ethenyl)cyclohexanone, 86921-84-8; 3,3,5-trimethyl-5-(4-methylphenyl)cyclohexanone, 53577-40-5; 3,3,5-trimethyl-5-(9-phenanthryl)cyclohexanone, 86921-85-9; 3-[(2-methylphenyl)-methyl]bicyclo[2.2.1]-2-heptanone, 86921-86-0; 2-cyclopenten-1-one, 930-30-3; 3-methyl-2-cyclopenten-1-one, 2758-18-1; 2-cyclohexen-1-one, 930-68-7; 3,5,5-trimethyl-2-cyclohexen-1-one, 78-59-1; 3-methylenebicyclo[2.2.1]-2-heptanone, 5597-27-3; 9-bromophenanthrene, 573-17-1; bis(9-phenanthryl)zinc, 86921-88-2; PhCH=CHCOPh, 94-41-7; o-$BrC_6H_4CH_3$, 95-46-5; p-$BrC_6H_4CH_3$, 106-38-7; p-BrC_6H_4Ph, 92-66-0; PhCH=CHBr, 103-64-0; $ZnBr_2$, 2699-45-8; $(o\text{-}CH_3C_6H_4)_2Zn$, 7029-31-4; $(p\text{-}CH_3C_6H_4)_2Zn$, 15106-88-4; $(p\text{-}PhC_6H_4)_2Zn$, 15106-90-8; $(PhCH{=}CH)_2Zn$, 86921-87-1.

Catechol Monoether Synthesis

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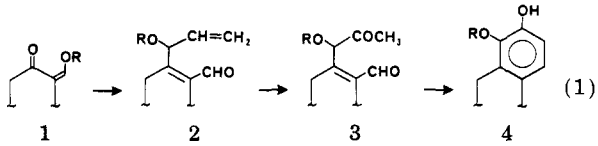
In earlier work we have demonstrated efficient methods for appending benzene rings, phenols, and pyridines onto α-methylene ketones.[1] The yields for these processes have been uniformly high, suggesting that the approach will be useful in total synthesis. The extension of this methodology to the synthesis of catechol monoethers will now be described.

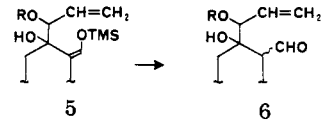
The catechol unit is a substructure of a large number of important natural products. A method for introducing this unit onto a ketone during the latter stages of a total synthesis would allow the consideration of novel strategies. A modification of our phenol synthesis suggested itself (eq 1). Addition of an alkoxyallyl nucleophile to the *O*-trimethylsilyl hydroxymethylene ketone **1** (R = $Si(CH_3)_3$) followed by hydrolysis would give enal **2**.[1] Palladium-catalyzed oxygenation[2] of the terminal alkene produces keto aldehyde **3**, which undergoes intramolecular aldol condensation and dehydration to form the catechol monoether **4**.



(1)

1 **2** **3** **4**

Potential difficulties concerning the regiochemistry of attack of the three-carbon oxygenated nucleophile and the regiochemistry of oxidation of the terminal alkene were identified at the outset. We were delighted to find that the zinc "ate" complex[3] derived from methoxyallyllithium[4] and zinc chloride attacks the carbonyl group of **1** and that the attack takes place exclusively at the α carbon of the nucleophile. Aqueous acidic hydrolysis during workup of the intermediate tertiary allylic alcohol **5** proceeded to give mixtures of enal **2** and β-hydroxy aldehyde **6** (eq 2).

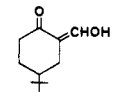
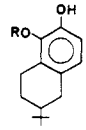
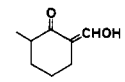
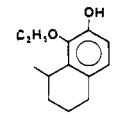
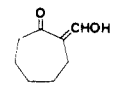
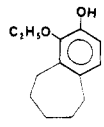
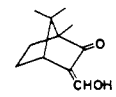
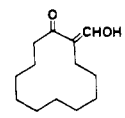
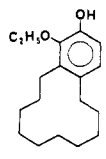
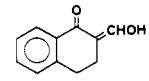
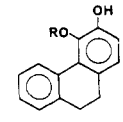
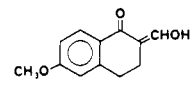
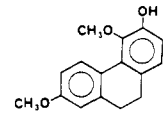
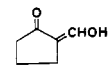
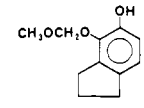


+ 2 (2)

5 **6**

Aldehyde **6** was the only product when **5** was treated with tetra-*n*-butylammonium fluoride in tetrahydrofuran. Since the palladium-catalyzed oxygenation of **6** produced a mixture of products, it was necessary to find an efficient route to **2**. Because **6** was stable to prolonged treatment with acid under a variety of conditions, it appeared that different mechanisms are responsible for the formation of **2** and **6**. Ionization of the tertiary allylic alcohol leads to **2**, whereas protonation of the trimethylsilyl enol ether leads

Table I. Catechol Monoethers

entry	starting material	catechol monoether[a]	yield[b] % (mp, °C)[c]
1		 R = CH_3, CH_2CH_3, CH_2OCH_3	78 (92) 73 (63) 61 (68-71)
2			45
3			63
4		*d*	
5			66
6		 R = CH_2CH_3, CH_2OCH_3	66 65
7			43 (91)
8			19[e]

[a] Full spectroscopic data for all products are presented in the supplementary information. [b] Overall yield from the α-hydroxymethylene ketone. [c] Melting points are uncorrected. Compounds for which no melting point has been recorded were obtained as oils. [d] Nucleophilic addition to the carbonyl group did not take place. [e] See text.

(1) (a) Tius, M. A.; Ali, S. *J. Org. Chem.* **1982**, *47*, 3163. (b) Tius, M. A.; Thurkauf, A.; Truesdell, J. W. *Tetrahedron Lett.* **1982**, *23*, 2823. (c) *Ibid.* **1982**, *23*, 2819.

(2) Tsuji, J.; Shimizu, I.; Suzuki, H.; Naito, Y. *J. Am. Chem. Soc.* **1979**, *101*, 5070. Tsuji, J. "Organic Synthesis with Palladium Compounds"; Springer-Verlag: Berlin, Heidelberg, New York, 1980.

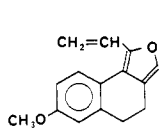
(3) We were able to demonstrate that the "ate" complex was involved by titration of the yellow alkoxyallyllithium solutions with one-third of an equivalent of the nonhygroscopic zinc chloride—*N,N,N',N'*-tetramethylethylenediamine (TMEDA) complex to a colorless endpoint; Isobe, M.; Kondo, S.; Nagasawa, N.; Goto, T. *Chem. Lett.* **1977**, 679.

(4) Evans, D. A.; Andrews, G. C.; Buckwalter, B. *J. Am. Chem. Soc.* **1974**, *96*, 5560. Still, W. C.; Macdonald, T. L. *Ibid.* **1974**, *96*, 5561. Still, W. C. *Tetrahedron Lett.* **1976**, 2115. Still, W. C.; Macdonald, T. L. *J. Org. Chem.* **1976**, *41*, 3620. Evans, D. A.; Baillargeon, D. J.; Nelson, J. V. *J. Am. Chem. Soc.* **1978**, *100*, 2242.

0022-3263/83/1948-3839$01.50/0

to **6**. After some experimentation, it was found that addition of a concentrated solution of **5** in dichloromethane to an excess of anhydrous pyridinium tosylate[5] produced **2** without contamination by **6**.

The resistance of **6** to dehydration is a consequence of the inductive effect of the adjacent alkoxy group, an effect that might have been expected to alter the regiochemistry of the oxidation step.[6] Nevertheless, the palladium-catalyzed oxidation produced keto aldehyde **3** rather than a dialdehyde in all of the cases we examined, save one (vide infra). The intramolecular aldol and dehydration reaction of **3** with methanolic potassium hydroxide at room temperature was fast and extraordinarily clean. Our results are summarized in Table I. Loss of the R group during the hydrolysis of **5** leads to the formation of vinylic furans.[7] For example, addition of the anion derived from the 2-ethoxyethyl ether of allyl alcohol to the *O*-trimethylsilyl hydroxymethylene ketone prepared from 6-methoxy-1-tetralone after aqueous acidic workup led to an air-sensitive compound that we have identified as vinyl furan **7**. 3-Alkoxypyridines can be prepared by treatment of the intermediate keto aldehydes with ethanolic ammonium acetate. For example, methoxypyridine **8** was prepared



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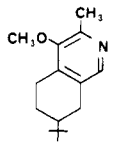
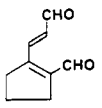


8



9

in 70% overall yield from 2-(hydroxymethylene)-4-*tert*-butylcyclohexanone. A limitation of the method became apparent in the case of camphor (entry 4). Addition of the alkoxyallyl anion did not take place at −20 °C, presumably due to steric hindrance about the carbonyl carbon. A more puzzling problem is presented by cyclopentanone (entry 8). In all other examples cited in Table I, oxidation took place to produce methyl ketones, whereas with cyclopentanone a mixture of keto aldehyde and dialdehyde (51%:35%) was formed reproducibly. The abnormal regiochemistry for the oxidation was observed when the adjacent alkoxy group was ethyl or methoxymethyl. Elimination of the β-alkoxy group gave dialdehyde **9**, which was identified on the basis of its spectroscopic properties. In our phenol work, no aberrant behavior was noted for cyclopentanone derivatives.

Methods for the regiospecific elaboration of substituted aromatic rings from nonaromatic precursors are proving their value in preparative chemistry.[8] The efficient route to catechol monoethers that has been described herein suggests a number of applications in total synthesis.

Experimental Section

Tetrahydrofuran was distilled from sodium benzophenone ketyl, methylene chloride was distilled from phosphorus pentoxide, and *N,N*-dimethylformamide was distilled from calcium hydride. Nuclear magnetic resonance (NMR) spectra were recorded either at 100 MHz (Varian XL-100 spectrometer) or at 300 MHz (Oxford magnet, Nicolet data system). Infrared spectra were recorded on a Beckman IR 10 instrument. Electron-impact mass spectra were recorded on a Varian MAT-311 instrument.

General Procedure for Catechol Monoether Annelation. A solution of 553 mg (7.67 mmol) of allyl methyl ether in 19 mL of dry tetrahydrofuran (THF) was treated for 10 min at −78 °C with 6.4 mL of a 1.2 M solution of *sec*-butyllithium in cyclohexane (7.67 mmol). A solution of anhydrous zinc chloride in THF was added dropwise via cannula to discharge the yellow color of the methoxyallyllithium. In a separate flask a solution of 200 mg (1.10 mmol) of 2-(hydroxymethylene)-4-*tert*-butylcyclohexanone in 12 mL of THF was treated with 362 μL of a chlorotrimethylsilane–trimethylamine mixture (ca. 1.3 equiv). A thick white precipitate formed. The trimethylsilyl enol ether was transferred by cannula to the solution of the anion, and the mixture was stirred for 10 min. The cooling bath was removed, and stirring was continued for an additional 10 min. The reaction mixture was partitioned between ether and 0.1 N HCl, dried over anhydrous $MgSO_4$, filtered and concentrated. A solution of the crude product in 2 mL of CH_2Cl_2 was added at 23 °C to an excess (ca. 10 equiv) of anhydrous pyridinium tosylate. The mixture was stirred for 10 min, diluted with CH_2Cl_2, and washed with water. Concentration followed by flash chromatography on silica gel furnished 221 mg (0.94 mmol, 85% yield) of the enal (cf. **2**).

A slow stream of oxygen was bubbled through a solution of 210 mg (0.89 mmol) of enal in 1.11 mL of *N,N*-dimethylformamide (DMF) containing 264 mg (2.67 mmol) of cuprous chloride, 16 mg (0.09 mmol) of palladium chloride, and 264 μL of water at 45 °C for 2.5 h. Saturated aqueous sodium dihydrogen phosphate was added to the heterogeneous reaction. The mixture was filtered through diatomaceous earth, washing thoroughly with CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2, and the combined organic phase was dried over anhydrous K_2CO_3 and concentrated. The crude material which contains DMF was dissolved in 17.7 mL of absolute ethanol, and the solution was deoxygenated with a stream of argon. Then 2.66 mL (2.66 mmol) of a 1 M solution of ethanolic KOH was added. The reaction was immediately acidified with 1 N HCl and most of the ethanol was removed in vacuo. Extraction with CH_2Cl_2 followed by drying over $MgSO_4$ and concentration provided the product. Flash chromatography gives 163 mg (0.69 mmol, 78% overall yield) of crystalline 2-*tert*-butyl-6-hydroxy-5-methoxy-1,2,3,4-tetrahydronaphthalene: mp 92 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.74 (s, 2 H, Ar), 5.41 (s, 1 H, ArOH), 3.76 (s, 3 H, OCH_3), 2.91 (ddd, J = 16.9, 4.8, 1 Hz, 1 H), 2.76 (ddd, J = 15.9, 4.7, 1 Hz, 1 H), 2.5 (m, 2 H), 2.0 (m, 1 H), 1.39 (ddt, J = 11.5, 4.7, 2 Hz, 1 H), 1.25 (m, 1 H), 0.92 (s, 9 H, *t*-Bu); IR (CH_2Cl_2) 3420, 2950, 1490, 1450, 1360, 1290, 1070, 1050, 1020 cm^{-1}; mass spectrum, m/e 234 (p), 220 (p-CH_3), 177, 145; Calcd for $C_{15}H_{22}O_2$ 234.1620, found 234.1642.

Acknowledgment. We thank the National Institutes of Health (Grant GM 30390-01) for generous financial support. NSF Grant CHE 81-00240 supported the purchase of the 300-MHz NMR spectrometer.

Registry No. **7**, 86902-31-0; **8**, 86902-32-1; **9**, 86902-33-2; 2-[(trimethylsilyl)oxymethylene]-4-(1,1-dimethyethyl)cyclohexanone, 83458-65-5; 2-[[(trimethylsilyl)oxy]methylene]-6-methylcyclohexanone, 86902-34-3; 2-[[(trimethylsilyl)oxy]methylene]cycloheptanone, 83458-47-3; 2-[[(trimethylsilyl)oxy]methylene]cyclopentanone, 86902-35-4; 2-[[(trimethylsilyl)oxy]methylene]cyclododecanone, 81857-33-2; 3,4-dihydro-2-[[(trimethylsilyl)oxy]-methylene]-1(2*H*)-naphthalenone, 86902-36-5; 3,4-dihydro-6-methoxy-2-[[(trimethylsilyl)oxy]methylene]-1(2*H*)-naphthalenone, 86902-37-6; 3-(hydroxymethylene)-1,7,7-trimethylbicyclo[2.2.1]-heptan-2-one, 15051-75-9; 5-(1,1-dimethylethyl)-2-(α-methoxyprop-2-enyl)cyclohex-1-enecarboxaldehyde, 86902-38-7; 5-(1,1-dimethylethyl)-2-[(α-ethoxyprop-2-enyl)cyclohex-1-enecarboxaldehyde, 86902-39-8; 5-(1,1-dimethylethyl)-2-[α-(methoxymethoxy)prop-2-enyl]cyclohex-1-enecarboxaldehyde, 86902-40-1; 3-methyl-2-(α-ethoxyprop-2-enyl)cyclohex-1-enecarboxaldehyde, 86902-41-2; 2-(α-ethoxyprop-2-enyl)cyclohept-1-enecarboxaldehyde, 86902-42-3; 2-(α-ethoxyprop-2-enyl)cyclododec-1-enecarboxaldehyde, 86902-43-4; 3,4-dihydro-1-(α-ethoxyprop-2-enyl)naphthalene-2-carboxaldehyde, 86902-44-5; 3,4-dihydro-1-[α-(methoxymethoxy)prop-2-enyl]naphthalene-2-carboxaldehyde, 86902-45-6; 3,4-dihydro-6-methoxy-1-(α-methoxyprop-2-enyl)-naphthalene-2-carboxaldehyde, 86902-46-7; 2-[α-(methoxymeth-

(5) Miyashita, M.; Yoshikoshi, A.; Grieco, P. A. *J. Org. Chem.* **1977**, *42*, 3772.

(6) During the performance of our work, a paper relevant to this question appeared: Tsuji, J.; Nagashima, H.; Hori, K. *Tetrahedron Lett.* **1982**, *23*, 2679.

(7) A similar reaction has been exploited for the synthesis of furans: Garst M. E.; Spencer, T. A. *J. Am. Chem. Soc.* **1973**, *95*, 250.

(8) For example, see: Boger, D. L.; Mullican, M. D. *Tetrahedron Lett.* **1982**, *23*, 4551, 4555. Boger, D. L.; Patel, M.; Mullican, M. D. *Ibid.* **1982**, *23*, 4559, and references cited therein.

oxy)prop-2-enyl]-2-enyl]cyclopent-1-ene-1-carboxaldehyde, 86902-47-8; 5-(1,1-dimethylethyl)-2-(α-methoxy-β-oxopropyl)-cyclohex-1-ene-1-carboxaldehyde, 86902-48-9; 5-(1,1-dimethylethyl)-2-(α-ethoxy-β-oxopropyl)cyclohex-1-ene-1-carboxaldehyde, 86902-49-0; 5-(1,1-dimethylethyl)-2-[α-(methoxymethoxy)-β-oxopropyl]cyclohex-1-ene-1-carboxaldehyde, 86902-50-3; 3-methyl-2-(α-ethoxy-β-oxopropyl)cyclohex-1-ene-1-carboxaldehyde, 86902-51-4; 2-(α-ethoxy-β-oxopropyl)cyclohept-1-ene-1-carboxaldehyde, 86902-52-5; 2-(α-ethoxy-β-oxopropyl)cyclododec-1-ene-1-carboxaldehyde, 86902-53-6; 3,4-dihydro-1-(α-ethoxy-β-oxopropyl)naphthalene-2-carboxaldehyde, 86902-54-7; 3,4-dihydro-1-[α-(methoxymethoxy)-β-oxopropyl]napthalene-2-carboxaldehyde, 86902-55-8; 3,4-dihydro-6-methoxy-1-(α-methoxy-β-oxopropyl)napthalene-2-carboxaldehyde, 86902-56-9; 2-[α-(methoxymethoxy)-β-oxopropyl]cyclopent-1-ene-1-carboxaldehyde, 86902-57-0; 5,6,7,8-tetrahydro-6-(1,1-dimethylethyl)-1-methoxynaphthalen-2-ol, 86902-58-1; 5,6,7,8-tetrahydro-6-(1,1-dimethylethyl)-1-ethoxynaphthalen-2-ol, 86902-59-2; 5,6,7,8-tetrahydro-6-(1,1-dimethylethyl)-1-(methoxymethoxy)-naphthalen-2-ol, 86902-60-5; 5,6,7,8-tetrahydro-8-methyl-1-methoxynapthalen-2-ol, 86902-61-6; 5,6,7,8,9-pentahydro-1-ethoxybenzocycloheptен-2-ol, 86902-62-7; 5,6,7,8,9,10,11,12,13,14-decahydro-1-ethoxybenzocyclododecen-2-ol, 86902-63-8; 9,10-dihydro-4-ethoxyphenanthren-3-ol, 86902-64-9; 9,10-dihydro-4-methoxymethoxyphenanthren-3-ol, 86902-65-0; 9,10-dihydro-4,7-dimethoxyphenanthren-3-ol, 86902-66-1; 2,3-dihydro-4-methoxymethoxy-1(*H*)-inden-5-ol, 86902-67-2; 4-(1,1-dimethylethyl)-2-[[(trimethylsilyl)oxy]methylene]-1-(α-methoxyprop-2-enyl)cyclohexan-1-ol, 86902-68-3; 4-(1,1-dimethylethyl)-2-[[(trimethylsilyl)oxy]methylene]-1-(α-ethoxyprop-2-enyl)cyclohexan-1-ol, 86902-69-4; 4-(1,1-dimethylethyl)-2-[[(trimethylsilyl)oxy]-methylene]-1-[α-methoxymethoxy)prop-2-enyl]cyclohexan-1-ol, 86902-70-7; 6-methyl-2-[[(trimethylsilyl)oxy]methylene]-1-[α-(methoxymethoxy)prop-2-enyl]cyclohexan-1-ol, 86902-71-8; 2-[[(trimethylsilyl)oxy]methylene]-1-(α-ethoxyprop-2-enyl)cycloheptan-1-ol, 86902-72-9; 2-[[(trimethylsilyl)oxy]methylene]-1-(α-ethoxyprop-2-enyl)cyclododecan-1-ol, 86902-73-0; 1,2,3,4-tetrahydro-2-[[(trimethylsilyl)oxy]methylene]-1-(α-ethoxyprop-2-enyl)napthalen-1-ol, 86902-74-1; 1,2,3,4-tetrahydro-2-[[(trimethylsilyl)oxy]methylene]-1-[α-(methoxymethoxy)prop-2-enyl]naphthalen-1-ol, 86902-75-2; 1,2,3,4-tetrahydro-6-methoxy-2-[[(trimethylsilyl)oxy]methylene]-1-(α-methoxyprop-2-enyl)-naphthalen-1-ol, 86902-76-3; 2-[[(trimethylsilyl)oxy]-methylene]-1-[α-(methoxymethoxy)prop-2-enyl]cyclopentan-1-ol, 86902-77-4; 4-(1,1-dimethylethyl)-2-(hydroxymethylene)cyclohexanone, 22252-96-6; 6-methyl-2-(hydroxymethylene)cyclohexanone, 15409-53-7; 2-(hydroxymethylene)cycloheptanone, 934-20-3; 2-(hydroxymethylene)cyclododecanone, 949-07-5; 1,2,3,4-tetrahydro-2-(hydroxymethylene)naphthalene-1-one, 40685-04-9; 1,2,3,4-tetrahydro-6-methoxy-2-(hydroxymethylene)naphthalen-1-one, 16252-53-2; 2-(hydroxymethylene)cyclopentanone, 930-91-6; allyl methyl ether, 627-40-7; allyl ethyl ether, 557-31-3; allyl methoxymethyl ether, 62322-45-6.

Supplementary Material Available: NMR, IR, and MS data for the products of Table I (3 pages). Ordering information is given on any current masthead page.

Relative Stabilization of an Iminium Ion by the Charge-Transfer Interaction of Arylthio Groups

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The evidence for an intramolecular charge-transfer (CT) interaction between a sulfide sulfur atom and a neighboring iminium ion has been reviewed for the thiaspirane class of alkaloids and their analogues.[1] The same review

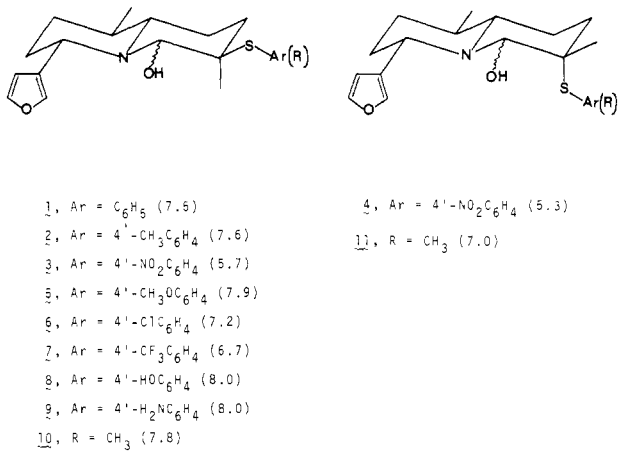
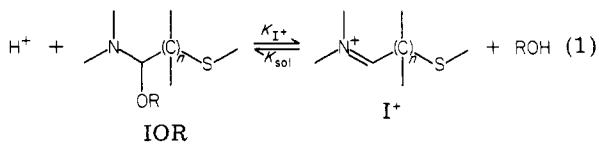


Figure 1. α-Thio hemiaminal derivatives of deoxynupharidine whose K'_{I^+} values have been determined. K'_{I^+} values are given in parentheses.

points out the usefulness of CT-circular dichroism (CD) in measuring the extent to which iminium ions are stabilized against solvolysis by the CT interaction with sulfur. Thus a reflection of this stabilization is log K'_{I^+} whose meaning follows from its derivation from the equilibrium reaction in eq 1 and expression 2. Arguments were given



(1)

$$K'_{I^+} = ([HOR][I^+])/([IOR][H^+]) \quad (2)$$

$$\log K'_{I^+} = pH_{1/2} \quad (3)$$

for reducing expression 2 to 3 wherein $pH_{1/2}$ represents the pH at which one-half of the original hemiaminal (IOR) was converted to iminium ion (I^+). Furthermore, it was demonstrated that a plot of the molecular ellipticity, $[\theta]$, against pH yielded S-shaped curves from which the value of $pH_{1/2}$ (or log K'_{I^+}) could be determined.[1] This paper concerns the extention of these measurements to several α-(arylthio)hemiaminal derivatives, **1–9** (Figure 1), of deoxynupharidine. Their preparation was reported earlier.[2] The study was undertaken to ascertain if additional stabilization to solvolysis would result from attaching electron-donating aryl substituents to sulfur. Possibly such substitution would enhance the electron availability at the interacting sulfur atom. The values of log K'_{I^+} are compared by way of a Hammett $\rho\sigma$ analysis[3] in order to assess the relative stabilization of the various aryl groups attached to the sulfur atom. Additional comparisons are made to the log K'_{I^+} values previously reported[1] for the methylthio derivatives **10** and **11**.

A plot of the log K'_{I^+} values against σ_p[4] for eight α-(arylthio) hemiaminal derivatives of deoxynupharidine is shown in Figure 2. Least-squares analysis of all the points gives a slope (ρ) of −1.56 with a correlation coefficient (r) of 0.9467. Two points, that for the p-NH_2 and that for the p-NO_2 substituents, appear to be responsible for the low value of r. The variance of the former point can be at-

(1) LaLonde, R. T. *Acc. Chem. Res.* **1980**, 13, 39.
(2) LaLonde, R. T.; Eckert, T. S. *Can. J. Chem.* **1981**, 59, 2298.
(3) Hammett, L. P. "Physical Organic Chemistry", 1st ed.; McGraw Hill: New York, 1941; pp 184–207.
(4) Values of σ_p were taken from the following: Ritchie, C. D.; Sager, W. F. In "Progress in Physical Organic Chemistry"; Cohen, S. C., Streitweiser, A., Taft, R. W., Eds.; Interscience: New York, 1964; Vol. 2, p 323.

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