Regiocontrolled Formation of a Novel Dioxadithiapentacene

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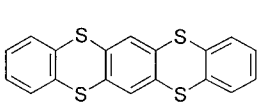
The synthesis,[1,2] crystal structure[2,3] and conductive properties[2] of tetrathiapentacene (**1**) have been investigated. Synthesis of alkyl- and alkoxy-substituted derivatives of **1**[4,5] and its 6-aza analog[2] have also been described. On the other hand, the corresponding dioxadithia analogues are practically unknown. Substructure **2** of C_{2v} symmetry is particularly rare, and the 1,3,9,11-tetranitro derivative may be the only known example.[6] Surprisingly, the C_{2h}-symmetric substructure **3** has not been reported.



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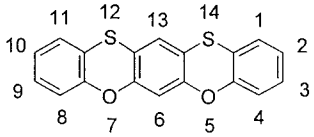

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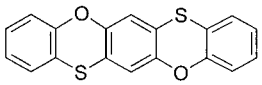

3

In the course of a drug discovery effort targeting phenoxathiin 10,10-dioxides as potential antidepressant agents,[7,8] we observed regiocontrolled formation of the 3,10-diisopropoxy derivative of **3**. Herein are described the details of this polycyclization and the X-ray crystal structure of the new ring system, which may be of interest to researchers in the field of organic charge-transfer complexes.

3-Isopropoxyphenoxathiin 10,10-dioxide was recently identified as a potent and selective inhibitor of monoamine oxidase-A (MAO-A), and analogues of this compound less prone to oxidative metabolism were of interest.[9] The preparation of fluorinated derivatives was proposed, and 2,3-difluoro-7-isopropoxyphenoxathiin 10,10-dioxide was identified as a viable target.

A base-mediated cyclization of 1,2,4,5-tetrafluorobenzene (**4**) with 5-isopropoxy-2-mercaptophenol (**5**) was envisioned as a straightforward route to the requisite phenoxathiin **7** (Scheme 1). Indeed, heating an equimolar mixture of **4** and **5** with 2 equiv of potassium *tert*-butoxide in DMF at reflux provided the desired phenoxathiin **7**, albeit in low yield (19%). The predominant product from this reaction was a pentacene, isolated in 55% yield, the ^{1}H and ^{13}C NMR spectra of which were consistent with structure **10**. None of the C_{2v}-symmetric diisopropoxypentacene analogous to structure **2** was detected. Pentacene formation was not optimized, although reaction of a 2:1 molar ratio of **5** to **4** should increase the yield of **10**.

The high nucleophilicity of the benzenethiolate anion of **5** coupled with the *para*-directing effect of the divalent sulfurs in **6** and **7** accounts for the observed regioselectivity. Two mechanisms for the formation of **10**, one proceeding through the intermediate phenoxathiin **7** and the other *via* polysulfide **8**, are outlined in Scheme 1.

Employing the same reaction conditions with excess tetrafluorobenzene (5 equiv) improved the yield of the phenoxathiin target and allowed for the isolation of intermediates along the polycyclization pathway. In this case, the isolated yield of **7** increased to 25%, while that of **10** decreased to 16%. The remaining product mixture consisted of the uncyclized polysulfide **8** and the partially cyclized phenoxathiin **9** isolated in 25 and 17% yields, respectively. All of the isolated products accounted for 83% of the 2-mercaptophenol limiting reagent (**5**).

Resubjecting polysulfide **8** to the reaction conditions for 30 min effected an 86% conversion to **10** (based on HPLC) along with lesser amounts of the intermediate phenoxathiin **9** (9%) and unreacted **8** (4%). Similar treatment of **9** resulted in quantitative conversion to **10**. These results are consistent with the formation of **10** *via* intermediate polysulfide **8**. The conversion of **7** to **9** is also likely to be a contributing pathway.

Recrystallization of **10** from ethyl acetate/hexanes provided a crystal suitable for X-ray analysis. Pentacene **10** crystallizes in the monoclinic crystal system and adopts a chair conformation in the solid state with torsion angles C11−S1−C6−C5 and C12−C7−O8−C9 (Figure 1) of 161.0 and 155.3°, respectively. This results in an interplanar angle between the inner benzene ring and each peripheral benzene ring of *ca.* 160°, which is about 30° larger than that described for **1**.

Dioxadithiapentacene **10** represents a new polyheterocycle, and its congeners may have applications in the study of polyheterocyclic electron donors. The regiocontrol observed in the formation of **10** also bodes well for a regioselective polycyclization of 4,5-dihalo-2-mercaptophenol monomers.

In closing, the 10,10-dioxide of phenoxathiin **7** is a potent and selective MAO-A inhibitor, and the details of its biological activity will be reported elsewhere.

Experimental Section

General Considerations. Melting points are uncorrected. ^{1}H NMR spectra were recorded at 200 and 300 MHz, and coupling constants are in Hz and are ^{1}H−^{1}H unless noted otherwise. Chemical shifts are reported in ppm relative to the

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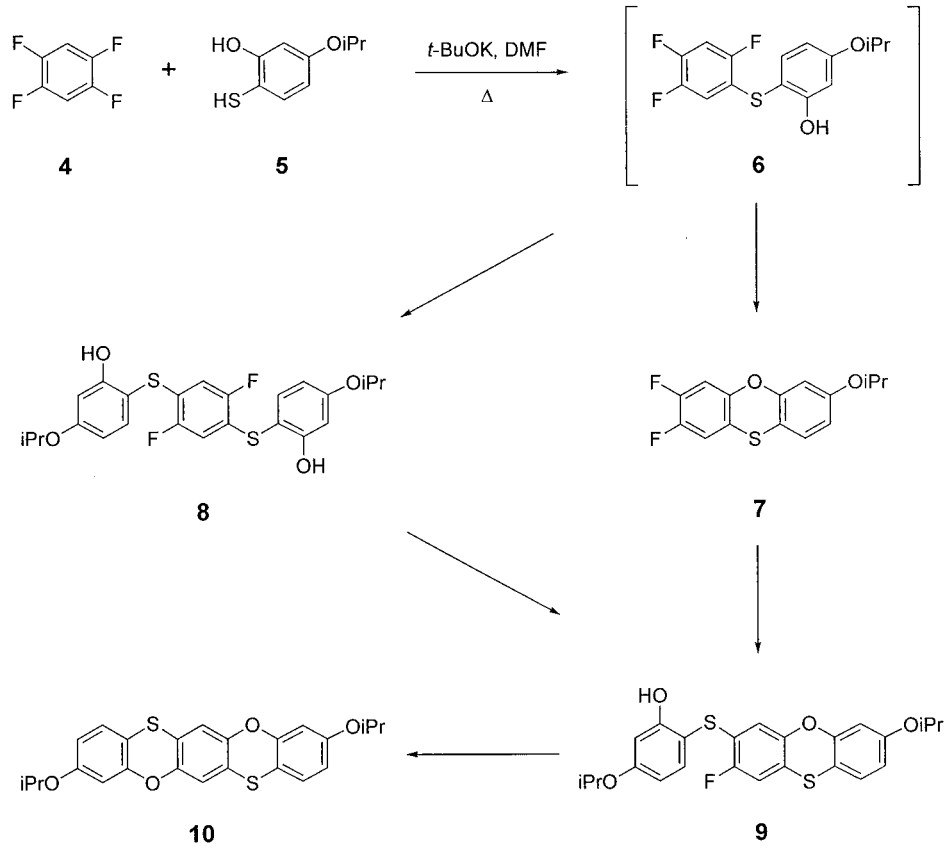
Scheme 1



residual protonated solvent resonance: $CDCl_3$, δ 7.26; DMSO-d_6, δ 2.50. The ^{13}C NMR spectra were recorded at 100 MHz, and chemical shifts are reported in ppm relative to the $CDCl_3$ resonance, δ 76.6. Analytical HPLC analyses were performed on a Waters Nova-Pak C-18 column (5 × 100 mm, 4 μm particle), with 70−90% MeOH/water/0.1% trifluoroacetic acid/0.1% triethylamine as eluent at 1.0 mL/min. Mass spectral analyses were performed by Oneida Research Services, Whitesboro, NY. Elemental analyses were performed by Atlantic Microlabs, Norcross, GA.

Polycyclization of 4 and 5. A solution of **5**[9] (2.71 g, 14.71 mmol) in DMF (23 mL) was added dropwise to a stirred slurry of potassium *tert*-butoxide (3.30 g, 29.42 mmol) in DMF (23 mL) at 0 °C. Stirring was continued for 10 min, and a solution of **4** (11.04 g, 73.54 mmol) in DMF (23 mL) was added. The mixture was heated at reflux for 18 h and concentrated at reduced pressure. The crude material was subjected to an aqueous workup with EtOAc and water, and the products were isolated by flash chromatography on silica gel with 10−20% CH_2Cl_2/hexanes as eluent, followed by EtOAc.

2,3-Difluoro-7-isopropoxyphenoxathiin (7). This compound eluted first (10% CH_2Cl_2/hexanes) and was isolated as a white solid (1.08 g, 3.67 mmol, 25% yield): mp 102−105 °C; ^1H NMR ($CDCl_3$) δ 7.0−6.8 (3H, m), 6.60 (1H, d, J = 9), 6.59 (1H, s), 4.48 (1H, sept, J = 6.0), 1.32 (6H, d, J = 6.0); MS m/z (%) 295 (MH^+, 100). Anal. Calcd for $C_{15}H_{12}F_2O_2S$: C, 61.21; H, 4.11; S, 10.89. Found: C, 61.11; H, 4.10; S, 10.80.

2,5-Difluoro-1,4-bis((2-hydroxy-4-isopropoxyphenyl)-thio)benzene (8). This compound eluted last (EtOAc) and was isolated as an off-white solid (0.871 g, 1.82 mmol, 25% yield). An analytical sample was obtained by recrystallization from EtOAc/hexanes: mp 167−170 °C; ^1H NMR (DMSO-d_6) δ 10.12

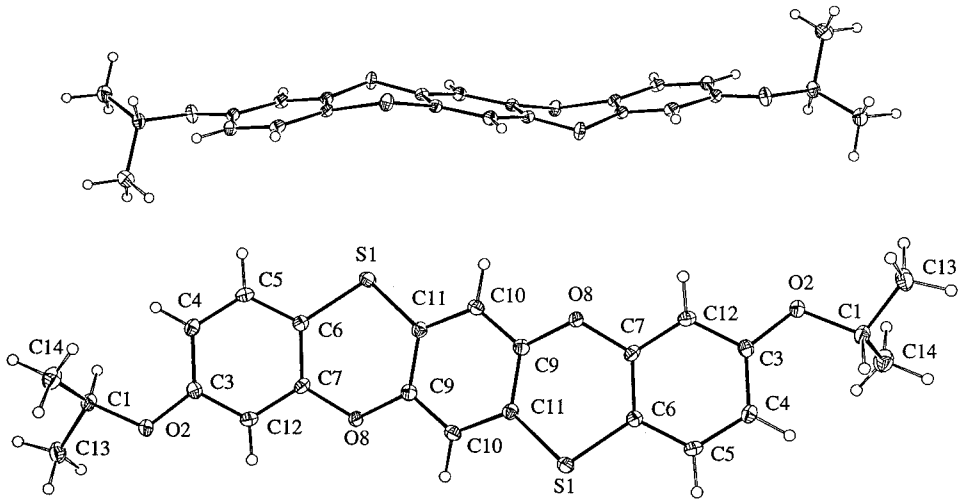


Figure 1. Crystal structure numbering system and conformation of **10**.

(1H, s), 7.23 (1H, d, $J = 8.5$), 6.51 (1H, d, $J = 2.5$), 6.44 (2H, m), 4.54 (1H, sept, $J = 6$), 1.25 (6H, d, $J = 6$); MS *m*/*z* (%) 479 (MH^+, 100). Anal. Calcd for $C_{24}H_{24}F_2O_4S_2$: C, 60.23; H, 5.05; S, 13.40. Found: C, 60.18; H, 5.07; S, 13.33.

2-((2-Fluoro-7-isopropoxy-3-phenoxathiinyl)thio)-5-isopropoxyphenol (9). This compound eluted third (20% CH_2Cl_2/hexanes) and was isolated as a colorless oil (0.586 g, 1.28 mmol, 17% yield): ^{1}H NMR (DMSO-d_6) δ 10.14 (1H, s), 7.29 (1H, d, $J = 8.6$), 7.23 (1H, d, $J_{HF} = 9.4$), 7.07 (1H, d, $J = 8.7$), 6.69 (1H, d, $J = 2.5$), 6.63 (1H, dd, $J = 8.7, 2.7$), 6.53 (1H, d, $J = 2.6$), 6.48 (1H, dd, $J = 8.6, 2.6$), 6.27 (1H, d, $J_{HF} = 6.6$), 4.55 (2H, m), 1.27 (6H, d, $J = 6$), 1.17 (6H, d, $J = 6$); MS *m*/*z* (%) 459 (MH^+, 100). Anal. Calcd for $C_{24}H_{23}FO_4S_2$: C, 62.86; H, 5.06; S, 13.98. Found: C, 62.78; H, 5.10; S, 14.06.

3,10-Diisopropoxy-5,12-dioxa-7,14-dithiapentacene (10). This compound eluted second (20% CH_2Cl_2/hexanes) and was isolated as a white solid (0.5 g, 1.14 mmol, 16% yield): ^{1}H NMR ($CDCl_3$) δ 6.94 (1H, d, $J = 8.8$), 6.75 (1H, s), 6.58 (1H, br m), 6.56 (1H, d, $J = 2$), 4.47 (1H, sept, $J = 6$), 1.31 (6H, d, $J = 6$); ^{13}C NMR ($CDCl_3$) δ 157.7 (C), 152.5 (C), 148.0 (C), 126.6 (CH), 119.2 (C), 114.9 (CH), 112.3 (CH), 109.1 (C), 105.4 (CH), 70.0 (CH), 21.5 (CH_3); MS *m*/*z* (%) 439 (MH^+, 100). Anal. Calcd for $C_{24}H_{22}O_4S_2$: C, 65.73; H, 5.06; S, 14.62. Found: C, 65.68; H, 5.10; S, 14.54.

Crystal Data for 10: molecular formula $C_{24}H_{22}O_4S_2$, molecular weight 438.55, monoclinic, space group $P2_1/n$, $a = 12.8970(8)$ Å, $b = 5.753(4)$ Å, $c = 14.2653(9)$ Å, $V = 1043.01(12)$ Å^3, $Z = 2$, $D_{calc} = 1.396$ Mg m^{-3}, $F(000) = 460.74$. Of 4944 reflections measured, 1830 were unique and 1461 which had $I > 3.0\sigma(I)$ were used in subsequent calculations. Data were collected on a Siemens SMART diffractometer using ω scans and monochromated Mo Kα radiation ($\lambda = 0.71073$ Å). The positions of all nonhydrogen atoms were determined by direct methods and refined anisotropically. The hydrogen positions were all located in difference syntheses and included in subsequent refinement cycles using the riding model and an idealized bond length of 0.96 Å. Least-squares refinement minimized $w(\Delta F)^2$ with weights based on counter statistics. The final agreement factors were $R_F = 0.043$ (0.058 for all data), $R_w = 0.049$ (0.053 for all data), and GOF = 2.03.[10]

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Supporting Information Available: X-ray data tables for **10** (6 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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