Chemistry of Thienopyridines. XXXVIII. Diels-Alder Reactions of Thienopyridine Sulfones. Part 2 [1,2]

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Received December 20, 1989

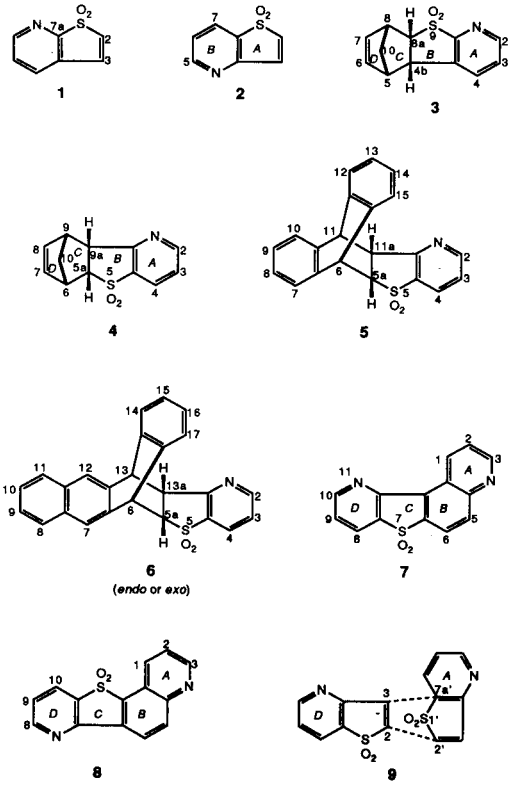
Thieno[3,2-*b*]pyridine 1,1-dioxide (**2**) undergoes Diels-Alder condensation with the dienophiles cyclopentadiene, anthracene, and naphthacene in a manner analogous to its isomer thieno[2,3-*b*]pyridine 1,1-dioxide (**1**). Compound **2** dimerizes in refluxing xylene with the loss of sulfur dioxide plus either the loss or transfer of hydrogen to give a small yield (*ca.* 2%) of pyrido[2',3':4,5]thieno[3,2-*f*]quinoline 7,7-dioxide (**7**) and its 5,6-dihydro derivative **12**. Formation of **7** and **12** are compared and contrasted with products reported from dimerization of **1** and of benzo[*b*]thiophene 1,1-dioxide and its derivatives.

J. Heterocyclic Chem., **27**, 1721 (1990).

In a preceding paper [2] we described the syntheses of thieno[2,3-*b*]pyridine 1,1-dioxide (**1**) and thieno[3,2-*b*]-pyridine 1,1-dioxide (**2**) and the Diels-Alder condensation of **1** with anthracene, naphthacene, and furan, as well as self-condensation of **1**. In the present paper we present Diels-Alder condensation reactions of **2** plus an additional condensation of **1**.

Both **1** and **2** react with cyclopentadiene to produce *endo-cis* adducts **3** and **4**, respectively, in yields of 68 ± 1%. The *endo-cis* geometry is assigned on the basis of the vicinal bridgehead proton-proton coupling constants, specifically J = 4.0 ± 0.3 Hz in the saturated five-membered carbocyclic ring and J = 8.4 ± 0.1 Hz in the dihydrothiophene ring [7]. Despite these close relationships in the products formed there was a marked difference in the reactivities of **1** and **2** toward cyclopentadiene under closely similar reaction conditions. Reaction of sulfone **2** occurred exothermically in an ice bath and was complete (as based on tlc analysis) in about 30 minutes. Contrariwise, sulfone **1** reacted sluggishly even at room temperature and required more than a day for completion. Sulfone **2** was refluxed with anthracene in xylene as solvent for 44 hours (exactly as reported for sulfone **1**), but the yields of adducts obtained were markedly different; 99% for **5**, but 45% for the adduct from **1** [2]. Both adducts were assigned the *cis* geometry (J ≃ 9 Hz). Thus, again, it appears that sulfone **2** is more reactive than **1** as a dienophile.

However, little difference between **1** and **2** was found in reaction with naphthacene, as based on yields of the adducts obtained under the reaction conditions employed with anthracene: 29% from **1** [2], 18% of **6** from **2**. In fact, tlc in the latter reaction indicated that unreacted **2** still remained after 44 hours of refluxing and little or no change occurred thereafter (total reaction time 96 hours). Ostensibly, the sulfones, naphthacene, and the adducts attain equilibrium mixtures in refluxing xylene.

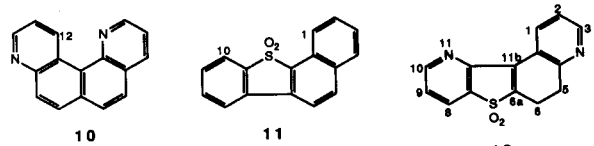


As expected, the electron-impact mass spectra of adducts **3-6** show fragmentation as per the retro-Diels-Alder reaction [8]. For compounds **3** and **4** both cyclopentadiene ions and thienopyridine sulfone (protonated plus non-protonated) ions are observed, though the relative abundances are considerably different, 1:1.55 for **3** and 1:0.84 for **4**. For adducts **5** and **6**, however, positive ions from the arene component dominate the spectrum with the arene cation-radical as the most abundant fragment and the protonated arene next in abundance [2].

In an effort to effect self-condensation of **2**, we refluxed

a solution of **2** in toluene for 30 hours. There was no evidence of reaction. At the higher temperature of refluxing xylene, however, the solution gradually darkened (even in a nitrogen atmosphere) and a number of minor products formed, as based on tlc analysis. The reaction was stopped after 40-50 hours, when unreacted **2** was still the major component, and the hydrate of a dimer of molecular formula $C_{14}H_8N_2O_2S$ (1-2% yield) was isolated. This dimer retains the sulfone functional group, does not undergo a retro-Diels-Alder reaction in mass spectrometry, can be sublimed with partial dehydration *in vacuo* at 190°, fluoresces in ultraviolet light, and contains only aromatic protons (plus water). We assigned a structure of either **7** or **8** to it. Helically shaped **7** would result from dimerization in the 2,2′:3,7a′ manner shown in structure **9** (*i.e.* in the *endo* configuration, with overlap of rings *A* and *D* in the transition complex), followed by loss of sulfur dioxide unit 1′ plus hydrogen atoms H-2 and H-3. Correspondingly, zigzag-shaped **8** would result from dimerization in the 2,7a′:3,2′ manner (*i.e.* in the *exo* configuration, with no overlap of rings *A* and *D* in the complex), plus loss of the same fragments.

The ^{1}H nmr spectrum of the dimer is qualitatively consistent with either **7** or **8** in general appearance, but chemical shifts of selected signals indicate that **7** is the correct structure. First, there is a doublet of doublets for one proton (H-1), J = 8.7 and 1.8 Hz (*cf.* $J_{3,4}$ = 8.2-8.3 Hz, $J_{2,4}$ = 1.7 Hz, $J_{2,3}$ = 4.1-4.2 Hz, in quinoline [9]) at 10.25 ppm, plus 2 doublet of doublets, J = 4-5 and 1-2 Hz, at 9.12 and 8.92 ppm for one proton each (H-3 and either H-10 in **7** or H-8 in **8**) for the three signals which occur furthest downfield. The large chemical shift for H-1 is ascribed either to a through-space effect of N-11 (with its non-bonding electron pair) in **7** or the sulfonyl group in **8**. To evaluate these relative effects we compare data for the model compounds quino[8,7-*f*]quinoline (**10**) and benzo[*b*]naphtho[2,1-*d*]thiophene 11,11-dioxide (**11**), all measured in the same solvent. In **10**, one has δ 11.4 for H-12 [10], while in **11** the signal for H-1 (furthest downfield) falls at δ 8.43. One can then estimate the chemical shift for H-1 in **8** by adding an increment of 0.34 to 8.43 (to give 8.79) to take account of the added effect of the γ-heteronitrogen atom N-4 [11]. The chemical shift for H-1 in our dimer lies between that of H-12 (observed) in **10** and H-1 (predicted) in **11**, but closer to the former (Δδ = −1.1 versus +1.46 ppm). The magnitude of the downfield shift induced by the non-bonding electrons of a nitrogen atom in a pyridine ring on the signal of an intramolecular, contraposed proton will vary inversely with the N-to-H distance [12]. These internuclear distances in **10** and **7** are estimated as 2.19 Å and 2.41 Å by molecular mechanics calculations on a computer [13]. We suggest that the large difference of +0.22 Å in N-to-H distances in these two compounds is consistent with the observation of Δδ = -1.1 in chemical shifts therein (*vide infra*).



10 11 12

During purification of the preceding, crystalline dimer, crude **7** was washed with acetone and the washings were evaporated to yield a solid mixture (*ca.* 1:1) of **7** and its 5,6-dihydro derivative **12**. The presence of **12** (not isolated in pure form) was revealed by observation of the ^{1}H nmr spectra (both 1D and 2D) of this mixture (see Figure 1). For the mixture there is a doubling of all of the corresponding signals for **7**, but with one major modification. Instead of the doublet of doublets for H-5 and H-6 in the aromatic region for **7** there occurs a doublet of triplets (centered at δ 3.18) for a total of four hydrogens (2 H-5 plus 2 H-6) in the aliphatic region for **12**. The 2D COSY nmr spectrum clearly shows separate connectivity relationships for two independent components. Noteworthy is the indication of weak long-range coupling between H-1 and H-5 of **7**, determined as $^5J_{H\text{-}1\text{-}H\text{-}5}$ = 0.85 Hz for this epi zigzag system by expansion of the H-1 signal (*cf.* $^5J_{H\text{-}1\text{-}H\text{-}4}$

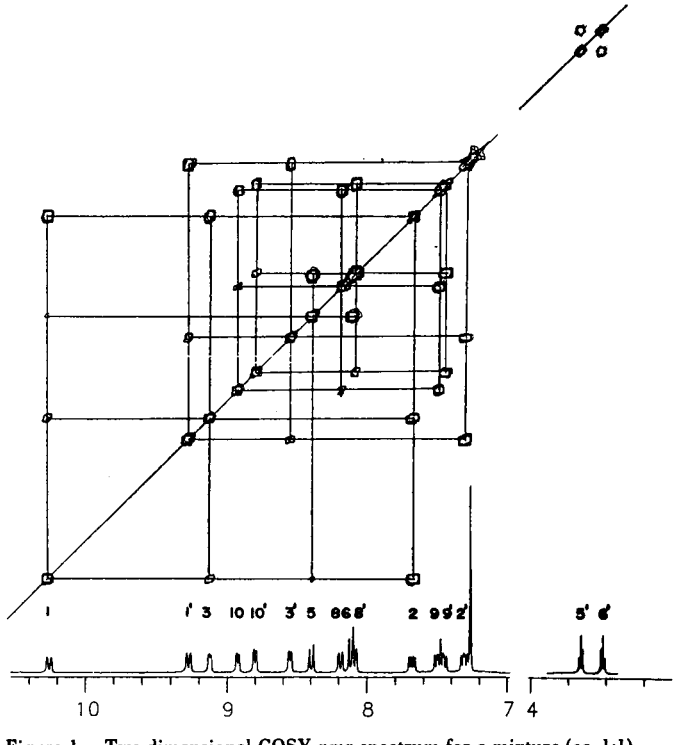
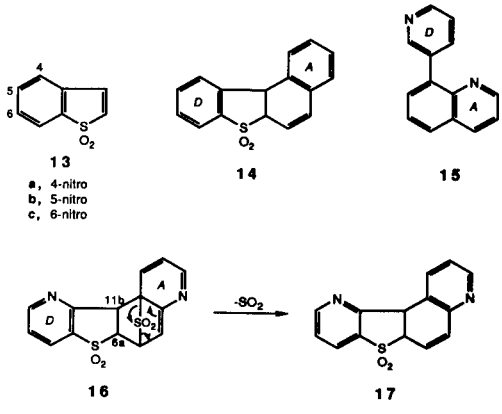


Figure 1. Two-dimensional COSY nmr spectrum for a mixture (*ca.* 1:1) of compounds **7** and **12** in deuteriochloroform. Signals ascribed to protons in compound **7** are designated by numbers without primes, while those for **12** are shown with primes. The rectangles clearly show two different sets of connectivities in these molecules. The weak, long-range coupling between H-1 and H-5 is readily apparent.

= 0.9 Hz reported for phenanthro[3,4-*b*]thiophene [14]). Also, the signal for H-1 in **12** occurs at δ 9.27, *i.e.* 0.98 ppm upfield from the resonance for H-1 in **7** and consistent with a larger internuclear distance (2.51 Å) between N-11 and H-1 in **12** [13].

It is of interest to compare the results of dimerization of the isosteric sulfones **1**, **2**, and benzo[*b*]thiophene 1,1-dioxide (**13**). All undergo dimerization in the *endo* configuration (*i.e.* with rings *A* and *D* *overlapping* in the transition complex), with subsequent secondary reaction. Thus, for **13** the adduct loses sulfur dioxide to yield **14** (74%) [15], while the adduct for **1** loses two moles of sulfur dioxide to form the pyridylquinoline **15** (25%) [2]. One expects the primary adduct of **2** to be **16**, which should form **17** on loss



of sulfur dioxide. Thermal dehydrogenation of **17** could then produce **7**, while two successive thermal [1,5]sigmatropic hydrogen shifts could give **12** [16]. Alternatively, the loss of hydrogen could precede loss of sulfur dioxide to give **7**, or the transfer of hydrogen could accompany loss of sulfur dioxide to give **12**. In fact, one can rationalize the low yields of **7** and **12** by assuming an unfavorable equilibrium toward formation of the dimeric *endo* transition complex [17] from **2**, with shifting of this equilibrium toward the production of isolable dimers only as a result of a nonfacile, subsequent step of dehydrogenation or internal hydrogen transfer.

One might expect to observe some similarities in dimerizations of **1**, **2**, and nitrobenzothiophene sulfones **13a-13c** [18]. However, the correlations are poor. 4-Nitro **13a** and 5-nitro **13b** derivatives dimerize in good yield; while the 6-nitro compound **13c** fails to undergo self-condensation (rather it forms only polymer and sulfur dioxide), though it does co-condense with **13**. Also by-products from condensation of **13b** consist of several aminosulfones, apparently formed from reduction of nitro groups by hydrogen released during the reaction [18].

EXPERIMENTAL [19]

endo-cis-5a,6,9,9a-Tetrahydro-6,9-methano[1]benzothieno[3,2-*b*]pyridine 5,5-Dioxide (**4**).

An ice-cold, stirred solution of 0.2 g (1.2 mmoles) of sulfone **2** in a mixture of 25 ml of ethyl acetate and 25 ml of petroleum ether (bp 60-90°) was treated with 0.13 ml (1.6 mmoles) of cyclopentadiene [20]. An exothermic reaction ensued. Completion of the reaction (in *ca.* 0.5 hour) was ascertained by thin layer chromatography with silica gel/ethyl acetate: R_f 0.73 for **2**, 0.50 for adduct. The residue from evaporation of the solvent was recrystallized from petroleum ether to give 194 mg (69%) of **4**, mp 162.5-164.5°. Further crystallizations gave colorless platelets, mp 162.5-163.5°; ir: 1302 and 1141 cm^{-1} (sulfone); ^1H nmr (hexadeuterioacetone): δ 8.78 (dd, $J_{2,3}$ = 5.0 Hz, $J_{2,4}$ = 1.3 Hz, 1H, H-2), 7.95 (dd, $J_{3,4}$ = 7.8 Hz, 1H, H-4), 7.48 (dd, 1H, H-3), 6.10 and 5.56 (2 dd, $J_{7,8}$ = 5.4 Hz, $J_{6,7}$ = $J_{8,9}$ = 3 Hz, 1H each, H-7 and H-8), 4.43 (dd, $J_{5a,9a}$ = 8.3 Hz, $J_{5a,6}$ = 4.3 Hz, 1H, H-5a), 4.21 (dd, $J_{9,9a}$ = 3.8 Hz, 1H, H-9a), 3.50 (pseudotriplet, 2H, H-6 and H-9), 2.80 (AB system, J = 8.7 Hz, Δδ = 33.6 Hz, 2 H-10); ms: m/e 233 (M^+, 7), 232 (12), 168 (**2**•H^+, 43), 167 (**2**$^+$, 41), 66 (cyclopentadiene$^+$, 100).

Anal. Calcd. for $C_{12}H_{11}NO_2S$: C, 61.78; H, 4.75; N, 6.01. Found: C, 61.83; H, 4.71; N, 6.03.

endo-cis-4b,5,8,8a-Tetrahydro-5,8-methano[1]benzothieno[2,3-*b*]pyridine 9,9-Dioxide (**3**).

A mixture of 0.2 g of sulfone **1**, 35 ml of ethyl acetate, 15 ml of petroleum ether, and 0.13 ml of cyclopentadiene was treated as in the preceding preparation of **4**. To complete the slower reaction the mixture was allowed to warm to room temperature overnight and kept at this temperature for an additional day; tlc data (silica gel/dichloromethane): R_f 0.17 for **3**, 0.08 for adduct [21]. Recrystallization of the product from ethyl acetate gave 188 mg (67%) of **3**, mp 170-172°, converted to prisms (mp 171.5-172°) on further recrystallizations from ethyl acetate/petroleum ether; ir: 1296, 1148, and 1116 cm^{-1} (sulfone); ^1H nmr (hexadeuterioacetone): δ 8.58 (d, $J_{2,3}$ = 4.5 Hz, 1H, H-2), 8.02 (d, $J_{3,4}$ = 7.6 Hz, 1H, H-4), 7.59 (dd, 1H, H-3), 6.10 and 5.57 (2 overlapping d, $J_{6,7}$ = 5.3 Hz, $J_{5,6} \simeq J_{7,8} < 2$ Hz, 2H total, H-6 and H-7), 4.34 (dd, $J_{4b,8a}$ = 8.5 Hz, $J_{4b,5}$ = 4.0 Hz, 1H, H-4b), 4.01 (dd, $J_{8,8a}$ = 3.7 Hz, 1H, H-8a), 3.50 (broad s, 2H, H-5 and H-8), 1.75 (AB system, J = 8.8 Hz, Δδ = 28 Hz, 2 H-10); ms: m/e 234 ([M + 1]$^+$, 1), 169 (52), 168 (**1**•H^+, 100), 167 (**1**$^+$, 35), 66 (cyclopentadiene$^+$, 87).

Anal. Calcd. for $C_{12}H_{11}NO_2S$: C, 61.78; H, 4.75; N, 6.01. Found: C, 62.08; H, 4.68; N, 5.96.

cis-5a,6,11,11a-Tetrahydro-6,11[1′,2′]-benzenonaphtho[2′,3′:4,5]thieno[3,2-*b*]pyridine 5,5-Dioxide (**5**).

A solution of 0.5 g (2.99 mmoles) of sulfone **2** and 1.06 g (5.96 mmoles) of anthracene in 9 ml of xylene was refluxed for 44 hours and then evaporated to dryness. The residue was chromatographed by means of silica gel/chloroform to give 1.02 g (99%) of **5** as a light yellow solid, mp 271-276°. Recrystallizations from acetone gave colorless prisms, mp 277-278°; ir (chloroform): 1310 and 1124 cm^{-1} (sulfone); ^1H nmr (deuteriochloroform): [22] δ 8.79 (dd, $J_{2,3}$ = 4.8 Hz, $J_{2,4}$ = 1.5 Hz, 1H, H-2), 7.67 (dd, $J_{3,4}$ = 7.1 Hz, 1H, H-4), 6.8-7.6 (m, 9H, H-3 plus benzene ring protons), 5.13 (d, $J_{5a,6}$ = 3.5 Hz, 1H, H-6), 5.00 (d, $J_{11,11a}$ = 2.6 Hz, 1H, H-11), 4.32 (dd, $J_{5a,11a}$ = 8.9 Hz, 1H, H-5a), 3.95 (dd, 1H, H-11a); ms: m/e 345 (M^+, 1), 179 (15), 178 (anthracene$^+$, 100).

Anal. Calcd. for $C_{21}H_{15}NO_2S$: C, 73.02; H, 4.38; N, 4.06. Found: C, 72.80; H, 4.27; N, 4.03.

cis-5a,6,13,13a-Tetrahydro-6,13[1',2']-benzenoanthra[2',3':4,5]-thieno[3,2-*b*]pyridine 5,5-Dioxide (**6**).

A solution of 0.86 g (5.1 mmoles) of sulfone **2** and 1.45 g (6.4 mmoles) of naphthacene (H. M. Chemical Co.) in xylene was refluxed for 96 hours. The dark orange-black mixture was filtered through a pad of filter-cel, washed with excess 5% hydrochloric acid, concentrated to a small volume, and diluted with ether. The resultant precipitate was recrystallized from xylene (charcoal) to give **6** (0.37 g, 18%) as a fine, white powder, mp 238-250°. Further recrystallizations from the same solvent gave white prisms, mp 304-306°; ir: 1309 and 1129 cm^{-1} (sulfone); ^1H nmr (deuteriochloroform): [23] δ 8.84 (d, $J_{2,3}$ = 4.3 Hz, 1H, H-2), 6.8-8.0 (m, 12H, H-3, H-4, H-7 to H-12, and H-14 to H-17), 5.28 and 5.15 (2 d, 1H, each, H-6 and H-13), 4.41 (dd, $J_{5a,13a}$ = 9.1 Hz, $J_{5a,6}$ = 3.7 Hz, 1H, H-5a), 4.06 (dd, $J_{13,13a}$ = 2.4 Hz, 1H, H-13a); ms: m/e 395 (M^+, 8), 331 (M^+ - SO_2, 4), 330 (5), 329 (4), 229 (21), 228 (naphthacene$^+$, 100), 226 (9), 114 (naphthacene $^{++}$, 3).

Anal. Calcd. for $C_{25}H_{17}NO_2S$: C, 75.93; H, 4.33; N, 3.54. Found: C, 76.09; H, 4.36; N, 3.35.

Dimerization of Thieno[3,2-*b*]pyridine 1,1-Dioxide.

A solution of 2.02 g (12.1 mmoles) of sulfone **2** in 165 ml of xylene was refluxed in an atmosphere of nitrogen gas for 40 hours. The dark solution still contained mainly unreacted **2**, as adjudged by tlc (R_f 0.40 for silica gel/dichloromethane-ethyl acetate, 4:1), plus various other components. The residue from evaporation of the filtered (celite) solution was chromatographed on a column of 205 g of silica gel with the aforementioned eluent and a fraction with R_f 0.21 (blue fluorescence) was isolated as the dimeric product, yield 41 mg, mp 279-288°.

This solid was washed with acetone and sublimed at 190° (0.1 mm) to yield cream-colored needles of pyrido[2',3':4,5]thieno-[3,2-*f*]quinoline 7,7-dioxide (**7**) hydrate, mp 320° dec; ir: 3430 (H-bonded water), 1297 and 1163 (sulfone), 1148, 810, 560 cm^{-1}; ^1H nmr (deuteriochloroform): high resolution [24, 25] δ 10.254 (ddd, $J_{1,2}$ = 8.70 Hz, $J_{1,3}$ = 1.76 Hz, $J_{1,5}$ = 0.85 Hz, 1H, H-1), 9.115 (dd, $J_{2,3}$ = 4.17 Hz, 1H, H-3), 8.916 (dd, $J_{9,10}$ = 4.99 Hz, $J_{8,10}$ = 1.61 Hz, 1H, H-10), 8.389 (dd, $J_{5,6}$ = 8.7 Hz, 1H, H-5), 8.183 (dd, $J_{8,9}$ = 7.78 Hz, 1H, H-8), 8.108 (d, 1H, H-6), 7.677 (dd, 1H, H-2), 7.495 (dd, 1H, H-9), 1.63 (s, water); ms: m/e 269 (22), 268 (M^+, 100), 239 (M^+ - CHO, 31), 212 (239$^+$ - HCN, 37), 211 (33), 187 (21).

Anal. Calcd. for $C_{14}H_8N_2O_2S \cdot \frac{1}{4}H_2O$: C, 61.64; H, 3.13; N, 10.27. Found: C, 61.84; H, 3.29; N, 9.90.

The acetone wash solution from purification of **7** was evaporated to dryness and sublimed *in vacuo* as before to give cream-colored solid, shown by 1D and 2D COSY nmr (Figure 1) to contain about equimolar amounts of **7** and 5,6-dihydro-**7** (**12**), combined overall yield 2%. Pure **12** was not isolated; its ^1H high resolution nmr spectrum in deuteriochloroform was obtained by difference [24]: δ 9.266 (dd, $J_{1,2}$ = 7.93 Hz, $J_{1,3}$ = 1.74 Hz, 1H, H-1), 8.792 (dd, $J_{9,10}$ = 5.08 Hz, $J_{8,10}$ = 1.58 Hz, 1H, H-10), 8.542 (dd, $J_{2,3}$ = 4.92 Hz, H-3), 8.084 (dd, $J_{8,9}$ = 7.68 Hz, 1H, H-8), 7.452 (dd, 1H, H-9), 7.305 (dd, 1H, H-2), 3.327 (t, $J_{5,6}$ = 8.5 Hz, 2H, 2 H-5), 3.035 (t, 2H, 2 H-6).

2D COSY ^1H NMR Spectrum [14,26].

The spectrum of the preceding mixture was measured with quadature detection over a period of 3.41 hours. The final seven-level contour map of the symmetrized 512 x 512 data matrix was plotted above the ^1H spectrum (Figure 1). Data-acquisition parameters were a 90° pulse width of 11 μs, spectral width 3003 Hz, dwell time 333 μs; post-acquisition delay 1.5 s. During data processing a sine-bell apodization function without phase shift was applied in both dimensions before Fourier transformations. The cross-peaks in the figure reveal the ^1H-^1H coupling pathways for the two separate compounds **7** and **12**.

Molecular Mechanics Calculations [13,27].

Computations were conducted using a Tektronix model 4211 graphic terminal attached offline to a VAX 8800 mainframe computer. The MACROMODEL (version 1.5) program used was obtained from the Department of Chemistry, Columbia University.

Benzo[*b*]naphtho[2,1-*d*]thiophene 11,11-Dioxide (**11**) [28].

A mixture of benzo[*b*]naptho[2,1-*d*]thiophene [29], glacial acetic acid, and excess 30% hydrogen peroxide was refluxed for one hour and processed in the manner used with triphenyleno-[1,12-*bcd*]thiophene 4,4-dioxide [30] to give **11**, mp 224-226°, lit 232-234° [28]; ir: 1291 and 1159 (sulfone) 1123, 754, 580 cm^{-1}; ^1H nmr (deuteriochloroform): δ 8.43 (d, $J_{9,10}$ = 8.4 Hz, 1H, H-1), 8.11 (d, $J_{1,2}$ = 8.4 Hz, 1H, H-10), 7.5-8.0 (m, other aromatic protons); ms: m/e 267 (21), 266 (M^+, 100), 237 (M^+ - CHO, 24), 221 (237$^+$ - O, 20), 218 (M^+ - SO, 28), 189 (218$^+$ - CHO, 21).

Acknowledgment.

One of the authors (S. K. S.) wishes to thank the Department of Chemistry, University of Oregon, for providing access to nmr and molecular graphics facilities.

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[19] Unless otherwise indicated, infrared spectra were determined on potassium bromide wafers by means of a Nicolet 5-DXB FTIR instrument and ^{1}H nmr spectra by means of a General Electric QE-300 instrument. Electron-impact mass spectra were obtained at 70 eV by Dr. Richard Wielesek of this laboratory on a VG 12-250 instrument. Elemental analyses were conducted by Desert Analytics, Tucson, Arizona.

[20] This procedure followed closely that reported for the reaction of cyclopentadiene with maleic anhydride; L. F. Fieser and K. L. Williamson, Organic Experiments, 4th Ed, D. C. Heath and Co., Lexington, Mass., 1979, p 177.

[21] Use of silica gel/ethyl acetate in tlc (as employed in the synthesis of **4**) gave identical R_f values for **1** and **3**.

[22] Obtained by means of a Varian XL-100 instrument.

[23] Spectrum determined by Yun Wang.

[24] Conditions used: 32 K data points, one zero-fill, no apodization, 5.46 s acquisition time. Some signal assignments are based on the 2D COSY experiment.

[25] These data represent a composite of information obtained from the low resolution ^{1}H nmr of pure **7** and the high resolution spectrum of the mixture of **7** and **12**, *vide infra*.

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