# (1). The Synthesis and Molecular Structure of 3-Azaphenoxathiin: Evidence in Support of Factors Responsible for Control of the Dihedral Angle

*Steven R. Caldwell (2) and Gary E. Martin (3)*

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

*Stanley H. Simonsen*

Department of Chemistry, The University of Texas at Austin, Austin, Texas 78712

*Ruth R. Inners*

South Carolina Magnetic Resonance Laboratory, University of South Carolina,
Columbia, South Carolina 29208

*and*

*M. Robert Willcott, III*

Department of Chemistry, University of Houston, Houston, Texas 77004
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The synthesis of the 3-azaphenoxathiin ring system and its molecular structure are reported. Based on $^{13}$C-nmr chemical shift additivities associated with the insertion of an annular nitrogen atom and the observed $^{13}$C-nmr shift of C$\alpha$, the title compound was predicted to have a dihedral angle $\theta = 160.2°$. The observed dihedral angle from the crystal structure was found to be $\theta = 167.07°$ which is in reasonably good agreement with the predicted value. It is proposed that the position of the annular nitrogen atom is solely in control of the observed dihedral angle.

As part of a search for potential new psychoactive heterocyclic ring systems, the syntheses of the parent 1-azaphenoxathiin system (4) and various benzo-substituted analogs (5-8) have been reported. The compounds thus far prepared have shown some psychoactive properties. In general the observed activity has not been clinically significant, however, one analog did display anti-depressant activity of the same order as imipramine which is widely used in clinical practice (8). While the 1-aza-phenoxathiin system has thus far failed to yield a highly psychoactive analog, corollary studies on the molecular structure of several of the substituted analogs (7) have shown these agents to be essentially planar, which is in direct contrast to the rationale for their original synthesis (5). Specifically, the 1-azaphenoxathiin ring system was selected based on the observed similarity between the

Scheme I



**SCHEME II**



phenoxathiin parent system, which has a molecular dihedral angle $\theta = 138°$ (9), and several clinically useful phenothiazines, all of which possess dihedral angles in the vicinity of $\theta = 140°$ (10-13). The observed disparity in molecular geometry has thus led us to investigate further

Figure 1. The fully decoupled $^{13}$C-nmr spectrum of 3-azaphenoxathiin (**4**) in deuteriochloroform.
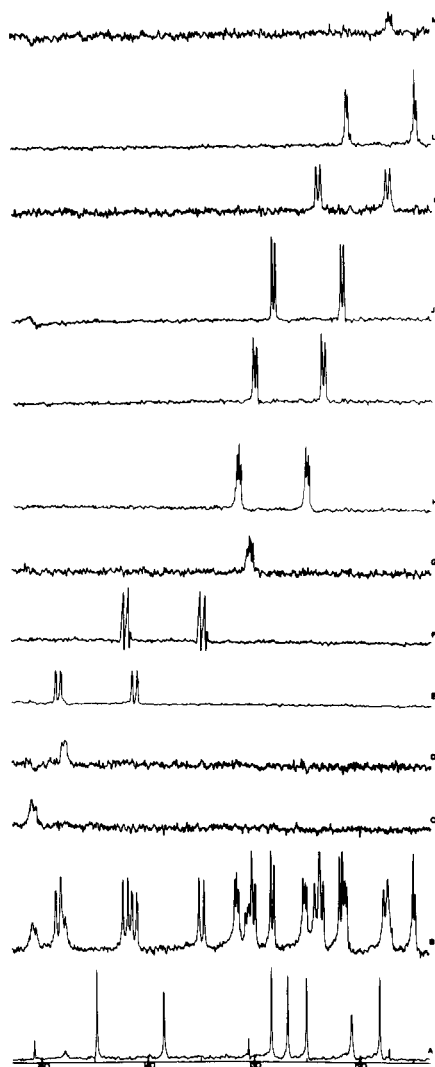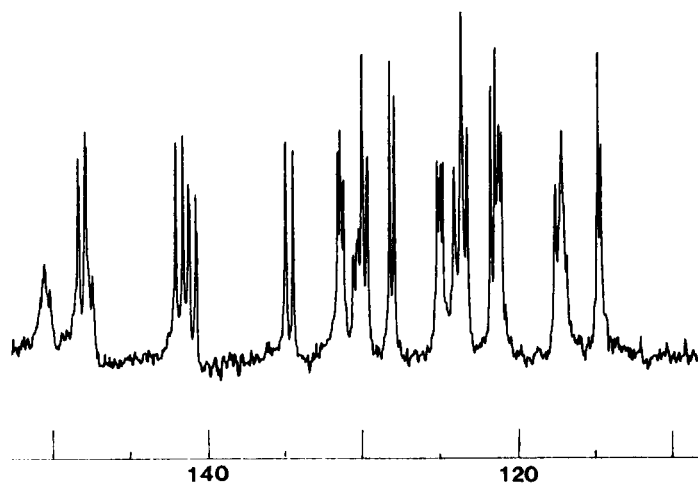


Figure 2. The $^1$H-$^{13}$C spin coupled spectrum of 3-azaphen-oxathiin (**4**) required under gated decoupling conditions.



Figure 3. Selectively excited $^1$H-$^{13}$C spin coupled sub-spectra of 3-azaphenxoathiin (**4**).

the factors responsible for the noted change in the dihedral angles. An outgrowth of these investigations has been our report on the correlation between the $^{13}$C-nmr chemical shift of the C$\alpha$ resonance and the molecular dihedral angle (14), followed by the recently reported synthesis of the 2-azaphenoxathiin (15) ring system. In a further extension of these studies, we now report the synthesis, and molecular structure of the 3-azaphenoxathiin ring system.

The synthesis of 3-azaphenoxathiin was based on the condensation of the disodium salt of 2-mercapthophenol, prepared according to the procedure of Turley and Martin (16), which was condensed with 4-chloro-3-nitropyridine (17) as shown in Scheme I. As in previous studies (3-7), the reaction proceeded through the intermediate phenolate sulfide (**3**) which was isolable by quenching the reaction
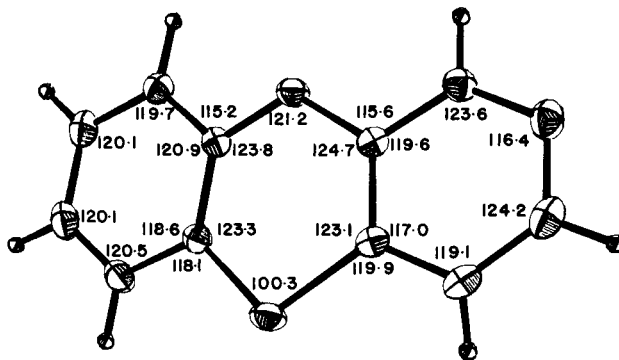


Figure 4. Bond angles of 3-azaphenoxathiin (**4**).

Table I

Calculated vs. Observed ^{13}C-Nmr Chemical Shifts of 3-Azaphenoxathiin (4)
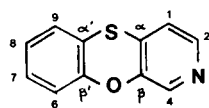


Chemical Shift (ppm)

| Carbon | Calculated | Observed | (a) |
|--------|-----------|----------|-----|
| α | 127.7 | 130.56 | + 2.9 |
| β | 145.6 | 148.04 | − 2.4 |
| α' | 119.0 | 117.99 | − 1.0 |
| β' | 150.0 | 150.96 | + 1.0 |
| 1 | 123.3 | 120.67 | − 2.6 |
| 2 | 144.6 | 144.93 | + 0.3 |
| 4 | 138.3 | 138.58 | + 0.3 |
| 6 | 117.3 | 117.24 | 0.0 |
| 7 | 126.6 | 126.73 | + 0.1 |
| 8 | 123.6 | 124.93 | + 1.3 |
| 9 | 126.9 | 128.33 | + 1.4 |

(a) Positive values denote downfield shifts while negative values denote upfield shifts relative to the calculate ^{13}C-nmr shift.

with water to afford the corresponding phenol sulfide (5). Based on this observation, it was certain that subsequent cyclization would afford the desired 3-azaphenoxathiin (4) in the absence of an unprecedented Smiles rearrangment. Refluxing the reaction mixture containing the inter-mediate phenolate sulfide (3) followed by isolation of the product in the usual fashion did afford a compound which contained an intense parent ion, M+, observed at m/z = 201 (100%) in the mass spectrometer. Fragment ions were also observed, as shown in Scheme II, which were consis-tent with the structure of 4, identities these ions confirmed by high resolution mass spectroscopy.

Examination of the [1]H-decoupled ^{13}C-nmr spectrum of 4, Figure 1, showed eleven clearly resolved resonances which were easily sub-grouped into protonated and non-protonated resonances based on the significantly lower in-tensity of the latter (18). Calculated ^{13}C-nmr chemical shifts for 4 were based on the observed chemical shift data for the parent phenoxathiin ring system (19) which was then incremented for the insertion of an annular nitrogen atom as previously described (4,15) to provide the results shown in Table I. Resonance assignments were based on chemical shift arguments in conjunction with [1]H-^{13}C spin-coupling constants obtained from the gated decoupled spectrum (20) of 4 which is shown in Figure 2. Because of the substantial overlapping of spin-multiplets shown in the fully coupled spectrum of 4, individual selectively excited sub-spectra were obtained (21-23) to facilitate the analysis of the spectrum, shown in Figure 3, the couping constants summarized in Table II.

While the assignments shown in Table I were generally straightforward, the possibility for permutation did exist

for at least one pair of resonances contained in the benzenoid portion of 4. In an effort to resolve this poten-tial ambiguity, the 400 MHz [1]H-nmr spectrum of 4 was obtained with the intent of following this experiment by selective on-resonance decoupling of the individual proton resonances with concurrent observation of the 100 MHz ^{13}C-nmr spectrum. Despite the significantly enhanced signal dispersion obtained in this experiment, the resonances of interest were still so strongly coupled that they were not amenable to selective decoupling.
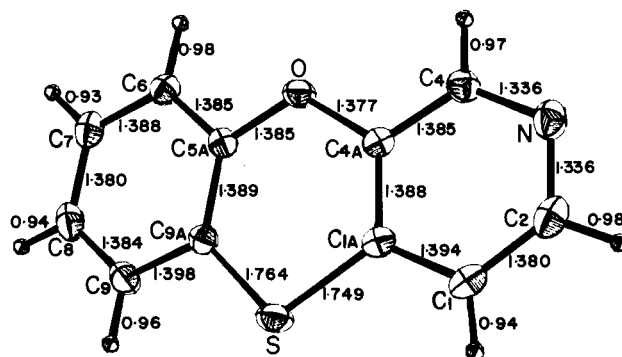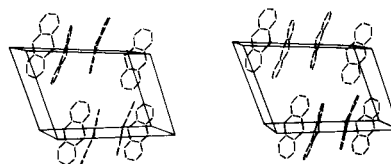


Figure 5. Bond lengths of 3-azaphenoxathiin (4).



Figure 6. Stereo view of the packing diagram of 3-aza-phenoxathiin (4).

A critical aspect of the synthesis of 3-azaphenoxathiin was our conviction that the position of the annular aza-substitution was the principle factor in control of the molecular dihedral angle. This premise is based on the additivities which may be calculated for the annular nitrogen of pyridine by subtracting the chemical shift for benzene, δ 128.6, from the observed chemical shifts of pyridine. The resultant additivities, positive values in-dicating a downfield shift while negative values corres-pond to an upfield shift, allow the prediction of 3-azaphenoxathiin chemical shifts as discussed above.

More importantly, however, they also lead to the observa-tion that the Cα position in 4, located para to the annular nitrogen, should be shifted downfield by only + 7.6 ppm in contrast to the + 21.0 ppm shift which the same posi-tion would experience in the 1-azaphenoxathiin ring system. The importance of the positioning of the annular nitrogen is seen when the effect of electron withdrawing substituents on the dihedral angles of the isosterically

Table II

$^1$H-$^{13}$C Spin-Coupling Constants for 3-Azaphenoxathiin (4)
Determined from the Gated Decoupled Spectrum Shown in Figure 2
and the Selectively Excited Sub-Spectra Shown in Figure 3

coupling constant (Hz)

| Carbon | $^1J_{CH}$ | $^2J_{CH}$ | $^3J_{CH}$ |
|--------|-----------|-----------|-----------|
| α | --- | --- | $^3J_{C\alpha H_4} = 5.4$ (a) |
|  |  |  | $^3J_{C\alpha H_2} = 8.4$ (a) |
| β | --- | --- | (b) |
| α' | --- | --- | $^3J_{C\alpha' H_6} = 4.4$ (a) |
|  |  |  | $^3J_{C\alpha' H_8} = 8.5$ (a) |
| β' | --- | --- | (b) |
| 1 | $^1J_{C_1H_1} = 165.9$ | $^2J_{C_1H_2} = 10.3$ |  |
| 2 | $^1J_{C_2H_2} = 181.1$ |  | $^3J_{C_2H_4} = 11.9$ |
| 4 | $^1J_{C_4J_4} = 182.1$ |  | $^3J_{C_4H_2} = 11.9$ |
| 6 | $^1J_{C_6H_6} = 163.6$ |  | $^3J_{C_6H_8} = 4.4$ |
| 7 | $^1J_{C_7H_7} = 162.9$ | $^2J_{C_7H_6}$ or | $^3J_{C_7H_9} = 7.8$ |
|  |  | $^2J_{7_7H_8} = 1.8$ |  |
| 8 | $^1J_{C_8H_8} = 163.6$ |  | $^3J_{C_8H_6} = 7.8$ |
| 9 | $^1J_{C_9H_9} = 163.3$ | $^2J_{C_9H_8} = 3.7$ | $^3J_{C_9H_7} = 6.1$ |

(a) Coupling constants which may be permuted. (b) Couplings poorly resolved.

Table 3

Least-Squares Planes Passing Through the Atoms
of the Pyridine and Benzene Rings

(1) Benzene Ring

$$0.6445X + 0.4943Y - 0.5833Z = -1.0940$$

| C5A | 0.020 Å | C9 | 0.012 |
|-----|---------|-----|-------|
| C6 | 0.003 | C9A | 0.020 |
| C7 | −0.019 | S | −0.022 |
| C8 | −0.007 | O | −0.009 |

(2) Pyridine Ring

$$0.4765X + 0.4853Y - 0.7330Z = -3.7775$$

| Cl | 0.000 Å | C4A | 0.024 |
|-----|---------|-----|-------|
| C2 | −0.029 | C10A | 0.022 |
| N | −0.005 | S | −0.003 |
| C4 | 0.028 | O | −0.038 |

Angle between planes (1) and (2): 167.07°.

related phenothiazines is considered (12). Thus, while chlorpromazine (2-chloropromazine) contains an electron withdrawing group *para* to the sulfur atom and has a dihedral angle, $\theta = 139.2°$ (10), substitution of a methoxyl group in the 2-position in the place of the chloro-group gives a consequent flattening of the molecule with an observed dihedral angle $\theta = 157.4°$ (24). Similar changes are also seen in the 2-substituted-10*H*-phenothiazines (25-27) and provide an even more closely analogous case relative to the system presently under investigation. Based

on these observations and the observed chemical shift for Cα $\delta = 130.6$, it was logical to conclude that **4** would be more folded than the 1-azaphenoxathiins (7) in which Cα resonates at $\delta$ 142.9 (average 7-chloro and 8-chloro-1-azaphenoxathiin), and somewhat less folded than the parent phenoxathiin ring system (9) in which Cα resonates at $\delta$ 119.9 (19). Specifically, using the data contained in our recent communication (14), which has been further updated by the inclusion of the data from our studies of the 1-nitrophenoxathiin system (28,29), 3-azaphenoxathiin was calculated to have a dihedral angle $\theta = 160.2°$, this based solely on the Cα chemical shift.

Crystallographic studies of **4** were conducted on a monoclinic crystal obtained from a sample of material which had been prepurified by crystallization from cyclohexane. The structure of the molecule was solved by direct methods using the MULTAN 76 program (30) with the hydrogen atoms subsequently located from a difference map. Bond lengths and bond angles of **4**, shown in Figures 4 and 5 respectively, were found to compare favorably to those reported for 7-chloro and 8-chloro-1-azaphenoxathiin (7). The most significant difference between **4** and the aforementioned 1-azaphenoxathiin analogs was the dihedral angle. Thus, while the 1-azaphenoxathiin analogs were nearly planar, exhibiting dihedral angles of $\theta = 175.73$ and $176.68°$ (7), 3-azaphenoxathiin (**4**), in contrast had a dihedral angle $\theta = 167.07°$ which agreed quite well with that predicted from the $^{13}$C-nmr data above. Equations for the least squares planes passing through the atoms of the pyridine ring and the benzene ring are given in Table 3 while the positional and thermal parameters for the non-hydrogen and hydrogen atoms of **4** are given in Tables 4 and 5, respectively.

We have shown from the synthesis, $^{13}$C-nmr shift assignments and the molecular structure of 3-azaphenoxathiin (**4**) that the position of the annular nitrogen appears to play a crucial role in controlling the dihedral ring system. Based on this observation, it may be possible to design and synthesize heterocyclic ring systems with predetermined molecular geometries to probe drug receptor interactions, although a great many questions still remain to be answered before such studies can be confidently undertaken. Further studies are at present underway in these laboratories and will be forthcoming.

EXPERIMENTAL

Table 4

Positional and Thermal and Parameters for Non-Hydrogen Atoms with Estimated Standard Deviations in Parentheses (a)

| Atom | X | Y | Z | U11 | U22 | U33 | U12 | U13 | U23 |
|------|---|---|---|-----|-----|-----|-----|-----|-----|
| S | .95592(4) | .76620(6) | .81190(3) | 454(2) | 272(2) | 434(2) | 23(1) | 171(1) | −65(1) |
| O | .9160(1) | 1.2345(2) | .8984(1) | 325(5) | 340(5) | 336(10) | 69(3) | 61(7) | −75(4) |
| C1 | 1.2122(2) | .8744(3) | .9329(1) | 396(10) | 403(9) | 437(10) | 106(6) | 222(7) | 54(8) |
| C2 | 1.3055(2) | 1.0115(3) | .9999(1) | 318(5) | 576(10) | 445(10) | 82(6) | 150(7) | 87(8) |
| N | 1.2759(1) | 1.2119(2) | 1.0292(1) | 331(5) | 539(9) | 376(10) | 5(6) | 89(7) | 16(4) |
| C4 | 1.1465(1) | 1.2773(3) | .9909(1) | 369(1) | 375(7) | 298(10) | 12(6) | 108(7) | 2(4) |
| C4A | 1.0450(1) | 1.1485(2) | .9250(1) | 316(5) | 298(7) | 263(10) | 34(6) | 120(7) | 37(4) |
| C5A | .8111(1) | 1.1564(2) | .8183(1) | 308(5) | 308(7) | 274(10) | −20(6) | 109(7) | 10(4) |
| C6 | .6962(1) | 1.2925(3) | .7868(1) | 330(5) | 373(7) | 365(10) | 22(6) | 137(7) | 8(4) |
| C7 | .5836(1) | 1.2249(3) | .7089(1) | 294(5) | 537(9) | 397(10) | −11(6) | 119(7) | 45(8) |
| C8 | .5867(2) | 1.0243(3) | .6625(1) | 336(5) | 598(10) | 361(10) | −142(6) | 106(7) | −37(8) |
| C9 | .7016(2) | .8886(3) | .6941(1) | 430(9) | 421(9) | 373(10) | −130(6) | 179(7) | −84(8) |
| C9A | .8155(1) | .9530(2) | .7729(1) | 345(5) | 302(7) | 308(10) | −35(6) | 157(7) | −1(4) |
| C10A | 1.0770(1) | .9425(2) | .8938(1) | 358(5) | 298(7) | 299(7) | 26(6) | 162(7) | 38(4) |

(a) All values of U are × 10⁻⁴. The anisotropic thermal parameters are of the form $\exp[-2\pi^2(U_{11}h^2a^{*2} + U_{22}k^2b^{*2} + U_{33}\ell^2c^{*2} + 2U_{12}hka^*b^* + 2U_{13}h\ell a^*c^* + 2U_{23}k\ell b^*c^*)]$.

Table 5

Positional and Thermal Parameters for Hydrogen
Atoms with Estimated Standard Deviations in Parentheses

| Atom | X | Y | Z | U |
|------|---|---|---|---|
| H1 | 1.242(2) | .737(3) | .916(1) | .043(5) |
| H2 | 1.402(2) | .967(3) | 1.029(1) | .058(5) |
| H4 | 1.402(2) | 1.424(3) | 1.011(1) | .037(4) |
| H6 | .696(2) | 1.432(3) | .821(1) | .044(4) |
| H7 | .507(2) | 1.316(4) | .691(1) | .055(5) |
| H8 | .510(2) | .986(3) | .608(1) | .062(5) |
| H9 | .705(2) | .744(3) | .666(1) | .041(4) |

and a source temperature of 250°. High resolution mass spectra were obtained on a Varian-Mat Model 731 high resolution mass spectrometer by direct probe insertion at an electron energy of 70 eV and a source temperature of 250° with a resolution of 10,000. 100 MHz ¹H-nmr spectra were obtained on a Varian XL-100-15 spectrometer operating in a Fourier transform mode and equipped with a Nicolet TT-100 data system using the following fixed parameters: sweep width, 1 KHz; pulse width, 8 $\mu$ seconds; pulse delay, 0.50 seconds; acquisition time, 5.46 seconds; data size 8 K before transformation; with the spectrometer locked to the deuterium resonance of the solvent. All proton chemical shifts are reported relative to TMS which is assumed to be located 724 Hz upfield of the residual chloroform signal which was used as a reference. All ¹³C-nmr studies were performed using the same instrument with the modifications previously described for the selective excitation experiments (22) using the following fixed parameters: sweep width, 5 KHz; pulse width, 6 $\mu$ seconds (30° tip angle); pulse delay, 3.0 seconds; acquisition time 0.82 seconds (4 K decoupled spectra) 1.64 seconds 8 K ¹H-¹³C coupled spectra); with a TT-760 decoupler operating at 20W with the decoupler power centered on the residual chloroform resonance of the proton spectrum. All ¹³C chemical shifts are reported relative to TMS which was taken as 76.9 ppm upfield of the center line of the deuteriochloroform multiplet which was uniformly used as a reference. The 400 MHz ¹H-spectra were acquired on a Bruker WH-400 spectrometer operating in the Fourier transform mode at 400.13 MHz with the following fixed instrument parameters: sweep width, 1 KHz; pulse width, 6 $\mu$ seconds; pulse delay, 1.0 seconds; acquisition time, 16.38 seconds (32 K data).

Crystal and Intensity Data.

Crystals of 3-azaphenoxathiin are monoclinic, space group P2₁/c, with a = 10.750(2), b = 5.824(1), c = 15.502 Å, $\beta$ = 113.22(1)°, Z = 4, V = 892.29 Å³. The lattice parameters were refined from Bragg angles of 45 reflections between 24.0 and 27.7° 2$\theta$ centered at −35° C on a Syntex P2₁ diffractometer using Mo K$\alpha$ radiation ($\lambda$ = 0.71069 Å) monochromatized with a graphite crystal. Intensity data for 1955 independent reflections (4° ≤ 2$\theta$ ≤ 60°) were measured at −35° by the $\omega$-scan technique with the scan rate varying from 2 to 5° min.⁻¹ depending upon the intensity. The total scan range for each reflection was 1° and background measurements were taken at both ends of the scan with $\omega$ displaced 1.0° from the K$\alpha$ peak; 308 reflections were less than 3$\sigma$(I) and were considered to be unobserved. The intensities of four standards were measured every 96 reflections; only statistical variations were found. Intensities were reduced to structure factor amplitudes by application of Lorentz and polarization corrections; absorption corrections were not made ($\mu$ = 3.17 cm⁻¹).

Structure Solution and Refinement.

The structure was solved by direct methods MULTAN76 (30), the hydrogens were located on a difference map. Full-matrix least squares refinement of all positional and thermal (anisotropic for non-hydrogen atoms and isotropic for hydrogen atoms) parameters converged at a conventional R R = $(\Sigma ||F_o| - |F_c||)/\Sigma |F_o|)$ of 0.029 and a weighted $R_w = [\Sigma w(|F_o| - |F_2|^2/\Sigma w |F_o|^2]^{1/2}$ of 0.040. When all 1955 reflections were included, R = 0.037 and $R_w$ = 0.043 using 1647 reflections for which I > 3$\sigma$(I). The final difference map was featureless. The final positional and thermal parameters are given in Tables 4 and 5. The computational details are noted elsewhere (31).

Synthesis of 3-Azaphenoxathiin (4).

To a stirred solution of 1.87 g (0.0017 mole) of 4-chloro-3-nitropyridine, prepared according to the procedure of Kruger and Mann (17), in 30 ml. of dry, freshly distilled N,N-dimethylformamide under dry argon purge was added 2.0 g. (0.0117 mole) of the disodium salt of 2-mercaptophenol as the dry powder (16). The reaction mixture darkened immediately after the addition of the mercaptophenol salt and was stirred at room temperature for 4 hours after which it was brought to reflux temperature overnight. After cooling, the reaction mixture was poured into 100 ml of chilled distilled water from which the organic material was extracted with 6 × 100 ml of ethyl acetate. The ethyl acetate extracts were combined and back extracted with 3 × 250 ml of distilled water, dried over anhydrous sodium sulfate and then concentrated to give 1.4 g.

(60% yield). Samples for the crystallographic studies and elemental analysis were first recrystallized from cyclohexane to give clear crystals melting 104.5-106° which were then sublimed at 80° at a pressure of 0.2 mm in a linear thermal gradient sublimator (31) to give colorless to faintly yellowish monoclinic crystals. The ir spectrum gave (cm⁻¹): 3000-2800, 1680, 1650, 1370, 1250, 1200, 1080, 750 and 650. The uv spectrum in 95% ethanol gave: log = 3.480 with a concentration of $1.66 \times 10^{-4}M$. Mass spectrum given as m/z clac/obs (% relative intensity): 201.02484/ 201.02470 (100); ¹H-nmr (deuteriochloroform): (100 MHz) δ 8.19, s, H4, 8.13, d, $J_{H_2H_4}$ = 5.27 Hz, H2, 7.02, m, 4H. ¹³C-Nmr decoupled and ¹H-¹³C coupled spectra are shown in Figures 1 and 2, respectively, while calculated vs. observed ¹³C-nmr chemical shifts are shown in Table I. ¹H-¹³C spin coupling constants are summarized in Table II and the ¹H-¹³C spin coupled selectively excited subspectra are shown in Figure 3.

*Anal.* Calcd. for $C_{11}H_7NOS$: C, 65.67; H, 3.48; N, 6.97. Found: C, 65.62; H, 3.51; N, 7.00.

Synthesis of 3-Nitro-4-(2₀-hydroxyphenylthio)pyridine (**5**).

The synthesis of **5**, an intermediate in the synthesis of **4**, in the phenolate form, was obtained by a procedure analogous to that above except that the reaction was quenched with water immediately following 4 hours of stirring at room temperature. Extraction and workup as above gave a yellow crystalline material which was purified by sublimation, 160°, 0.03 mm to give yellow crystals, 0.9 g, mp 201-202°. The ir spectrum gave (cm⁻¹): 3600-3200 (broad), 1590, 1540, 1510, 1450, 1390, 1350, 1300, 1250, 1230, 1200, 1160, 1130, 1100, 1060, 1040, 870, 840, 760, 740, 700. The mass spectrum gave m/z 248 (M+, 71%), 249 (8%). The ¹³C-nmr spectrum contained the following resonances: 158.81 (C2'), 152.26 (C6), 148.39 (C3), 146.77 (C2), 140.94 (C4), 137.12 (C6'), 133.24 (C4), 120.92 (C5 or C5'), 120.71 (C5 or C5'), 166.75 (C1') which were tentatively assigned from the spin-coupled spectrum.

*Anal.* Calcd. for $C_{11}H_8N_2O_3S$: C, 53.23; H, 3.23; N, 11.29. Found: C, 53.20; H, 3.29; N, 11.31.

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