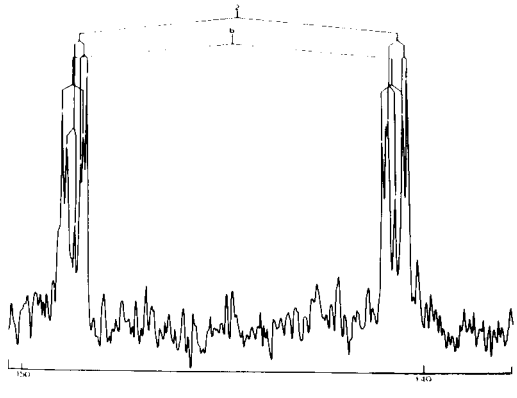


Figure 12. Selectively excited ^{1}H-^{13}C coupled subspectrum for C2/C6 resonances of 1,7-diazaphenoxathiin (**14**) in deuteriochloroform.

1,9-diazaphenoxathiin (**4**), $^{2}J_{C_3H_2}$ = 9.41 Hz, Table II. The observed couplings, 9.17 and 10.35 Hz, were in good accord with these predictions and were observed for the resonances located at δ 122.87 and 120.79, respectively. In

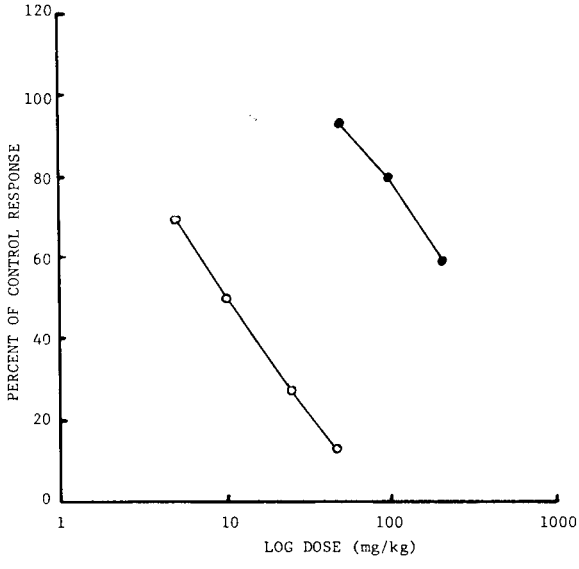


Figure 13. Spontaneous motor depression studies with 1,9-diazaphenoxathiin (**4**) (●) and 1,7-diazaphenoxathiin (o).

contrast, a coupling of 7.18 Hz was observed for the resonance at δ 123.96, which is typical of the three bond couplings of pyridine (25). Thus, the resonance observed at δ 123.96 was assigned to C4. The resonances for C3 and C9, although they could be discriminated from C4 on the basis of the observed two bond couplings, could not be unequivocally assigned on this same basis. The resonance at δ 120.79 did however exhibit a fine coupling which was assigned as $^{4}J_{C_9H_6}$ = 1.09 Hz and is presumed to be a result of the location of C9 relative to the annular nitrogen, this premise substantiated by the observed coupling, $^{4}J_{C_3H_6}$ = 1.7 Hz for pyridine (25). The resonance for C3, in contrast, although electronically similar to C9, did not have a proton properly positioned to permit the same type of spin-coupling, this behavior also corroborated by that for C3 of 1,9-diazaphenoxathiin (Table II).

With the development of selective excitation techniques (20) it is probable that more wide spread utilization of spin-coupling constants for total assignment of the ^{13}C-nmr spectra of heterocycles will be undertaken. Further studies directed toward the development of new applications of spin-coupling constants for assignment purposes are presently underway in these laboratories and will be reported.

In light of the interesting depression of spontaneous motor activity which we have previously reported for several 1-azaphenoxathiin analogs (16,19), we were interested in examining the capacity of **4** and **14** in this pharmacologic screen. The test compounds were suspended in a mixture of 5% Tween 80 + 95% isotonic saline and various doses were administered to test animals intraperitoneally. After one hour the depression of spontaneous motor activity was measured in photocell cages and is expressed as a percentage of control response. In this test protocol, 1,9-diazaphenoxathiin (**4**) exhibited relatively little spontaneous motor activity depression even at relatively high dosage levels, as shown in Figure 13. The administration of 1,7-diazaphenoxathiin (**14**) produce strikingly different results, giving significant spontaneous motor activity depression at doses as low as 5 mg./kg., an effect comparable to that observed with chlorpromazine.

While there is no clearly defined basis to account for the substantial disparity observed in the pharmacologic action of the two compounds, it is attractive to speculate that the position of the second annular aza-substitution is a key factor responsible for the observed and significant difference. Further, it is plausible that the position of the 7-aza-substituent approximates the position which would be occupied by the terminal amino nitrogen attached to the propyl side chain of chlorpromazine and thus, may stimulate the same receptor site, as illustrated by Figure 14. More detailed pharmacologic investigations of **14** are presently underway and will be reported elsewhere.

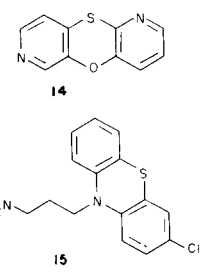


Figure 14. Comparative illustration of the possible orientation of 1,7-diazaphenoxathiin and the *N,N*-dimethylamino-*n*-propyl side chain of chlorpromazine (**15**) which might account for the unprecedentely high capacity for 1,7-diazaphenoxathiin to induce spontaneous motor activity depression in mice.

EXPERIMENTAL

Melting points were obtained in open capillary tubes in a Thomas-Hoover melting point apparatus and are reported uncorrected. Infrared spectra were recorded on a Perkin-Elmer model 283 spectrophotometer as potassium bromide pellets. ^{1}H-nmr spectra were recorded in deuteriochloroform on a Varian Associates model XL-100 spectrometer operating at 100.060 MHz in the Fourier transform mode. The following fixed operating parameters were employed for the ^{1}H-nmr spectral acquisition: pulse width, 10.0 μseconds; pulse delay, 1.00 second; sweep width, 1500 Hz; acquisition time, 2.7279 seconds; data size 16 K; apodization, −0.1 second. ^{13}C-nmr spectra were acquired on the same instrument operating at 25.158 MHz in the Fourier transform mode. Additional equipment utilized in the ^{13}C-nmr spectral acquisition were a Nicolet Technology Corporation model NT-440 multi-observe nuclei accessory (MONA), a TT-760 decoupler with a measured $\gamma H_2/2\pi$ = 2.9 kHz, and a Varian model 4311 variable frequency attenuator inserted in line between the pulse amplifier and the probe to facilitate the execution of the selective excitation pulse sequence (20). Low resolution mass spectra were measured on a Hewlett-Packard model 5350 GC/MS system equipped with a model 5933-A data system. All samples were introduced by direct probe insertion at a source temperature of 250° and an ionizing energy of 70 eV. Spontaneous motor activity testing was conducted in photocell cages obtained from Woodard Research Corp.

Disodium Salt of 2-Mercapto-3-pyridinol (**1**).

The disodium salt of 2-mercapto-3-pyridinol was prepared by the reaction of free 2-mercapto-3-pyridinol with sodium ethoxide freshly prepared in an excess of anhydrous ethanol according to the procedure of Martin, *et al.* (16).

Synthesis of 1,9-Diazaphenoxathiin (**4**).

To a three necked flask containing 30 ml. of dry distilled *N,N*-dimethylformamide was added 1.5 g. (0.0094 mole) of 2-chloro-3-nitropyridine (**2**). To the stirred solution under an argon atmosphere at room temperature was added 1.62 g. (0.0094 mole) of the sodium salt of 2-mercapto-3-pyridinol (**1**), as the dry powder. The mixture which darkened immediately was stirred at room temperature for 2 hours and then brought to reflux for an additional 4 hours. The entire reaction mixture was poured into 100 ml. of cold distilled water and extracted with 4 × 125 ml. portions of ethyl ether. The combined extracts were back extracted with 4 × 200 ml. distilled water, dried over anhydrous magnesium sulfate and concentrated to give a crude crystalline product. The crude material was chromatographed over a silica gel column eluted with cyclohexane:ethyl acetate (4:1) to give the desired product, **4**, 1.5 g. (79% yield), m.p. 127.5-129°, and a minor fraction which was subsequently identified as **5**. For compound **4**; ir: λ (cm^{-1}) 1590, 1455, 1420, 1280, 1220, 1100, 795; ms: m/e (% relative intensity) 202 (100), 203 (11), 204

(4), 175 (21), 169 (12), 167 (13), 158 (28), 147 (21), 146 (15), 131 (13), 82 (15) and 69 (19); ^{1}H-nmr (deuteriochloroform): δ 8.11 (dd, $J_{H_2H_3}$ = 4.71, $J_{H_2H_4}$ = 2.24 Hz, 1H) H2, 6.99 (dd, $J_{H_3H_2}$ = 4.71, $J_{H_3H_2}$ = 8.17 Hz, 1H) H3, 7.14 (dd, $J_{H_4H_3}$ = 8.18, $J_{H_4H_2}$ = 2.24 Hz, 1H) H4 (see also Figure 1). ^{13}C-nmr spectra are shown in Figures 2 and 3 and the data summarized in Tables I and II.

Anal. Calcd. for $C_{10}H_6N_2OS$: C, 59.41; H, 2.97; N, 13.86. Found: C, 59.65; H, 3.01; N, 14.00.

Synthesis of Sodium 2-Pyridyl Mercaptide (**6**).

The synthesis of sodium-2-pyridyl mercaptide (**6**) was conducted according to the procedure previously described by Martin and Turley (18).

Synthesis of Sodium 3-Pyridylphenolate (**8**).

The synthesis of the sodium salt of 3-pyridinol to provide the phenolate (**8**) was conducted according to the procedure of Martin and Turley (18).

Synthesis of 2-(2'-Pyridylthio)-3-nitropyridine (**7**).

The synthesis of 2-(2'-pyridylthio)-3-nitropyridine (**7**) was conducted by dissolving 4.2 g. (0.0265 mole) of 2-chloro-3-nitropyridine (**2**) in 60 ml. of distilled *N,N*-dimethylformamide with stirring. The reaction vessel was then purged with zero grade Argon followed by the slow addition of 3.51 g. (0.0265 mole) of the sodium salt of 2-mercaptopyridine (**7**). The solution was stirred at room temperature for 8 hours and then poured into 50 ml. of ice water which was extracted with 6 × 100 ml. of diethyl ether. The ether layers were combined and then back extracted with 3 × 100 ml. of distilled water, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The oily residue was crystallized from a mixture of cyclohexane/acetone (4/1) to give 2.2 g. (35% yield) of the desired product, m.p. 114-115°; ms: m/e (% relative intensity) 233 (5.0), 188 (12), 187 (100), 149 (18), 78 (30). The ^{13}C-nmr spectrum of **7** is shown in Figure 6 and resonance assignment is shown in Figure 7. ^{1}H-^{13}C spin-coupling constants are tabulated in Table III.

Anal. Calcd. for $C_{10}H_7N_3O_2S$: C, 51.50; H, 3.00; N, 18.03. Found: C, 51.26; H, 3.09; N, 17.91.

Synthesis of 2-(2'-Pyridyloxy)-3-nitropyridine (**9**).

The synthesis of 2-(2'-pyridyloxy)-3-nitropyridine (**9**) was conducted by dissolving 3.35 g. (0.026 mole) of 2-chloro-3-nitropyridine (**2**) in 250 ml. of absolute ethanol, to which was then added 3.35 g. (0.0286 mole) of **8**. The solution of refluxed overnight and the solvent removed under reduced pressure to give a light brown oil which was then taken up in methylene chloride, extracted with 2 × 60 ml. of 20% sodium hydroxide and 3 × 50 ml. distilled water. The methylene chloride layer was then concentrated under reduced pressure and then chromatographed over silica gel 60, eluted with a 1:1 mixture of cyclohexane:ethylacetate. The resultant crude yellow crystalline material was recrystallized from cyclohexane/acetone to give 3.4 g. (60% yield) of **9** as yellow plates melting 60-61°; ms: m/e (% relative intensity): 217 (36), 216 (6), 200 (55), 171 (19), 170 (60), 142 (20), 116 (36), 89 (29), 82 (15), 78 (49), 66 (34), 51 (100). The ^{13}C-nmr spectrum of **9** is shown in Figure 8 while the resonance assignments are shown in Figure 7. ^{1}H-^{13}C Spin-coupling data for **9** are tabulated in Table IV and are consistent with the structure of **9**.

Anal. Calcd. for $C_{10}H_7N_3O_3$: C, 55.29; H, 3.22; N, 19.35. Found: C, 55.52; H, 3.28; N, 19.42.

Synthesis of 2-[2'-(3'-Nitropyridylthio)]-3-[2''-(3''-nitropyridyloxy)]pyridine (**5**).

The synthesis of **5** was conducted in a manner analogous to that for **4**. To 25 ml. of *N,N*-dimethylformamide was first added 1.00 g. (0.0063 mole) of 2-chloro-3-nitropyridine (**2**), followed by the slow addition of 0.46 g. (0.0029 mole) of the disodium salt of 2-mercapto-3-pyridinol (**1**). The reaction mixture was stirred at room temperature for 6 hours and then poured into 100 ml. of ice water and extracted with 10 × 50 ml. of ethyl acetate. The combined ethyl acetate extracts were then back extracted with 4 × 250 ml. of distilled water and dried over anhydrous sodium sulfate and concentrated to an oil under reduced pressure. The oil was dissolved in about 5 ml. of a 4:1 mixture of cyclohexane:ethyl acetate and chromatographed over a silica gel 60 column eluted first with the same solvent mixture followed by pure ethyl acetate. The product was crystallized by addition of small quantities of petroleum ether to the fractions containing **5** to give 0.116 g. (16% yield), m.p. 136-137°. The low resolution mass spectrum was obtained and is illustrated in Figure 4. The decoupled ^{13}C-nmr spectrum of **5** is shown in Figure 5 and the resonance assignments are shown in Figure 7. ^{1}H-^{13}C Spin-couplings for **5** are tabulated in Table V.

Anal. Calcd. for $C_{15}H_9N_5O_5S$: C, 48.19; H, 2.87; N, 16.88. Found: C, 47.93; H, 2.66; N, 16.93.

Synthesis of 1,7-Diazaphenoxathiin (**14**).

The synthesis of **14** was conducted by dissolving 4.0 g. (0.0252 mole) of 4-chloro-3-nitropyridine, prepared according to the procedure of Kruger and Mann (31), in 50 ml. of distilled *N,N*-dimethylformamide under an argon purge. To this solution was then added 4.31 g. of **1**, as a dry powder, over a period of 30 minutes. The reaction mixture was stirred at room temperature for 12 hours and was then brought to reflux overnight. The cool reaction mixture was then poured into 100 ml. of ice water which was then extracted with 4 × 250 ml. of ethyl acetate. The combined extracts were then back extracted with 4 × 500 ml. of distilled water and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to give 3.0 g. (58% yield) of **14** as yellowish crystals, m.p. 147-148°; ir: (cm^{-1}) 1590, 1560, 1540, 1480, 1440, 1420, 1280, 1210, 1080, 900, 870, 810, 800, 790 and 690. The 100.060 MHz ^{1}H-nmr spectrum is shown in Figure 9; δ 8.17 (s, H6), 8.15 (d, $J_{H_8H_9}$ = 5.14 Hz, H8), 8.12 (dd, $J_{H_2H_3}$ = 4.4 Hz, $J_{H_2H_4}$ = 1.8 Hz, H2), 7.18 (dd, $J_{H_4H_3}$ = 8.15 Hz, $J_{H_4H_2}$ = 1.8 Hz, H4), 7.02 (dd, $J_{H_3H_2}$ = 4.4 Hz, $J_{H_3H_4}$ = 8.15 Hz, H3), 6.98 (d, $J_{H_9H_8}$ = 5.12 Hz, H9). The decoupled ^{13}C-nmr spectrum of **14** is shown in Figure 10, while the calculated *vs.* observed chemical shifts are shown in Table VI. The ^{1}H-^{13}C spin-coupled spectrum of **14** is shown in Figure 11 and the individual couplings are shown in Table VII; ms: m/e (% relative intensity) M+ 202 (100), 203 (12), 204 (5), 175 (12), 169 (6), 158 (20), 147 (12), 146 (10), 82 (18) and 79 (32).

Anal. Calcd. for $C_{10}H_6N_2OS$: C, 59.41; H, 2.97 and N, 13.86. Found: C, 59.05; H, 3.06; N, 14.00.

REFERENCES AND NOTES

(1) Abstracted in part from the M.S. thesis of Steven R. Caldwell, Universty of Houston, College of Pharmacy, 1979, Present address, Hoescht-Roussel Pharmaceuticals, Inc., Somerville, N.J.

(2) To whom inquiries should be addressed. For the preceeding paper in this series, see Chemistry of the Phenoxathiins and Isosterically Related Heterocycles XI, *J. Heterocyclic Chem.*, **17**, 989 (1980).

(3) T. Charpentier, *Compt. Rend.*, **235**, 59 (1952).

(4) S. Courvoisier, J. Fournel, R. Ducrot, M. Kolsky and P. Koetchet, *Arch. Int. Pharmacodyn*, **92**, 305 (1952).

(5) J. Delay, T. Deniker and J. M. Harl, *Ann. Med. Psychol. France*, **110**, 112 (1952).

(6) H. E. Lehman and G. E. Hanrahan, *A. M. A. Arch. Neurol. Psychiat.*, **71**, 227 (1954).

(7) W. A. Schuler and H. Klebe, *Ann. Chem.*, **653**, 172 (1962).

(8) A. R. Gennar, *J. Org. Chem.*, **24**, 1156 (1959).

(9) M. L. Gale and F. Sowinski, *J. Am. Chem. Soc.*, **80**, 1651 (1958).

(10) A. J. Saggiomo, P. N. Craig and M. Gordon, *J. Org. Chem.*, **23**, 1906 (1958).

(11) P. N. Craig, M. Gordon, J. J. Lafferty, B. M. Lester, A. J. Saggiomo and C. I. Zirkle, *ibid.*, **26**, 1138 (1961).

(12) F. H. Clarke, U. S. Patent 3,118,884 (1964).

(13) C. O. Okafor, *Int. J. Sulfur Chem., B*, **6**, 345 (1971).

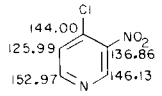
(14) C. O. Okafor, *J. Chem. Soc., Chem. Commun.*, 878 (1974).

(15) C. O. Okafor, *J. Heterocyclic Chem.*, **13**, 107 (1976).

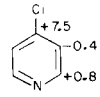
(16) G. E. Martin, J. C. Turley, L. Williams, M. L. Steenber and J. P. Buckley, *ibid.*, **14**, 1067 (1977).

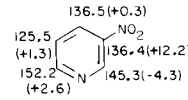
(17) G. E. Martin, J. C. Turley and L. Williams, *ibid.*, **14**, 1249 (1977).
(18) G. E. Martin and J. C. Turley, *ibid.*, **15**, 609 (1978).
(19) G. E. Martin, J. C. Turley, J. D. Korp and I. Bernal, *ibid.*, **15**, 721 (1978).
(20) G. E. Martin, *ibid.*, **15**, 1539 (1978).
(21) G. E. Martin, *ibid.*, **17**, 429 (1980).
(22) S. R. Caldwell and G. E. Martin, *ibid.*, **17**, 989 (1980).
(23) A. J. Parker, "Organic Sulfur Compounds", N. Kharsch, Ed., Pergamon Press, New York, N.Y., 1966, p. 103.
(24) R. Freeman and H. D. W. Hill, *J. Magn. Reson.*, **5**, 278 (1971).
(25) M. Hausen and H. J. Jakobsen, *ibid.*, **10**, 74 (1973).
(26) S. A. Sojka, F. J. Dinan and R. Kolarczyk, *J. Org. Chem.*, **44**, 307 (1979).
(27) F. W. Wehrli and T. Wirthlin, "Interpretation of Carbon-13 NMR Spectra", Heyden and Sons, Inc., New York, N.Y., 1976, p. 49.
(28) G. C. Levy and G. N. Nelson, "Carbon-13 Nuclear Magnetic Resonance for Organic Chemists", Wiley-Interscience, New York, N.Y., 1972, p. 98.

(29) the additivity coefficients for a pyridyl bearing a 3-nitro substituent can be calculated from the ^{13}C-nmr chemical shifts of 4-chloro-3-nitropyridine (**12**) by subtracting the chemical shifts contribution due to the 4-chloro substituent, and then taking the difference relative to pyridine to obtain the additivity coefficient which is shown in parentheses.



12





(30) J. C. Turley and G. E. Martin, *Spectrosc. Lett.*, **11**, 681 (1978).
(31) S. Kruger and F. G. Mann, *J. Chem. Soc.*, 2755 (1955).
(32) L. R. Isenbrandt, R. K. Jensen and L. Petrakis, *J. Magn. Res.*, **12**, 143 (1973).
(33) Y. Takeuchi and N. Dennis, *J. Am. Chem. Soc.*, **96**, 3657 (1974).
(34) A. R. Tarpley and J. H. Goldstein, *J. Chem. Phys.*, **76**, 515 (1972).

(35) Caution should be exercised when dealing with models for spin-coupling constant behavior since they are quite sensitive to changes in ring geometry and may lead to erroneous conclusions. Pyrrole, for example (F. J. Weigert and J. D. Roberts, *J. Am. Chem. Soc.*, **90**, 3543 (1968)) exhibits somewhat larger two bond couplings: $^{2}J_{C_2H_3}$ = 7.6 Hz; $^{2}J_{C_3H_2}$ = 7.8 Hz; $^{2}J_{C_3H_4}$ = 4.6 Hz.