Chemistry of the Phenoxathiins IV. Synthesis of 9-Substituted 1-Azaphenoxathiins

Gary E. Martin and James C. Turley

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

Received January 19, 1978

In an extension of recently reported syntheses of the 1-azaphenoxathiin nucleus as well as several 7-substituted analogs, the synthesis of several 9-substituted members of this series is now reported. In addition, the first ^{13}C-nmr spectral evidence of an interaction between a sulfur atom and the oxygen of an *ortho*-nitro group which has been previously observed only in X-ray crystallographic studies is also described. The possible consequences of this interaction on the reaction pathway leading to the cyclization of the 9-substituted 1-azaphenoxathiin nucleus is also presented.

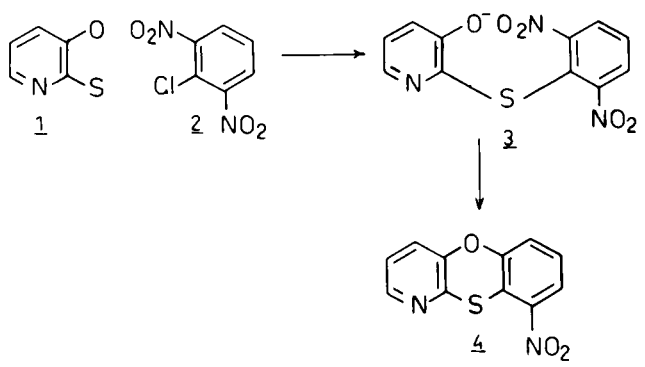
J. Heterocyclic Chem., **15**, 609 (1978)

The synthesis of several 7-substituted 1-azaphenoxathiins (1) as well as the parent ring system (2) have recently been reported. We would now like to report the results of initial investigations into the synthesis of several 9-substituted 1-azaphenoxathiin analogs.

The synthetic pathway leading to the 9-substituted analogs, as in earlier studies (1,2), relied on the condensation of a suitable functionalized substrate with the disodium salt of 2-mercapto-3-pyridinol (1). Thus, as shown in Scheme I, the synthesis of the 9-nitro-1-azaphenoxathiin requires the initial attack of the mercaptide ion on 2,6-dinitro-chlorobenzene (**2**) to yield the intermediate dinitrophenyl sulfide (**3**). The sulfide then subsequently went on to cyclize giving the desired product (**4**). Interestingly, although the nitro groups are not favorably positioned in terms of activation, the reaction still proceeds smoothly to give desired product.

On the basis of the formation of **4**, the synthesis of 9-chloro-1-azaphenoxathiin (**7**) was undertaken in a similar fashion, as shown in Scheme II. The reaction of **1** with 2,3-dichloronitrobenzene (**5**) was expected to result in the formation of the intermediate sulfide (**6**). However, unlike the corresponding sulfide (**3**) shown in Scheme I, **6**, on rotation about the α′-carbon-sulfur bond, has two different displaceable substituents available for reaction with the pyrindinolate ion. Upon cyclization there are thus two possible 9-substituted isomers formed in the reaction.

SCHEME I



Displacement of the nitro group, as desired, would result in the formation of 9-chloro-1-azaphenoxathiin **7**, while alternatively, displacement of the chloro-substituent would result in the formation of **4** described previously.

In addition to the possibilities just described another possibility also exists as shown in Scheme II. This route involves the synthetically unfavored (3,4) displacement of the 3-chloro-substituent from **5** to give the sulfide intermediate (**8**). It is to be expected that in the event **8** is formed, that cyclization should occur to give 6-nitro-1-azaphenoxathiin (**9**), as this displacement would be synthetically favored.

Following the completion of the isolation of the crude reaction product from Scheme II, the material was subjected to column chromatography on a 200 g. silica gel column eluted with cyclohexane-ethylacetate (4:1). The crystalline material isolated by this procedure was bright-orange, melting at 147-151°. However, on subjecting a sample of the isolate to mass spectrometry it was observed that there were two strong parent ions, one at m/e = 235, exhibiting a typical chlorine isotope pattern thus confirming

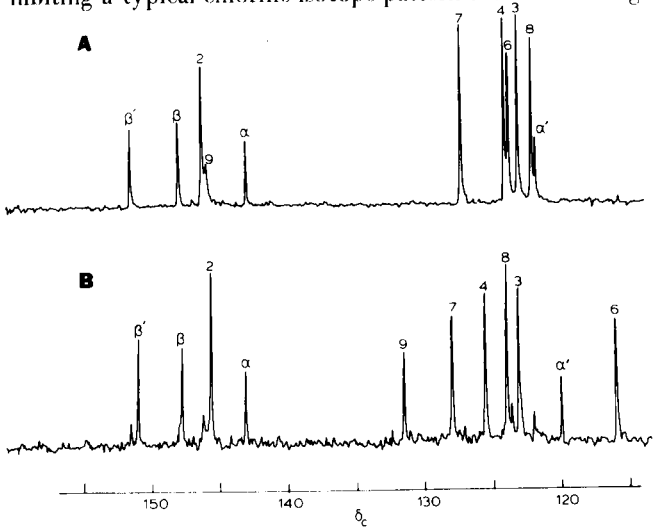
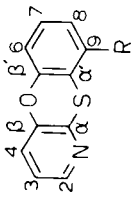


Figure 1. 25.2 MHz FT-^{13}C-nmr Spectrum of the Aromatic Region of, A. 9-Nitro-1-azaphenoxathiin (**4**), B. 9-Chloro-1-azaphenoxathiin (**7**).

Table I

25.2 MHz FT-^{13}C-nmr Calculated *vs.* Observed Chemical Shift Data of 9-Substituted 1-Azaphenoxathiin.



	R	Substituent Location	Analogs α	β	α′	β′	2	3	4	6	7	8	9
Calcd.	-NO_2	9 (**4**)	143.5	147.9	114.2	149.7	144.7	122.2	124.7	123.2	127.8	118.8	147.7
Calcd.	-NO_2	6 (**9**)	143.5	147.9	119.9	145.2	144.7	122.2	124.7	137.4	122.1	124.5	133.5
Obs.	-NO_2	9 (**4**)	142.3	147.2	121.2 (a)	150.8	145.5	122.4	123.4 (b)	123.1 (b)	126.7	121.4 (b)	145.2
Calcd.	-Cl	9 (**7**)	143.5	147.9	119.4	150.1	144.7	122.2	124.7	115.5	128.2	124.0	133.9
Obs.	-Cl	9 (**7**)	142.8	147.4	119.8	150.6	145.3	122.9	125.3	115.8	127.7	123.7	131.3

(a) Unambiguously confirmed by coupled spectrum. (b) Could not be unambiguously assigned.

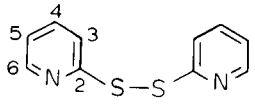
Table II

Uv Spectral Data of 9-Nitro-1-azaphenoxathiin (**4**) and 7-Nitro-1-azaphenoxathiin (**2**) in Absolute Ethanol.

7-Nitro		9-Nitro	
λ	log E	λ	log E
214	3.880	224	4.235
224	3.797	---	---
246	3.621	---	---
261	3.574	291	3.826
311	3.383	---	---
370	3.320	398	3.344

Table III

Observed 25.2 MHz FT-^{13}C-nmr Chemical Shifts of 2,2′-Dipyridyl Sulfide. Observed Additivity Parameters ( ).



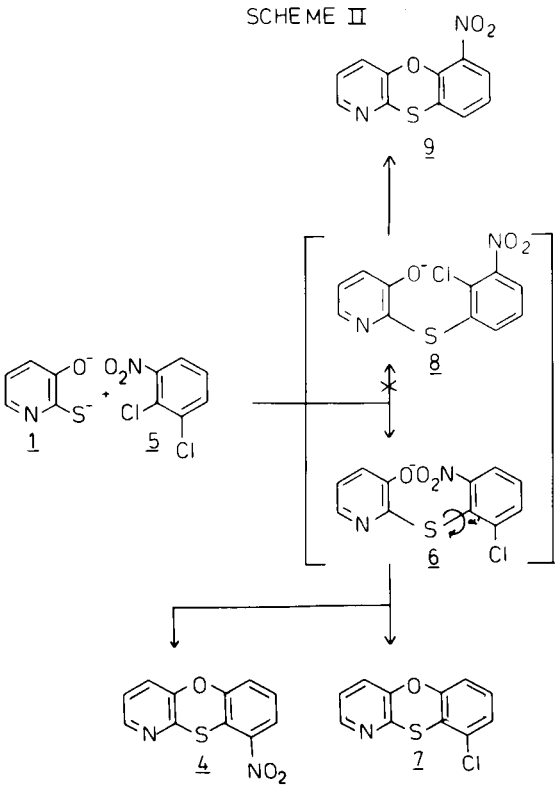
2	3	4	5	6
158.6 (+9.0)	119.5 (-4.7)	137.1 (+0.9)	120.9 (-3.3)	149.3 (-0.3)

the formation of **7**, with the other ion at m/e = 246, probably representing **4**, although initially **9** could not be ruled out. Further examination of what was now obviously a mixture of at least two products by ^{13}C-nmr served to confirm this.

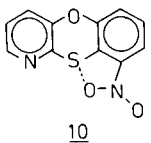
Though the products formed in Scheme II were not initially separable chromatographically, they were found to be readily separable by fractional sublimation at 100° and 0.04 mm Hg in a linear thermal gradient sublimation. By this procedure, two pure products comprising the mixture were obtained and found to be present to the extent of 59.1% of the desired product **7** and 40.9% of the undesired product *nitro*-substituted product which was either **4** or **9**.

Following the completion of the separation, the ^{13}C-nmr spectrum of each compound was obtained. As shown in Figure 1B and Table I, the sample corresponding to **7** was found to give excellent correlation of the calculated *vs.* observed ^{13}C-nmr chemical shifts. The overall isolated yield of **7** obtained was 10.6%. The compound isolated, whose ^{13}C-nmr spectrum is shown in Figure 1A was found to be spectrally identical to an authentic sample of **4** produced in Scheme I. However, although it may readily be concluded that there is no correlation between the observed data and the calculated ^{13}C-chemical shifts of 6-nitro-1-azaphenoxathiin **9**, there was also a discrepancy between the observed and the calculated values for both samples of compound **4**.

SCHEME II



As shown in Table I, the observed discrepancy was present at the α'- and 8-positions, flanking the point of attachment of the nitro-substituent. It has been proposed on the basis of a number of X-ray crystal structures (5-9), that nitro groups *ortho* to sulfur or selenium atoms experience an interaction between one of the oxygens of the nitro group and either the sulfur or the selenium atom to form a *pseudo*-5-membered ring. In the case of **4**, such an interaction is possible, and should it occur, it would result in the formation of the 2*H*-Pyrido[2',3':5,6][1,4]-oxathiino[2,3,4-*hi*][2,1,3]benzoxathiol-11-ium-2-olate (**10**).

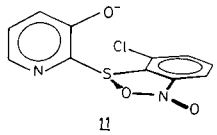


10

As shown in **10**, the formation of the S-O-N bond would be expected to lock the nitro group in a planar configuration resulting in a greater degree of conjugation which would be expected to result in a bathochromic shift in the uv spectrum of **4** relative to, for example, 7-nitro-1-azaphenoxathiin (2), which could not experience this interaction. When such a comparison was made, as shown in Figure 2 and Table II, there was a pronounced 30 nm bathochromic shift in the uv spectrum of **4**.

Since the shift in the uv spectrum of **4** relative to the 7-substituted analog (2) represents a change in the electronic nature of the nitro group, the discrepancy between the calculated and observed chemical shifts at the α' and 8 positions is not wholly inexplicable. It is logical to assume that the greater degree of conjugation as a result of the enhanced planarity of the nitro group would increase electron withdrawl from the positions *ortho* to the substituent, thus resulting in a deshielding of these nuclei thereby causing the observed discrepancy.

A further consequence of the interaction between the sulfur and the *ortho*-nitro group may be reflected in the formation of **4** during the synthesis of the chloro-isomer (**7**) shown in Scheme II. If the *ortho*-sulfur nitro group interaction occurs in the intermediate pyridinolate sulfide, as shown by **11**, electronic effects similar to those already observed in **4** would be expected to result. Further, as a result of the formation of the *pseudo*-five member ring, it is conceivable that the nitro-group may be somewhat stabilized to displacement, thereby increasing the likelihood of displacement of the chloro-substituent, which otherwise would not be expected to be as readily displaced.

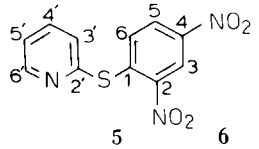


11

To examine the feasibility of the *ortho*-sulfur nitro-group interactions in intermediates such as **11**, 2'-pyridyl-2,4-dinitrophenyl sulfide (**14**) was synthesized as shown in Equation 1. The reaction was conducted by preparing sodium-2-pyridylmercaptide (**12**) by the general method previously reported (1) and then reacting the resultant

Table IV

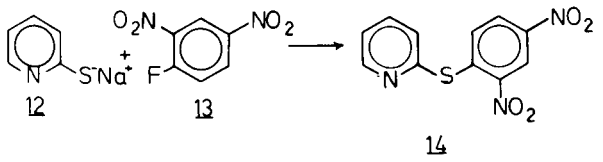
25.2 MHz FT-^{13}C-nmr Calculated *vs.* Observed Chemical Shift Data for 2'-Pyridyl-2,4-dinitrophenyl Sulfide (**14**).



	1	2	3	4	5	6	2'	3'	4'	5'	6'
Calcd.	136.8	151.9	119.5	147.9	130.1	132.8	158.6	119.5	137.2	120.9	149.3
Obs.	148.9	145.4(a)	126.6	149.9(a)	129.3	130.6	152.6	120.9	138.3	124.2	151.4

(a) Were not unambiguously assignable.

product with fluoro-2,4-dinitrobenzene in DMF to yield **14**. It was anticipated that if the interaction between the sulfur and the nitro-group did indeed occur that irregularities in the calculated *vs.* observed ^{13}C-chemical shifts would be observed at the 1- and 3-positions of the phenyl ring.



12 13 14

EQN 1

Chemical shift values of **14** were calculated using observed chemical shifts for 2,2′-dipyridyl disulfide shown in Table III, and the reported additivity parameters for diphenyl sulfide (10) and the nitro-group (11). The resultant calculated chemical shifts for **14** and the corresponding observed chemical shift data are shown in Table IV. As originally anticipated, there was a substantial deshielding observed for **14** at the 1- and 3-positions of the phenyl ring which tends to support the existence of an interaction of the type represented by **11**. Based on these observations, the formation of **4** in Scheme II may indeed be related to the existence of intermediates of the type represented by **11**. That the 4-nitro substituent was not responsible in any way for the observed discrepancies is shown by the excellent agreement between calculated and observed data ofr bis(4-nitrophenyl) sulfide (**15**) shown in Table V.

Further studies are presently being conducted to determine more precisely the nature of the interaction between the sulfur and nitro-group oxygen atoms, as well as their effect on reaction pathways and the pharmacologic activity of the 9-substituted-1-azaphenoxathiins. Results of these studies are forthcoming.

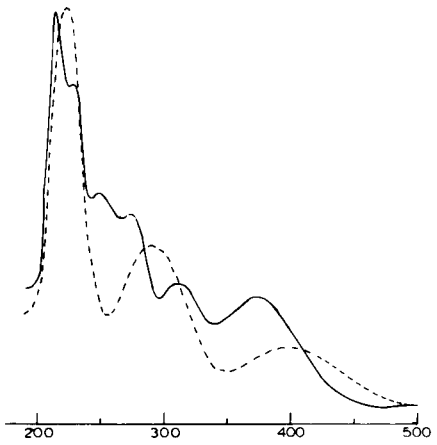
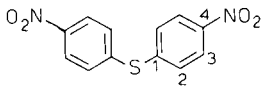


Figure 2. Uv Spectrum in Absolute Ethanol of 9-Nitro-1-azaphenoxathiin (**4**) (—) and 7-Nitro-1-azaphenoxathiin (**2**) (—).

Table V

25.2 MHz FT-^{13}C-nmr Calculated *vs.* Observed Chemical Shift Data for bis(4-Nitrophenyl)Sulfide (**15**).



	1	2	3	4
Calcd.	141.6	131.9	124.3	147.0
Obs.	142.5	131.0	124.5	147.1

EXPERIMENTAL

Melting points were determined in open capillary tubes in a Thomas-Hoover apparatus and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer Model 283 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 (22° flip angle), pulse delay 10.00 seconds, sweep width 5 KHz. Uv spectra were recorded on a Beckmann Model DB-GT spectrophotometer in absolute ethanol. Mass spectra were obtained on a Hewlett-Packard model 5930 GC/MS system equipped with a Model 5933-A data system at an electron energy of 70 eV.

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

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-pyridine as in the procedure of Martin (1). The resultant salt obtained by this procedure was used with further purification.

9-Nitro-1-Azaphenoxathiin (**4**).

To a well stirred solution of 2.369 g. (0.0117 mole) of 2,6-dinitrochlorobenzene in 50 mp. dry distilled DMF under dry argon purge at room temperature was added 2.00 g. (0.0117 mole) of the disodium salt of 2-mercapto-3-pyridinol (**1**). Immediately upon addition of the salt there was a darkening of the reaction mixture. The reaction was stirred at room temperature overnight and was then brought to reflux for 48 hours. The solution was then allowed to cool to room temperature after which it was poured into 200 ml. of ice water. The resultant aqueous solution was extracted with 1.5 l. of ether in six portions which were then combined and back extracted with three X 400 ml. portions of distilled water. The ether extract was then dried over anhydrous sodium sulfate and concentrated to give a reddish oil which recrystallized from ethanol to give 0.575 g. (20% yield) of bright red needle crystals, m.p. 142-143°; ir ν max: 3420, 3060, 2920, 1600, 1580, 1520, 1420, 1338, 1304, 790, 735 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ = 8.00, dd, (αH) 1H; 7.75, dd, (8H), 1H; 7.00, m, 4H; ms m/e (% relative intensity): 246 (100), 247 (14), 248 (8), 216 (18), 200 (31), 188 (15); ^{13}C-nmr: see Figure 1A and Table I; uv: see Figure 2 and Table II.

Anal. Calcd. for $C_{11}H_6N_2O_3S$: C, 53.66; H, 2.44; N, 11.38. Found: C, 53.66; H, 2.80; N, 11.39.

9-Chloro-1-Azaphenoxathiin (**7**).

To a solution of 1.114 g. (0.0058 mole) of 2,3-dichloronitrobenzene in 30 ml. dry distilled DMF under dry argon purge was added 1.00 g. (0.0058 mole) of **1**. The reaction was stirred at room temperature for 4 hours and was then brought to reflux for 24 hours. After cooling, the reaction mixture was poured into 100 ml. ice water and extracted with one l. of ether in four equal portions. The combined ether extracts were then back extracted with four X 250 ml. portions of distilled water and dried over anhydrous sodium sulfate. After drying, the ether extract was concentrated to an oil which would not crystallize from absolute ethanol. The resultant ethanolic solution was then concentrated to an oil once again and chromatographed over a 200 g. silica gel column eluted with cyclohexane-ethyl acetate (4:1) to ultimately yield 0.250 g. reddish orange crystals, m.p. 147-151°. Examination of the ^{13}C-nmr spectrum of this material showed it to still be contaminated which was in agreement with results from the mass spectrum which showed strong ions at m/e 235 and 246. At this point a variety of solvent systems were examined by tlc but were found to be uniformly unsatisfactory and incapable of resolving the mixture. The final procedure attempted was fractional sublimation in a linear thermal gradient sublimator (12) set at 100° with a pressure of 0.04 mm Hg, which neatly separated the material into two components. The slower subliming component, 0.098 g., m.p. 145° was shown on the basis of ^{13}C-nmr and m/s to unequivocally be **4** (Overall yield 6.9%) see Figure 1A. The more volatile component, 0.144 g. of orange-red needles, m.p. 103-104° was shown to be **7**, the desired product of the reaction, by ^{13}C-nmr, see Figure 1B. Overall yield of the desired product was 10.6%; ir ν max: 3400, 2925, 1525, 1455, 1445, 1430, 1418, 1280, 1205, 1095, 915, 790, 765 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ = 8.12, dd, (αH) 1H; 7.10, m, 5H; ^{13}C-nmr: see Figure 1B and Table I; ms m/e (% relative intensity): 235 (100), 236 (18), 237 (36), 219 (34), 200 (30).

Anal. Calcd. for $C_{11}H_6ClNOS$: C, 56.17; H, 2.55; N, 5.95. Found: C, 56.12; H, 2.47; N, 5.78.

Sodium Pyridyl-2-mercaptide (**12**).

To a solution of 0.020 mole of sodium methoxide in 100 ml. of absolute methanol was added 2.50 g. (0.020 mole) of 2-mercaptopyridine, after which the solution was refluxed overnight. The resultant salt (**12**) was isolated as previously described for the disodium salt of 2-mercapto-3-pyridinol (1) and was used as such without further purification, m.p. 205-207°.

2′-Pyridyl-2,4-dinitrophenyl Sulfide (**14**).

To a solution of 1.900 g. (0.0107 mole) of 2,4-dinitrofluorobenzene in 30 ml. of dry distilled DMF under dry argon purge at 0° was added 1.430 g. (0.0107 mole) of sodium pyridyl-2-mercaptide (**12**). The reaction mixture darkened immediately on addition of the salt and stirring was continued for 4 hours. Upon completion of the reaction, the entire reaction mixture was chromatographed directly over a silica gel column eluted with chloroform. The yellow oily material collected on concentration of the eluate was recrystallized from ethanol to give 2.35 g. of **14** (79% yield) as fine yellow needles, m.p. 110-111°; ir ν max: 3160, 1600, 1580, 1510, 1450, 1360, 1340, 1100, 1045, 915, 835, 740 cm^{-1}; ^{1}H-nmr (deuteriochloroform) δ: 8.70, d, (3H), 1H; 8.55, dd (6′H) 1H; 8.10, dd, (5H), 1H; 7.50, m, 3H; ms m/e (% relative intensity): 276 (8), 231 (60), 185 (80), 184 (28), 78 (100); ^{13}C-nmr: see Table IV.

Anal. Calcd. for $C_{11}H_7N_3O_4S$: C, 45.04; H, 2.39; N, 14.33. Found: C, 44.91; H, 2.31; N, 14.30.

Acknowledgement.

The author would like to thank Drs. M. R. Willcott, III, Department of Chemistry, University of Houston and W. vE. Doering, Department of Chemistry, Harvard University for helpful discussion and Mrs. Deborah Jones for excellent preparation of this manuscript.

REFERENCES AND NOTES

(1) G. E. Martin, J. C. Turley, L. Williams, M. L. Steenberg and J. P. Buckley, *J. Heterocyclic Chem.*, **14**, 1069 (1977).

(2) G. E. Martin, J. C. Turley and L. Williams, *ibid.*, **14**, 1249 (1977).

(3) A. J. Parker, in "Organic Sulfur Compounds", Vol. 1, N. Kharsch, Ed., Pergamon Press, New York, N. Y., 1966, p. 103.

(4) R. F. Miller, Master's Thesis, University of Houston (1976).

(5) J. S. Ricci and I. Bernal, *J. Chem. Soc.*, 806 (1970).

(6) R. Eriksen and S. Hauge, *Acta Chem. Scand.*, **26**, 3153 (1972).

(7) R. Eriksen, *ibid.*, **A29**, 517 (1975).

(8) J. D. Korp, I. Bernal, R. F. Miller, J. C. Turley, L. Williams, and G. E. Martin, submitted to *J. Heterocyclic Chem.*, (1977).

(9) J. D. Korp, I. Bernal and G. E. Martin, unpublished data.

(10) M. S. Cahuhan and I. W. J. Still, *Can. J. Chem.*, **53**, 2880 (1975).

(11) G. C. Levy and G. N. Nelson, "Carbon-13 NMR for Organic Chemists", Wiley Interscience, New York, N. Y., 1972, p. 81.

(12) Thermal Gradient Sublimator manufactured by Scientific Instrument Acessories, 1106 High Rd., Austin, Texas, 78746.