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Semisynthetic Pyrrolizidine Alkaloid Antitumor Agents

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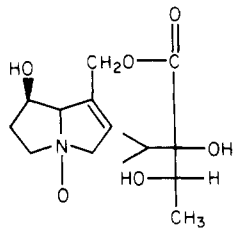
A new semisynthetic pyrrolizidine alkaloid, 9-*O*-[(±)-2-hydroxy-2-phenylbutyryl]retronecine *N*-oxide (**2a**), was synthesized and found to be more active than indicine *N*-oxide (1) on which it was modeled. 9-*O*-[(*S*)-(+)-2-hydroxy-2-phenylbutyryl]retronecine (**5**) and its diastereomer, 9-*O*-[(*R*)-(−)-2-hydroxy-2-phenylbutyryl]retronecine (**6**), were prepared, and their detailed ^{1}H NMR spectra are presented. Conformational analyses of these molecules in solution are discussed on the basis of their NMR analyses and knowledge of their absolute configurations.

The pyrrolizidine alkaloids are known to be hepatotoxic and mutagenic.[1] In 1968 Culvenor found that the pyrrolizidine alkaloids exhibited antitumor activity and concluded that this activity was widely distributed among the members of this class of compounds.[2] However, due to their known hepatotoxicity the pyrrolizidine alkaloids were never used in clinical trials. More recently, Kugleman et al. found that the antitumor constituent of *Heliotropium indicum* Linn was indicine *N*-oxide (1).[3] This compound



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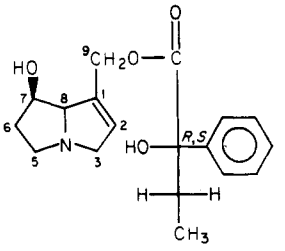


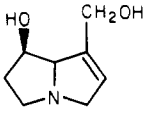
2
2a (*N*-oxide)

did not show the hepatotoxicity normally associated with this class of compounds. Indicine *N*-oxide, therefore, became the first pyrrolizidine alkaloid to be tested in clinical trials. It was found to be effective against advanced gastrointestinal cancer,[4] and in cases of leukemia and melanoma.[5]

In order to better understand the structural features necessary for the antitumor activity, we undertook the syntheses of new pyrrolizidine alkaloid analogues modeled on indicine. We now report the synthesis of 9-*O*-[(±)-2-hydroxy-2-phenylbutyryl)retronecine *N*-oxide (**2a**), which in a preliminary PS tumor screen has shown significant antitumor activity, and is more active than indicine *N*-oxide.[6]

†National Science Foundation Undergraduate Research Participant, 1980.

The choice of 2-hydroxy-2-phenylbutyric acid as the new necic acid side chain was made because of its similarity to 2,3-dihydroxy-2-isopropylbutyric acid, the necic acid of indicine, and its ease of synthesis. This acid is well-known and easily resolved, giving us the ability to examine the effect of chirality at the α-hydroxy position on the antitumor activity of the molecule. The synthesis of **2** requires the necine base retronecine (**3**), the necic acid, and a method of coupling the α-hydroxy acid to the C-9 position of retronecine.



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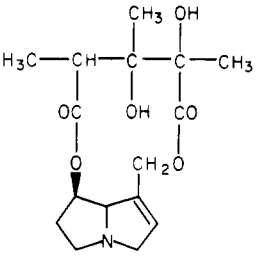

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Although retronecine has been synthesized by Geissman et al.,[7a] and more recently by Tufariello et al.,[7c] and Keck et al.,[7b] it was more easily obtained by the hydrolysis of the pyrrolizidine alkaloid monocrotaline (**4**), which itself

(1) Bull, L. B.; Culvenor, C. C. J.; Dick, A. T. "The Pyrrolizidine Alkaloids"; North-Holland Publishing Co.: Amsterdam, 1968.
(2) Culvenor, C. C. J. *J. Pharm. Sci.* **1968**, *57*, 1112.
(3) Kugelman, M.; Liu, W. C.; Axelrod, M.; McBride, T. J.; Rao, K. V. *Lloydia* **1976**, *39*, 125.
(4) Kovach, J. S.; Ames, M. M.; Powis, G.; Moertel, C. G.; Hahn, R. G.; Cregan, E. T. *Cancer Res.* **1979**, *39*, 4540.
(5) Personal communication from Dr. Matthew Suffness, Head, Plant and Animal Products Section, Natural Products Branch, Developmental Therapeutics Program, National Cancer Institute.
(6) Antitumor screening was carried out under the auspecies of the National Cancer Institute. Preliminary screening in the P-388 lymphocytic leukemia system indicated a T/C of 166 at 300 mg/kg.
(7) (a) Geissman, T. A.; Waiss, A. J., Jr. *J. Org. Chem.* **1961**, *27*, 139. (b) Kech, G. E.; Nickell, D. G. *J. Am. Chem. Soc.* **1980**, *102*, 3632. (c) Tufariello, J. J., Lee, G. E. *Ibid.* **1980**, *102*, 373.

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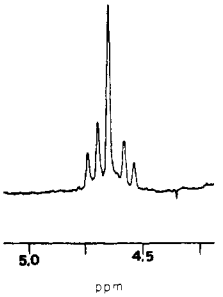


Figure 1.

Figure 2.

is readily isolated from the seeds of *Crotalaria spectabilis*.[8]

The new necic acid analogue 2-hydroxy-2-phenylbutyric acid was synthesized from propiophenone through its cyanohydrin. The enantiomeric mixture was then resolved by using the quinine salt.[9]

The final step in the synthesis of **2** involved the coupling reaction. In previously reported related syntheses, this reaction has been carried out by using a transesterification,[10] or the reaction of retronecine with the appropriate acid chloride.[11] Recently, Hoskins et al.[12] reported the regioselective esterification of retronecine by a method which appeared useful for the esterification involving hindered hydroxy acids. This method is based on the formation of an acyl imidazole, prepared by using 1,1′-carbonyldiimidazole (CDI), and its subsequent regioselective reaction with the allylic hydroxyl group in retronecine.

The initial reaction was carried out by allowing a racemic mixture of 2-hydroxy-2-phenylbutyric acid to react with CDI in dry chloroform and then adding an equimolar amount of retronecine. The 60-MHz ^{1}H NMR of the product confirmed not only that the reaction had taken place but also that the product was the C-9 retronecine derivative rather than the C-7 isomer. This was discernible from the shift in the position of the C-9 protons from δ 4.14 to 4.69 in going from retronecine to the product.

In the 60-MHz NMR spectrum of diastereomeric mixture **2**, the C-9 protons appeared as a broad singlet with a width at half height of 9 Hz, while the C-2 proton appeared as two peaks separated by 0.07 ppm, and all of the other absorbances appeared as broad signals. The 300-MHz NMR spectrum of the same sample indicated that there were two overlapping spectra, one for each of the diastereomers. However, the C-9 protons appeared as an AB quartet with a sharp singlet in the middle (Figure 1).

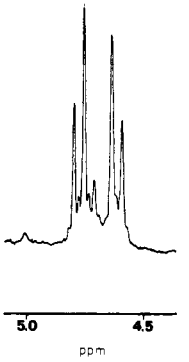
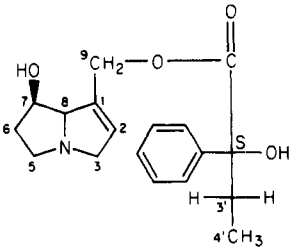


Figure 3.

Table I. Chemical Shifts[a] and Coupling Constants for 9-*O*-[(*S*)-(+)-2-Hydroxy-2-phenylbutyryl]retronecine (5)



5

proton	chemical shift, δ	proton	chemical shift, δ
2	5.57 (br s)	7	4.07 (dd)
3α	3.82 (d)	8	4.01 (br s)
3β	3.29 (dd)	9	4.71 (s)
5α	3.21 (ddd)	3′	2.24 (dq)
5β	2.67 (ddd)	3′	2.03 (dq)
6β	1.89 (ddd)	4′	0.86 (t)
6α	1.83 (ddd)	*o*, *p*	7.26 (m)
		m	7.53 (m)

Coupling Constants (Hz)

$J_{3\alpha 3\beta}$ = 15.7	$J_{3\beta 8\alpha}$ = 5.3	$J_{5\alpha 5\beta}$ = 9.2	$J_{5\alpha 6\alpha}$ = 7.3
$J_{5\alpha 6\beta}$ = 1.3	$J_{5\beta 6\alpha}$ = 11.3	$J_{5\beta 6\beta}$ = 6.2	$J_{6\beta 6\alpha}$ = 13.0
$J_{6\alpha 7\alpha}$ = 3.3	$J_{7\alpha 8\alpha}$ = 3.3	$J_{3'3'}$ = 14.1	$J_{3'4'}$ = 7.3

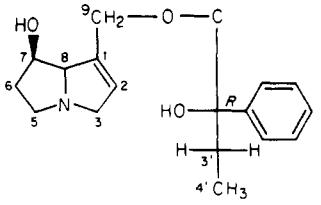
[a] Multiplicities are given in parentheses.

In order to prepare each pure diastereomer of **2**, we resolved 2-hydroxy-2-phenylbutyric acid using quinine and repeated the synthesis of **2** using the optically pure acids of known absolute configuration.[13] The 300-MHz ^{1}H NMR spectra indicated the diastereomer formed with (*S*)(+)-2-hydroxy-2-phenylbutric acid exhibited a singlet (Figure 2), and the one from the (*R*)-(−)-2-hydroxy-2-phenylbutyric acid showed an AB quartet (Figure 3) for the C-9 protons. Tables I and II show the correct absolute configurations of the two diastereomers with complete NMR analyses, obtained at 300 MHz.

The differences in the appearance of the C-9 protons at the two different field strengths can be explained by calculating $\Delta\nu/J$ for the AB quartet observed in spectrum of **2**. Thus at 300 MHz $\Delta\nu/J$ = 3.6, and calculating this value at 60 MHz leads to $\Delta\nu/J$ = 0.73, indicating that the

(8) Adams, R.; Rogers, E. F. *J. Am. Chem. Soc.* **1939**, *61*, 2815.
(9) McKenzie, A.; Ritchie, A. *Chem. Ber.* **1937**, *70*, 23.
(10) Kochethov, N. K.; Likhosherstov, A. M.; Kulahov, V. N. *Tetrahedron* **1969**, *25*, 2313.
(11) Mattocks, A. R. *J. Chem. Soc. C* **1969**, 2698.
(12) Hoskins, W. M.; Crout, D. H. G. *J. Chem. Soc., Perkin Trans. 1* **1977**, 538.
(13) Mitsui, S.; Imaizami, S.; Senda, Y.; Konno, K. *Chem. Ind. (London)* **1964**, 233.

Table II. Chemical Shifts[a] and Coupling Constants for 9-*O*-[(*R*)-(−)-2-Hydroxy-2-phenylbutyryl]retronecine (6)



6

proton	chemical shift, δ	proton	chemical shift, δ
2	5.69 (br s)	8	4.02 (br s)
3α	3.83 (d)	9β	4.82 (d)
3β	3.36 (dd)	9α	4.66 (d)
5α	3.23 (ddd)	3′	2.39 (dq)
5β	2.72 (ddd)	3′	2.09 (dq)
6β	2.29 (ddd)	4′	0.91 (t)
6α	2.09 (ddd)	*o*, *p*	7.32 (m)
7	4.07 (br s)	*m*	7.57 (m)

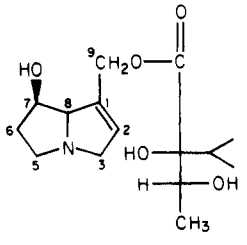
Coupling Constants (Hz)

$J_{3\alpha3\beta}$ = 15.4	$J_{3\beta8\alpha}$ = 4.4	$J_{5\alpha5\beta}$ = 9.1	$J_{5\alpha6\alpha}$ = 7.5
$J_{5\alpha6\beta}$ = 0.8	$J_{5\beta6\alpha}$ = 11.9	$J_{5\beta6\beta}$ = 6.3	$J_{6\beta6\alpha}$ = 12.9
$J_{6\alpha7\alpha}$ = 3.7	$J_{9\alpha9\beta}$ = 13.2	$J_{3'3'}$ = 14.2	$J_{3'4'}$ = 7.4

[a] Multiplicities are given in parentheses.

two inner peaks of the AB quartet would only be separated by 3.2 Hz. If one includes the line width of the peaks and add to that the singlet from the diastereomer **6**, then one would observe a broad singlet.

The large differences in the magnetic environments of the C-9 protons of the two diastereomers are a reflection of their preferred solution conformations. The preferred solution conformations arise from hydrogen bonding between the ester carbonyl and the adjacent hydroxyl[14] and also between the ester oxygen and the C-7 hydroxyl. The most stable arrangement of the aromatic ring and the ethyl group with these restrictions is above the plane of the necine base. In this conformation, the C-9 β proton is in the plane of the double bond in both **5** and **6**. The aromatic ring in **5** is positioned over the C-9 α proton apparently leading to a magnetic equivalence of the C-9 α and C-9 β protons. In **6**, the aromatic ring is above the C-9 β proton so that there is an additive effect at the C-9 β proton and no effect at the C-9 α proton, leading to a nonequivalence of these two protons. This conformational analysis can also be used to interpret the differences in the C-9 protons of indicine, which appear as an AB quartet, and in its diastereomer, intermedine (**7**), where they appear



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as a singlet[15] at 60 MHz.[16] If one invokes the conformational restrictions discussed above, in indicine both the double bond and the C-3′ hydroxy group are positioned near the C-9 β proton, leading to a large difference in the magnetic environments of the C-9 protons, while in intermedine (**7**) the double bond is near the C-9 β proton and the hydroxyl group is over the C-9 α proton, leading to their being essentially equivalent.

We are now preparing analogues of our semisynthetic compounds to screen for antitumor activity. The ^{1}H NMR spectra of these compounds will help to confirm our analyses of the solution conformations in this class of pyrrolizidine alkaloids and their analogues.

Experimental Section

General Methods. Proton nuclear magnetic resonance (^{1}H NMR) spectra were obtained by using either a Varian T-60 spectrometer or a Bruker WM-300 spectrometer equipped with an Aspect 2000 data system. Chemical shifts are reported relative to internal Me_4Si (δ 0) or $CHCl_3$ (δ 7.24). IR spectra were recorded on a Perkin-Elmer 237B spectrophotometer. Optical rotations were taken on a JASCO ORD-UV-5 instrument. Mass spectra were obtained by using a Varian MAT 112S spectrometer interfaced with an SS200 data system. Melting points were taken on a Kofler hot stage and are uncorrected. Medium-pressure liquid chromatography was carried out on a system constructed of Chromatix or Altex columns and fittings with ICN alumina (0.032–0.063 nm) as an absorbant and a FMI Model RP pump operating at 30–50 psi through an FMI pulse dampener as a pressure source.

All solvents used were distilled commercial grade. Dry $CHCl_3$ was prepared by passing distilled $CHCl_3$ through a column of activity I alumina just prior to use.

Monocrotaline. The crushed seeds (4.0 kg) from *Crotalaria spectabilis* were soaked in 2.5 L of 95% ethanol in a Soxhlet apparatus at room temperature. The ethanol was then pumped (FMI metering pump) from the bottom of the Soxhlet apparatus through a glass column, containing 200 g of Dowex 50W-X8 (20–50 mesh) cation-exchange resin in the H^+ form, back to the top of the Soxhlet. After the solvent was circulated for 24 h, the cation-exchange resin was poured into a separatory funnel and washed with 1 L of 1 N ammonia and 1 L of water. The combined aqueous material was extracted four times with 300 mL of chloroform. The combined chloroform extracts were dried ($MgSO_4$), filtered, and removed in vacuo, leaving 31.8 g of monocrotaline. The ethanol extract was replaced with fresh solvent, and the cation-exchange resin was regenerated with 1 M H_2SO_4. The seeds were extracted four times in this manner, yielding a total of 75.7 g (1.9%) of monocrotaline, mp 202–204 °C (lit.[8] mp 197–198 °C). All of the physical properties were identical with those previously reported.[1]

Retronecine. Monocrotaline was hydrolyzed to yield retronecine as previously described by Hoskins et al.[12] mp 118.0–118.5 °C (lit.[8] mp 121 °C).

2-Hydroxy-2-phenylbutyric Acid. 2-Hydroxy-2-phenylbutyric acid was prepared as described previously.[17] The material was resolved using quinine as described by McKenzie and Ritchie.[9] After four recrystallizations from 95% ethanol the quinine salt was dissolved in 6 M H_2SO_4. The hydroxy acid that precipitated was recrystallized from benzene, yielding colorless crystals: mp 127–129 °C (lit.[9] mp 128–129 °C); $[\alpha]^{24}_{589}$ +29.0° (*c* 1.97, ethanol) (lit.[9] $[\alpha]^{20}_{D}$ +32.7°). The quinone salt obtained from the mother liquor of the first recrystallization was hydrolyzed with 6 M H_2SO_4, giving colorless crystals: mp 119–124 °C; $[\alpha]^{24}_{589}$ −27.9°.

9-*O*-[(±)-2-Hydroxy-2-phenylbutyryl]retronecine (2). 1,1′-Carbonyldiimidazole (1.62 g, 0.010 m) and (±)-2-hydroxy-2-phenylbutyric acid (1.80 g, 0.010 mol were dissolved in 40 mL of dry $CHCl_3$ under an argon atmosphere. After the mixture was stirred for 45 min, retronecine (1.55 g, 0.010 m) was added. After 22 h, the $CHCl_3$ solution was washed with three 15-mL portions of saturated $NaHCO_3$. The $CHCl_3$ layer was dried ($MgSO_4$), filtered, and evaporated in vacuo, leaving 3.3 g of colorless oil. The oil was chromatographed on activity III alumina (230–400 mesh) with 1% methanol/chloroform. A colorless oil (2.46 g, 80%) pure by TLC (R_f 0.59, 10% methanol/chloroform on silica gel)

(14) Culvenor, C. C. J.; Dal Bon, R. *Aust. J. Chem.* **1964**, *17*, 1296.
(15) Culvenor, C. C. J.; Smith, L. W. *Aust. J. Chem.* **1966**, *19*, 1955.
(16) Although the C-9 proton of intermedine appears as a singlet at 60 MHz, 300-MHz ^{1}H NMR reveals that they are not equivalent and appear as an AB quartet ($\Delta\nu/J$ = 2.7).

(17) Smith, L., *J. Prakt. Chem.* **1911**, *84*, 743.

and NMR was obtained. All attempts at crystallization were unsuccessful: IR ($CHCl_3$) 3700–3300 (br), 2950–2800 (br), 1725 cm^{-1}; ^1H NMR ($CDCl_3$), composite of Table I and Table II; EIMS m/e (relative intensity) 317 (M^+, 0.6), 148 (10), 139 (15), 138 (89), 135 (22), 105 (17), 94 (42), 93 (100), 80 (24), 77 (17), 57 (44); CIMS m/e (relative intensity) 318 ($M^+ + 1$, 83), 138 (100); high-resolution MS, molecular ion m/e 317.1524, calcd. for $C_{18}H_{23}NO_4$ 317.1628.

9-*O*-[(±)-2-Hydroxy-2-phenylbutyryl]retronecine *N*-Oxide (2a). To a solution of 0.974 g (3.07 mmol) of **2** in 3.75 mL of ethanol was added 1.0 mL of 30% hydrogen peroxide. This mixture was kept at 4 °C in a refrigerator for 2 days. The excess peroxide was destroyed by the addition of MnO_2. The solution was then filtered and the solvent removed in vacuo, leaving a colorless viscous oil. The presence of *N*-oxide was determined by using a Mattocks test.[18] TLC on silica gel with 10% methanol/$CHCl_3$ as the solvent showed a single spot at R_f 0.47 as compared to R_f 0.59 for the free alkaloid. This difference in R_f of 0.1 is typical for pyrrolizidine alkaloid *N*-oxides:[1] ^1H NMR ($CDCl_3$) characteristic peaks δ 0.85 (br t, 3 H, J = 5.0 Hz), 4.69 (br s, 2 H), 5.51 (br s, 1 H), 7.29 (br m, 3 H), 7.47 (br m, 2 H); EIMS m/e (relative intensity) 165 (1), 155 (4), 138 (22), 136 (22), 135 (100), 117 (23), 106 (12), 105 (49), 104 (12); CIMS m/e (relative intensity) 318 (M + 1, 36), 300 (11), 163 (16), 139 (13), 138 (100), 136 (14), 135 (20).

9-*O*-[(*S*)-(+)-2-Hydroxy-2-phenylbutyryl]retronecine (5). A solution of 1,1'-carbonyldiimidazole (0.218 g, 1.35 mmol) and (+)-2-hydroxy-2-phenylbutyric acid (0.212 g, 1.29 mmol) in 15 mL of dry $CHCl_3$ under an argon atmosphere was stirred for 15 min to allow for the complete evolution of CO_2. To this was then added retronecine (0.2058 g, 1.33 mmol), and the solution was stirred for 20 h at room temperature. The $CHCl_3$ was washed with 10 mL of saturated $NaHCO_3$. The aqueous layer was extracted with 10 mL of $CHCl_3$, and the combined $CHCl_3$ extracts were dried ($MgSO_4$), filtered, and reduced in vacuo, leaving 0.3844 g (94%) of a colorless viscous oil: ^1H NMR ($CDCl_3$) see Table I; IR ($CHCl_3$) 3650–3400, 3100–2800, 1725 cm^{-1}; $[\alpha]^{20}_{589}$ +4.6° (c 2.19, MeOH); EIMS m/e (relative intensity) 317 (M^+, 2), 139 (18), 138 (95), 136 (14), 135 (32), 105 (11), 94 (41), 93 (100), 80 (26); CIMS m/e (relative intensity) 318 ($M^+ + 1$, 44), 300 (11), 139 (13), 138 (100), 136 (16), 135 (20); high-resolution MS, molecular ion m/e 317.1588, calcd. for $C_{18}H_{23}NO_4$ 317.1628.

9-*O*-[(*R*)-(−)-2-Hydroxy-2-phenylbutyryl]retronecine (6). The reaction was carried out exactly as described for **5** except that (−)-2-hydroxy-2-phenylbutyric acid was used: ^1H NMR ($CDCl_3$) see Table II; $[\alpha]^{20}_{589}$ + 6.0° (c 3.16, MeOH); EIMS exactly the same as for **5**; high-resolution MS, molecular ion m/e 317.1660, calcd. for $C_{18}H_{23}NO_4$ 317.1628.

Acknowledgment. We thank Dr. S. Gabriel for his partial assistance in the experimental work. We also thank the National Cancer Institute, NIH (Grant No. CA-23277 and CA-31490) for support and the National Science Foundation (Grant No. CHE 79-08659) for an equipment grant for the purchase of the Bruker WM-300 NMR spectrometer.

Registry No. (±)-**2a**, 81340-07-0; **3**, 480-85-3; **4**, 315-22-0; (+)-(*S*)-**5**, 81340-08-1; (−)-*R*-**6**, 81370-87-8; (+)-2-hydroxy-2-phenylbutyric acid, 24256-91-5; (−)-2-hydroxy-2-phenylbutyric acid, 3966-31-2.

(18) Mattocks, A. R. *Anal. Chem.* **1967**, *39*, 443.

Stabilization of Carbanions by Polarization of Alkyl Groups on Nonadjacent Atoms

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Equilibrium acidities in dimethyl sulfoxide solution have been found to increase along the series Me, Et, *i*-Pr, *t*-Bu for 9-substituted fluorenes when the alkyl group, R, is separated from the fluorene ring by a CH_2, S, or SO_2 moiety. This is a reversal of the effect observed when R is attached directly to the fluorene ring. Separation of the *t*-Bu group from the fluorene ring by a second CH_2 moiety causes the acidifying effect to disappear. A stabilizing, through-space polarization of the alkyl group by the negative charge of the carbanion center is identified as the source of the acid-strengthening effect. Evidence is presented which shows that alkyl groups on nonadjacent carbon atoms stabilize proximate carbanions and thereby may cause acid-strengthening effects also in 9-(2,4,6-trimethylphenyl)fluorene, 9-[(2-methylphenyl)thio]fluorene, 9-[(2-methylphenyl)sulfonyl]fluorene, (alkylthio)acetonitriles, (*tert*-butylsulfonyl)acetonitrile, bis(*tert*-butylthio)phenylmethane, bis(alkylsulfonyl)methanes, alkylthio alkyl sulfoxides, *tert*-butyl methyl sulfone, and *tert*-butyl benzyl sulfone. α-Phenylthio groups are shown to cause substantially larger acidity increases than α-methylthio groups when substituted for a hydrogen atom at the acidic site of fluorene, acetonitrile, or methyl phenyl sulfone. Evidence is presented to show that this is not due to a polarizability effect of phenyl per se, but may be due to enhancement of the polarizability of sulfur by phenyl.

Stabilization of alkoxide ions in the gas phase increases along the series MeO^-, EtO^-, *i*-PrO^-, *t*-BuO^- because the alkyl groups become better able to stabilize the negative charge by polarization as they increase in size.[1,2] These effects dictate the acidity order MeOH < EtOH < *i*-PrOH < *t*-BuOH in the gas phase. In solution this acid-strengthening polarizability effect is overshadowed by other effects. For example, in the dipolar nonhydroxylic solvent dimethyl sulfoxide the acidity decreases progressively along the series MeOH, EtOH, *i*-PrOH, *t*-BuOH by a total of about 2.4 pK_a units.[3] Here the acidity order is believed to be dictated primarily by a progressive decrease in specific solvation of the alkoxides with increasing size of the alkyl group, augmented by an electron-releasing

(1) Brauman, J. I.; Blair, L. K. *J. Am. Chem. Soc.* **1970**, *92*, 5986–5992.
(2) Taft, R. W.; Taagepera, M.; Abboud, J. L. M.; Wolf, J. F.; De Frees, D. J.; Hehre, W. J.; Bartmess, J. E.; McIver, R. T. *J. Am. Chem. Soc.* **1978**, *100*, 7765–7767.
(3) Olmstead, W. N.; Margolin, Z.; Bordwell, F. G. *J. Org. Chem.* **1980**, *45*, 3295–3299.

0022-3263/82/1947-2504$01.25/0