washed with water and ethanol, and dried. There was obtained 6.6 g (75%) of **11** as a brown solid: mp 297–300 °C; its mp, mmp, and IR and ^{1}H NMR spectra were identical with those of an authentic sample of **11** prepared by the known method.[9]

Acknowledgment. We thank Industrial Laboratory, Kodak Park, Eastman Kodak Co., for IR, NMR, and mass spectra, and elemental analyses. We are grateful to Mr. Francesco Debellis for some experimental help.

Registry No. **1a**, 24522-44-9; **1b**, 621-03-4; **4a**, 27241-31-2; **4b**, 4149-06-8; **5a**, 78515-46-5; **5b**, 61239-31-4; **6c**, 92694-92-3; **6d**, 92694-93-4; **6e**, 92694-94-5; **7a**, 84104-39-2; **7b**, 84104-44-9; **7c**, 84104-40-5; **7d**, 84104-41-6; **7e**, 84104-53-0; **8a**, 52472-98-7; **8b**, 2311-90-2; **8c**, 84104-31-4; **8d**, 14230-56-9; **8e**, 92694-95-6; **11**, 34320-82-6; acetic anhydride, 108-24-7; 2-(2,4-di-*tert*-pentylphenoxy)hexanoyl chloride, 63059-55-2; 2-(3-pentadecylphenoxy)butyl chloride, 62609-88-5; (4-nitrophenoxy)acetyl chloride, 20142-88-5.

Lithiation Reaction of 2,5-Dibromothiophene. ^{13}C NMR Spectra of 3-Substituted Derivatives

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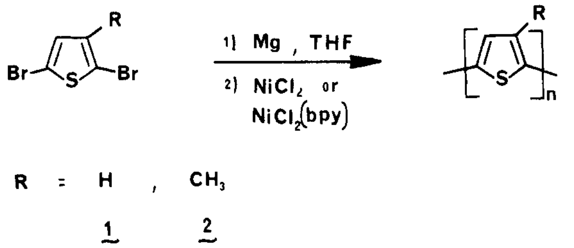
Received May 30, 1984

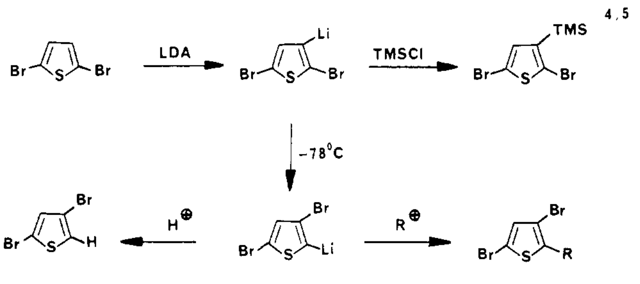
Poly(2,5-thienylenes), after doping with iodine, have been shown to exhibit significant conductivity. The polymeric materials were obtained by transition-metal-induced polymerization of the bis Grignard compounds derived from 2,5-dibromothiophene, **1**, and 2,5-dibromo-3-methylthiophene, **2**.[1] The polymeric material derived from **2** exhibited improved conductivity in comparison with that of **1** (eq 1).



(1)

Very recently we showed that conducting polymeric materials could be synthesized in a homogeneous reaction via the corresponding organolithium compounds that were obtained from either **1** or **2**.[2a,b] We also became interested in synthesizing 3-organometal-substituted poly(2,5-thienylenes) and to investigate their ability to conduct an electric current. In light of the well-documented "halogen dance" exhibited by halogenated thiophenes[3-5a] when they are treated with lithium organics, it was essential we demonstrate that **1** reacts with 2 equiv of *n*-butyllithium (the lithiation reagent used by us) to give the expected 2,5-dilithiothiophene rather than other positional isomers. We also had to show that treatment of **1** with various organometal electrophiles after lithiation with lithium diisopropylamide (LDA) gives the desired 3-substituted 2,5-dibromothiophenes. Proof of position of lithiation has now been accomplished either by transformation of the lithiated products to known compounds or by ^{1}H and ^{13}C NMR spectroscopic analysis of the 3-substituted derivatives.

Scheme I



R : various alkyl and carbonyl species

Scheme II

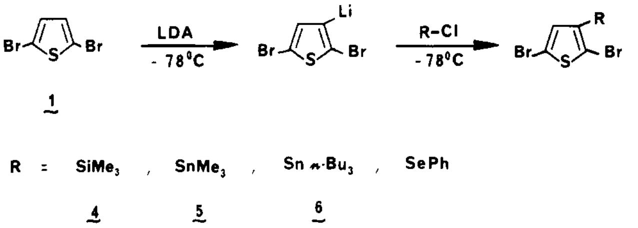


Table I. ^{13}C NMR Spectral Data for 2,5-Dibromothiophene Derivatives

compd	carbon	δ^a (ppm)	CH coupling const,[b] Hz
1	C_2 (C_5)	111.5[c] (114.3)	$^2J = {}^3J = 7.8$
	C_3 (C_4)	130.2[c] (131.3)	$^1J = 173.5$; $^2J = 4.5$
4	C_2	116.5 (118.7)	
	C_3	137.4 (143.7)	
	C_4	134.4 (135.7)	$^1J = 178.1$
	C_5	116.5 (113.2)	
	C_6	−0.8	
5	C_2	117.9[d]	
	C_3	137.1	
	C_4	133.1	$^1J = 177.0$
	C_5	116.7[d]	
	C_6	−7.7	$^1J = 129.5$
6	C_2	117.9[d]	
	C_3	137.7	
	C_4	133.2	
	C_5	116.6[d]	
	C_6	11.4	
	C_7	28.9	
	C_8	27.2	
	C_9	13.6	

[a] $CDCl_3$ solution with δ referred to the 77.0 ppm line; precision 0.1 ppm. Values in parentheses are predicted (see text). [b] Absolute values; precision 0.5 Hz. [c] Reference 6 lists 111.4 and 130.1 ppm. [d] Assignments for C_2 and C_3 are tentative and may be reversed.[9]

The reaction of 2,5-dibromothiophene (**1**) with LDA has been studied previously.[4,5a] Thus, Davies et al.[4] found that **1** reacted with LDA, and subsequent quenching of the lithiated product with trimethylsilyl chloride gave 2,5-dibromo-3-(trimethylsilyl)thiophene, **4**. Kano et al.[5a] confirmed this result; however, they also observed formation of 2,4-dibromothiophene or 2-substituted 3,5-dibromothiophenes, respectively, when quenching the in-

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[1] Yamamoto, T.; Sanechika, K.; Yamamoto, J. *J. Polym. Sci., Polym. Lett. Ed.* **1980**, *18*, 9 and references therein.

[2] (a) Amer, A.; Zimmer, H.; Mulligan, K. J.; Mark, H. B., Jr.; Pons, S.; McAteer, J. F. *J. Polym. Sci. Polym. Lett. Ed.* **1984**, *22*, 77. (b) Amer, A.; Zimmer, H.; Mulligan, K. J.; Mark, H. B., Jr., to be submitted for publication.

[3] Gronowitz, S.; Holm, B. *Acta Chem. Scand.* **1969**, *23*, 2207.

[4] Davies, G. M.; Davies, P. S. *Tetrahedron Lett.* **1972**, 8507.

[5] (a) Kano, S.; Yuasa, Y.; Yokomatsu, T.; Shibuya, S. *Heterocycles* **1983**, *20*, 2035. (b) To check whether reacting **1** with an excess of LDA would lead to an Li-Br exchange in addition to the observed H-Li exchange, **1** in THF was treated with 2 equiv of LDA at −78 °. After hydrolysis **1** was recovered quantitatively.

0022-3263/84/1949-5250$01.50/0

termediate organolithium compound with water or with a variety of carbon nucleophiles (Scheme I).

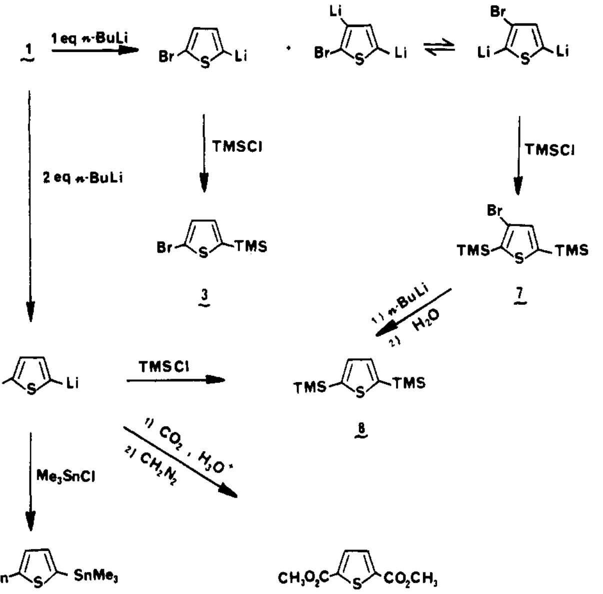
We also found that reaction of 1 with LDA, followed by quenching with trimethylsilyl chloride, gave 4.[5b] When employing trimethyltin chloride, tri-*n*-butyltin chloride, or phenylselenyl chloride instead of trimethylsilyl chloride, we observed analogous reactions giving the corresponding 3-substituted organometal derivatives. In all three cases the substitution occurred at the 3-position, as shown by a careful analysis of the ^{13}C NMR spectra of the organometal-substituted dibromothiophenes (Scheme II). These data are summarized in Table I. The ^{13}C spectrum of 1 has been published,[6] and the positions of its resonances are well correlated with values predicted from the spectrum of thiophene itself ($C_{2,5}$, 124.4 ppm; $C_{3,4}$, 126.2 ppm),[7] and the incremental shifts caused by bromine substitution at aromatic carbons.[7,8] We also report in Table I the ^{13}C–H coupling constants for 1, which are in full accord with the chemical shift assignments.

Although introduction of a trimethylsilyl group in the 3-position (compound 4) lifts the symmetry equivalance of C_2/C_5 and C_3/C_4, the former pair remain accidentally equivalent, with both C_2 and C_5 deshielded by ca. 5 ppm compared to 1. Differentiation of the C_3 and C_4 resonances was based on (a) the magnitude of $^1J_{C-H}$ for C_4, (b) the greater intensity of the (proton-bound) C_4 signal, (c) the analogous deshielding effects of silicon substitution on a benzene ring,[7] and (d) the known proclivity of the site of substitution in thiophenes to exhibit the largest incremental shift.[8] The predicted values are in good agreement with those observed, with an average absolute deviation of ca. 3 ppm.

In the case of the 3-trimethylstannyl derivative 5, the C_3 and C_4 resonances were also assigned on the basis of the one-bond C–H coupling constant for C_4.[9] Both C_3 and C_4 are somewhat downfield of the corresponding resonances in 4, but once again the site of attachment (C_3) experiences the larger shift. Assignment of the C_2/C_5 resonances is more difficult because the difference in chemical shifts is only ca. 1 ppm. We assign the slightly downfield of the pair to C_2, owing to its proximity to the tin atom.[8]

The ring carbon resonances of tri-*n*-butylstannyl derivative 6 were virtually superimposable on those of 5 and therefore readily assigned.[9] The butyl carbons were assigned by comparison with those of tri-*n*-butyltin chloride.[10]

Scheme III



With *n*-butyllithium as lithiating reagent for 1, we found that the results of the reaction were dependent on the amount of *n*-butyllithium used. Thus, we found that 1 reacts with 1 equiv of *n*-butyllithium to give 2-bromo-5-lithiothiophene as main product. As a result of a "halogen dance" 3-bromo-2,5-dilithiothiophene and 2-bromo-3,5-dilithiothiophene were formed in lesser amounts. This was shown by quenching the lithiation product with trimethylsilyl chloride, which yielded 2-bromo-5-(trimethylsilyl)thiophene, 3 (62%), and 3-bromo-2,5-bis(trimethylsilyl)thiophene, 7 (38%). The structure of the latter product was determined by debromination with butyllithium (aqueous workup), which resulted in formation of 2,5-bis(trimethylsilyl)thiophene, 8. When 1 was lithiated within 5 h with 2 equiv of *n*-butyllithium, only 8 was obtained after being quenched with trimethylsilyl chloride. Also, quenching of the lithiated compound with trimethylstannyl chloride gave the analogous 2,5-bis(trimethylstannyl)thiophene. The position of the substituents and thus the position of the lithiation of 1 was determined by two independent methods. (A) Treatment of the known compound 7[4] with *n*-butyllithium followed by quenching with water gave rise to formation of 8. (B) The dilithiated compound derived from 1 was treated with excess dry ice and the resulting dicarboxylic acid was converted into the dimethyl ester with diazomethane. The resulting diester, mp 146–147 °C, was identical with the known dimethyl thiophene-2,5-dicarboxylate (Scheme III).[11a,b]

Experimental Section

Melting points were determined with a Mel-Temp apparatus and are uncorrected, as are the boiling points. Infrared spectra (IR) were recorded by using a Perkin-Elmer Model 599 spectrometer calibrated against the 1601-cm^{-1} band of polystyrene. The ^{1}H NMR spectra were recorded on a Varian T-60 spectrometer. The ^{13}C NMR spectra were recorded on an IBM NR-80 (20 MHz) and/or a Nicolet NT300 narrow-bore spectrometer (75.5 MHz), with 1180 E data system. Chemical shifts are expressed in δ relative to tetramethylsilane as internal standard; MS data were obtained on a Perkin-Elmer RMU-7 mass spectrometer and/or a Kratos MS80 instrument with a DS-55 data system. Elemental analyses were performed at M-H-W Laboratories, Phoenix, AZ. All reactions involving organolithium intermediates were performed under a blanket of argon. Tetrahydrofuran (THF) was purified by continuous distillation under Argon from benzophenone and sodium metal. The reported yields are from isolated purified materials. ^{13}C NMR data appear in Table I.

Reaction of 2,5-Dibromothiophene (1) with LDA, Followed by Quenching with Trimethylsilyl Chloride. 2,5-Dibromo-3-(trimethylsilyl)thiophene (4). To a stirred solution of 5.05 g (0.05 mol) of diisopropylamine in dry tetrahydrofuran (THF) at −78 °C was added dropwise 33.3 mL (0.05 mol of 1.5 M) of *n*-BuLi in *n*-hexane. After being stirred for 30 min, a solution of 10.9 g (0.045 mol) of 1[2] in 10 mL of dry THF was added and stirring was continued for 30 min. Then 8.2 g (0.075 mol) of trimethylsilyl chloride in 5 mL of dry THF was added dropwise

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(6) Johnson, L. F.; Jankowski, W. C. "Carbon-13 NMR Spectra"; R. E. Krieger: New York, 1978; spectrum #44.

(7) Silverstein, R. M.; Bassler, G. C.; Morrell, T. C. "Spectrometric Identification of Organic Compounds", 4th ed.; Wiley: New York, 1981; p 265 ff.

(8) Stothers, J. B. "Carbon-13 NMR Spectroscopy"; Academic Press: New York, 1972; p 256 ff.

(9) Satellites from ^{117}Sn and ^{119}Sn coupling were too weak to be of value in making assignments.

(10) Lycka, A.; Snobb D.; Handlir, K.; Holecek, J.; Nadvornik, M. *Collect. Czech. Chem. Commun.* **1981**, *46* 1383.

(11) (a) Steinkopf, W. "Die Chemie des Thiophens"; Th. Steinkopf Verlag: Dresden, 1941. (b) Birkinshaw, H.; Chaplen, P. *Biochem. J.* **1955**, *60*, 255.

to the yellow brown reaction mixture at −78 °C. After 30 min the bright yellow reaction mixture was warmed to 0 °C and hydrolyzed. The organic phase was separated and dried over anhydrous $MgSO_4$ and the THF distilled off. The resulting brown residue was distilled in vacuum: bp 103 °C (1 mm); yield 12 g (91%); IR (film) 840 cm^{-1} (CSi);[12] ^{1}H NMR ($CDCl_3$) δ 0.33 (s, 9 H) 7.0 (s, 1 H); mass spectrum, *m/e* (% intensity) 316 ($M^+ + 2$, 5), 314 (M^+, 12), 312 ($M^+ - 2$, 5), 301 ($M^+ + 2 - CH_3$, 27), 299 ($M^+ - CH_3$, 50), 297 ($M^+ - 2CH_3$, 32), 220, 218 ($M^+ - CH_3 - Br$, 11, 12), 205, 203, 201 ($M^+ - CH_3 - Br$, 55, 100, 49), 177, 175 ($M^+ - 2CH_3 - SiBr$, 57, 62), 160 ($M^+ - 3CH_3 - SiBr$, 5), 139, 137 ($M^+ - CH_3 - 2Br$, 82, 60), 111, 109, 107 ($M^+ - CH_3 - SiBr - Br$, 58, 94, 42), 97, 95, 93 ($M^+ - 2CH_3 - SiBr - Br$, 8, 55, 20), 81 (Br, 62), 73 ($(CH_3)_3Si$, 75), 43 ($C_3H_7^+$, 98), 15 (CH_3, 28); no spectra or other physical constants are given in ref 4 or 5.

Reaction of 2,5-Dibromothiophene with 1 Equiv of *n*-BuLi, Followed by Quenching with Trimethylsilyl Chloride at −55 °C. A solution of 10.9 g (0.045 mol) of **1** in 100 mL of dry THF was treated with 33.3 mL (0.05 mol of 1.5 M) of *n*-BuLi in *n*-hexane at −50 to −55 °C. After being stirred for 30 min, the tan reaction mixture was quenched with 8.2 g (0.075 mol) of trimethylsilyl chloride in 5 mL of dry THF at −50 to −55 °C. After being warmed to 0 °C, the mixture was hydrolyzed. The organic phase was separated and dried over anhydrous $MgSO_4$ and the THF distilled off. The remainder was distilled in vacuum to give 10 g (76%), bp 73–100 °C (1 mm). After fractional distillation using a 15 cm Vigreux column two compounds, 2-bromo-5-(trimethylsilyl)thiophene, **3**, and 3-bromo-2,5-bis(trimethylsilyl)thiophene, **7**, were obtained. Compound **3** (bp 58 °C (0.5 mm); yield 62%) gave the following spectral data: IR (film) 830 cm^{-1} (SiC); ^{1}H NMR ($CDCl_3$) δ 0.3 (s, 9 H), 6.95 (dd, 2 H, $J_{AB} = 3$ Hz); mass spectrum, *m/e* (relative intensity), 236 ($M^+ + 2$, 17), 234 (M^+, 17), 221 ($M^+ + 2 - CH_3$, 95), 219 ($M^+ - CH_3$, 100), 139 ($M^+ + 2 - CH_3 - Br$, 100), 137 ($M^+ - CH_3 - Br$, 95), 109 ($M^+ + 2$, $-3CH_3$, −Br, 35), 73 ($(CH_3)_3Si^+$, 31), 53 ($C_4H_5^+$, 38), 43 ($C_3H_7^+$, 52). Compound **7** (bp 92 °C (0.5 mm); yield 38%) showed the following spectral data: IR (film) 830 cm^{-1} (CSi); ^{1}H NMR ($CDCl_3$) δ 0.30 (s, 9 H), 0.40 (s, 9 H), 7.17 (s, 1 H); mass spectrum, *m/e* (relative intensity) 308 ($M^+ + 2$, 10), 306 (M^+, 10), 293 ($M^+ + 2 - CH_3$, 65), 291 ($M^+ - CH_3$, 65), 139 ($M^+ - (CH_3)_3Si - Br$, 48), 73 ($(CH_3)_3Si$, 100).

Debromination of 3-Bromo-2,5-bis(trimethylsilyl)thiophene, 7. A solution of 1.2 g (3.9 mmol) of **7** in 20 mL of dry THF was treated with 2.7 mL (4 mmol of a 1.5 M) of *n*-BuLi in *n*-hexane at −50 to −55 °C. After being stirred for 30 min at this temperature, the reaction mixture was hydrolyzed. When at room temperature, the organic phase was separated and dried over anhydrous $MgSO_4$ and the solvent distilled off. The residue was purified by a vacuum distillation, to give **8**: 1 g (44%); bp 101 °C (20 mm). ^{1}H NMR, MS, and IR spectra and GC retention time of **8** obtained by this reaction were identical with those of the product that was produced by reaction of **1** and 2 equiv of *n*-BuLi. Anal. Calcd for $C_{10}H_{20}SSi_2$: C, 52.56; H, 8.82; S, 14.03. Found: C, 52.86; H, 8.99; S, 14.21.

Reaction of 1 with 2 Equiv of BuLi, Followed by Quenching with Trimethylsilyl Chloride. A solution of 5.5 g (0.0225 mol) of **1** in 100 mL of dry THF was treated with 33.3 mL (0.05 mol of 1.5 M) of *n*-BuLi in *n*-hexane at −50 to −55 °C. After being stirred for 30 min, a solution of 8.2 g (0.075 mol) of trimethylsilyl chloride in 10 mL of dry THF was added dropwise at −50 to −55 °C. The yellow reaction mixture turned to bright yellow and gave a precipitate. After the reaction mixture was hydrolyzed, the organic phase was separated and dried over anhydrous $MgSO_4$ and the solvent was distilled off. For purification, the brown residue was distilled in vacuum and shown to be **8** (89%).

2,5-Bis(trimethylstannyl)thiophene. A solution of 5.5 g (0.0225 mol) of **1** in 100 mL of dry THF was treated with 33.3 mL (0.05 mol of 1.5 M) of *n*-BuLi in *n*-hexane at −50 to −55 °C. After being stirred for 30 min, the yellow reaction mixture was quenched with a solution of 10 g (0.05 mol) of trimethyltin chloride in 10 mL of dry THF. The reaction mixture turned to bright yellow, and a precipitate was obtained by lowering the temperature below −60 °C. After being stirred for 4 h at −50 to −55 °C, the reaction mixture was hydrolyzed and the separated organic phase was dried over anhydrous $MgSO_4$ and the solvent distilled off. The solid product was recrystallized from ether to give 8.5 g (92%): mp 98 °C; ^{1}H NMR ($CDCl_3$) δ 0.36 (s, 18 H), 7.4 (s, 2 H). Anal. Calcd for $C_{10}H_{20}SSn_2$: C, 29.31; H, 4.92, S, 7.82. Found: C, 29.34; H, 4.84; S, 7.90.

2,5-Dibromo-3-(tri-*n*-butylstannyl)thiophene (6). A solution of 33.3 mL (0.005 mol of 1.5 M) of *n*-BuLi in *n*-hexane was added dropwise to a stirred solution of 5.05 g (0.05 mol) of diisopropylamine in 100 mL of dry THF at −78 °C. After being stirred for 30 min, a solution of 10.9 g (0.045 mol) of **1** in 10 mL of dry THF was added dropwise to the LDA solution. To this orange reaction mixture was added a solution of 16.3 g (0.05 mol) of tri-*n*-butyltin chloride in 10 mL of dry THF at −78 °C. After being stirred for 1 h at −78 °C, the mixture was allowed to warm to 0 °C and hydrolyzed. The organic phase was separated and dried over anhydrous $MgSO_4$ and the solvent distilled off. The remaining brown oil could not be distilled and decomposed at high temperature (over 200 °C). Purification by chromatography was attempted on a dry-packed silica gel column. Flushing of the column with petroleum ether (30–60 °C) removed the product from the impurities. Evaporation of the petroleum ether gave 20 g (84%) of a bright yellow oil: ^{1}H NMR ($CDCl_3$) 0.6–1.8 (m, 27 H), 7.0 (s, 1 H). Anal. Calcd for $C_{16}H_{28}Br_2SSn$: C, 36.19; H, 5.31; Br, 30.10; S, 6.04. Found: C, 36.08; H, 5.39; Br, 30.22; S, 6.15.

2,5-Dibromo-3-(phenylselenyl)thiophene. A solution of 33.3 mL (0.05 mol of 1.5 M) of *n*-BuLi in *n*-hexane was syringed into a stirred solution of 5.05 g (0.05 mol) of diisopropylamine in 100 mL of dry THF at −78 °C. After being stirred for 30 min, a solution of 10.9 g (0.045 mol) of **1** in 10 mL of dry THF was added dropwise. The orange reaction mixture was stirred for 30 min, when a solution of 8 g (0.045 mol) of phenylselenyl chloride in 20 mL of dry THF was added. After being stirred for 4 h at −78 °C, the bright yellow reaction mixture was allowed to warm up to 0 °C and hydrolyzed. The separated organic phase was dried over anhydrous $MgSO_4$ before the solvents were distilled off. The yellow residue was purified by a vacuum distillation, bp 180 °C (0.5 mm), to give 14 g (78.4%). Final purification was achieved by chromatography on a silica gel column using petroleum ether 30–60 °C as eluant: ^{1}H NMR ($CDCl_3$) δ 7.0 (s, 1 H), 7.1–7.8 (m, 5 H). Anal. Calcd for $C_{10}H_6Br_2SSe$: C, 30.26; H, 1.52; Br, 40.25; S, 8.07. Found: C, 29.99; H, 1.79; Br, 40.06; S, 8.31.

2,5-Dibromo-3-(trimethylstannyl)thiophene (5). A solution of 33.3 mL (0.05 mol of 1.5 M) of *n*-BuLi in *n*-hexane was syringed into a stirred solution of 5.05 g (0.05 mol) of diisopropylamine in 100 mL of dry THF at −78 °C, and then 10.9 g (0.045 mol) of **1** in dry THF (10 mL) was added. The yellow reaction mixture was stirred for 30 min and then treated with a solution of 8 g (0.04 mol) of chlorotrimethyltin in 20 mL of dry THF at −78 °C. After further being stirred for 4 h at −78 °C and warmed up to 0 °C, the mixture was hydrolyzed. The organic phase was separated and dried over anhydrous $MgSO_4$ and the solvent distilled off. For final purification, the yellow residue was distilled in vacuum to give 12 g (74%): bp 105 °C (0.5 mm); ^{1}H NMR ($CDCl_3$) δ 0.43 (s, 9 H), 7.0 (s, 1 H). Anal. Calcd for $C_7H_{10}Br_2SSn$: C, 20.77; H, 2.49; Br, 39.48; S, 7.92. Found: C, 21.00; H, 2.66; Br, 39.48; S, 8.12.

Thiophene-2,5-dicarboxylic Acid. To a solution of 5.5 g (0.0225 mol) of **1** in 100 mL of dry THF was added 33.3 mL (0.05 mol of 1.5 M) of *n*-BuLi solution in *n*-hexane was added dropwise at −50 to −55 °C. After being stirred for 5 h, the light yellow reaction mixture as poured onto dry ice. The colorless suspension was allowed to warm up and then acidified with 2 N aqueous HCl. The aqueous layer was extracted two times with 50 mL of ether, dried over anhydrous $MgSO_4$, and combined with the organic layer. When the solvent was distilled off, a light brown solid product was obtained. Crystallization from water gave colorless crystals, which did not melt without decomposition;[11a] yield 3.0 g (95%); IR (KBr, cm^{-1}) 3600–2000 (broad band −COOH), 1650 (C=O stretch); ^{1}H NMR (Me_2O-d_6) δ 7.66 (s, 2 H), 11.56 (s br, 2 H).

Dimethyl Thiophene-2,5-dicarboxylate. The acid (0.43 g) was converted into its dimethyl ester by the usual diazomethane

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[12] Pretsch, E.; Clerc, T.; Seibl, J.; Simon, W. "Tabellen zur Strukturafklärung Organischer Verbindungen"; Springer-Verlag: Berlin-Heidelberg-New York, 1981.

method. On removal of the ether a light yellow crystalline residue, a melting point of 141 °C was obtained. Recrystallization from methanol gave needles: mp 146–147 °C;[11b] yield 0.4 g (77.5%); IR (KBr) 1700 cm^{-1} (C=O, ester); ^{1}H NMR (CDCl$_3$) δ 3.9 (s, 6 H), 7.66 (s, 2 H).

Acknowledgment. Financial assistance through NSF-Grant CHE 8205873 and NSF Grant PCM 8219912 toward purchase of the Kratos MS 80 instrument system is gratefully acknowledged. We thank the Lithium Corp. of America (Dr. R. O. Bach), Bessemer City, NC 28016, for generous gifts of *n*-butyllithium.

Registry No. **1**, 3141-27-3; **3**, 18246-28-1; **4**, 38611-18-6; **5**, 93041-05-5; **6**, 93041-06-6; **7**, 93041-07-7; **8**, 17906-71-7; LDA, 120-40-1; THF, 109-99-9; *n*-BuLi, 109-72-8; HCl, 7647-01-0; *n*-hexane, 110-54-3; trimethylsilyl chloride, 75-77-4; 2,5-bis(trimethylstannyl)thiophene, 86134-26-1; trimethyltin chloride, 1066-45-1; tri-*n*-butyltin chloride, 1461-22-9; 2,5-dibromo-3-(phenylselenyl)thiophene, 93041-08-8; phenylselenyl chloride, 5707-04-0; thiophene-2,5-dicarboxylic acid, 4282-31-9; dry ice, 124-38-9; dimethyl thiophene-2,5-dicarboxylate, 4282-34-2; diazomethane, 334-88-3.

Synthesis of Unsymmetrical 1,4-Bis[(aminoalkyl)amino]anthracene-9,10-diones for Antineoplastic Evaluation

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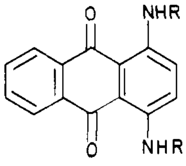
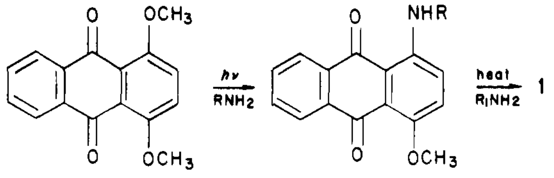
Recently the synthesis and antineoplastic evaluation of a number of symmetrically substituted 1,4-bis[(aminoalkyl)amino]anthracene-9,10-diones such as **1a** have been reported.[1] Compound **1b** and its 5,8-dihydroxy-substituted congener have shown outstanding antineoplastic activity.



1a, R = R$_1$ = $(CH_2)_2NH_2$
1b, R = R$_1$ = $(CH_2)_2NH(CH_2)_2OH$

As part of a drug development program, we report a convenient two-step synthetic sequence commencing with 1,4-dimethoxyanthracene-9,10-dione (**2**) which lends itself to the synthesis of symmetrically and unsymmetrically substituted analogues related to **1**. This two-step photolytic–thermolytic procedure is outlined in Scheme I and allows a facile preparation of unsymmetrical analogues of 1 to further define the structure–activity relationship of this new class of antitumor agents.

Scheme I



2 **3**

Table I. Photolytic Substitutions of 2 Leading to 3

3	R	% yield
a	$CH_2CH{=}CH_2$	44
b	$(CH_2)_3CH_3$	51
c	$(CH_2)_2NH_2$	26
d	$(CH_2)_3NH_2$	28
e	$(CH_2)_2NHCOCH_3$	31
f	$(CH_2)_3NHCOCH_3$	35
g	$(CH_2)_4NHCOCH_3$	30
h	$(CH_2)_5NHCOCH_3$	39
i	$(CH_2)_2N(CH_3)_2$	2

Table II. Thermal Substitutions of 3 Leading to 1

1	R	R^1	% yield
c	$CH_2CH{=}CH_2$	$CH_2CH{=}CH_2$	28
d	$(CH_2)_3CH_3$	$CH_2C_6H_5$	64
e	$(CH_2)_3CH_3$	$(CH_2)_2N(CH_3)_2$	58
f	$(CH_2)_2NHCOCH_3$	$(CH_2)_2N(CH_3)_2$	72
g	$((CH_2)_3NH_2$	$(CH_2)_2N(CH_3)_2$	55
h	$(CH_2)_3NHCOCH_3$	$(CH_2)_2N(CH_3)_2$	70
i	$(CH_2)_4NHCOCH_3$	$(CH_2)_2N(CH_3)_2$	79
j	$(CH_2)_5NHCOCH_3$	$(CH_2)_2N(CH_3)_2$	92

Several experimental procedures have been utilized for the preparations of symmetrical substituted analogues of 1. Treatment of quinizarin (1,4-dihydroxyanthracene-9,10-dione) or leucoquinizarin (followed by a subsequent oxidation step) with various diamines has found general applicability.[1,2] In certain cases such as **1a** or **1b**, competitive cyclizations can occur to form quinoxalines.[1d,3] Other methods which have led to symmetrical derivatives are the treatment of 1,4-dichloroanthracene-9,10-dione with allkylamines[4] and heating borate esters of quinizarin with arylamines.[5]

This research is patterned after the observation of Griffiths and Hawkins[6] who found that 1-methoxyanthracene-9,10-dione on photolysis in the presence of primary alkylamines afforded the corresponding 1-(alkylamino)anthracene-9,10-diones. It is generally observed in aromatic nucleophilic photochemical substitutions that the position meta to an electron-withdrawing group is activated relative to the ortho or para positions. This is in direct contrast to thermal displacments in which electron-withdrawing groups must be ortho or para to the leaving group.

Irradiation of a methylene chloride solution of **2** in the presence of allylamine, 1-aminobutane, and several α,ω-diamines lead to the monosubstituted products **3** in 30–51% yields (Table I). In the examples where α,ω-diamines were used, purification of the free amine was

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