Synthesis of 2-*exo*-Hydroxy-4-thiahomoadamantane and Some Related Derivatives[1]

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Received April 6, 1983

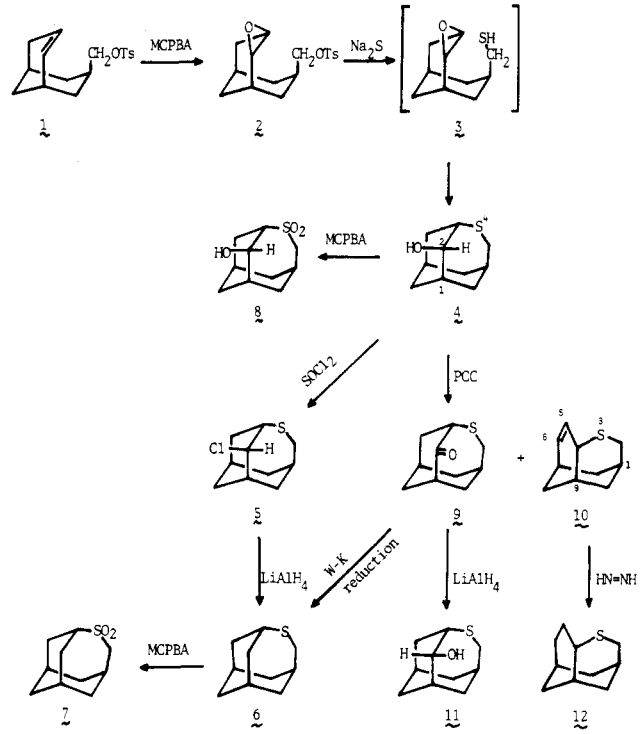
Treatment of 3-*endo*-((tosyloxy)methyl)-6,7-epoxybicyclo[3.3.1]nonane (**2**) with sodium sulfide gave 2-*exo*-hydroxy-4-thiahomoadamantane (**4**) in good yields. PCC oxidation of **4** afforded the corresponding ketone **9** and 3-thiatricyclo[5.3.1.$0^{4,9}$]undec-5-ene (**10**) as a skeletally rearranged product via an episulfonium ion **13**. Reduction of the 2-chloro derivative of **4** and/or the Wolff–Kishner reduction of **9** gave 4-thiahomoadamantane (**6**). Diimide reduction of **10** gave 3-thia-2-homoprotoadamantane (**12**), an isomer of **6**.

The synthesis, chemistry, and pharmacology of heteroadamantanes and related hetero-cage compounds have attracted considerable attention recently.[2] Bicyclo[3.3.1]non-6-ene-3-*endo*-carboxylic acid,[3] -carbinol,[3a,4] and -nitrile,[3c,d,5] available from adamantanone or its derivatives, are useful precursors to 4-substituted 2-azaadamantanes[6] and 2-substituted 4-heterahomoadamantanes.[7,8] However, there have been no reports on the synthesis of 4-thiahomoadamantanes, and therefore we wish to describe here the facile synthesis of 2-substituted 4-thiahomoadamantanes and some related chemistry.

Results and Discussion

Oxidation of 3-*endo*-((tosyloxy)methyl)bicyclo[3.3.1]-non-6-ene[9] (**1**) with *m*-chloroperbenzoic acid (MCPBA) gave the corresponding 6,7-epoxide (**2**) in good yield. Treatment of the epoxide **2** with sodium sulfide in aqueous dimethyl sulfoxide (Me_2SO) at 60 °C according to Johnson's procedure[10] afforded 2-*exo*-hydroxy-4-thiahomoadamantane (**4**) in 81% yield, probably via thiol **3** as in the transannular N and O cyclizations[7,8] (Scheme I). The assigned skeletal framework of **4** and stereochemistry of the 2-hydroxy substituent followed in part from its mode of synthesis as well as chemical conversions summarized in Scheme I. The exo epoxidation of 3-endo-substituted bicyclo[3.3.1]non-6-enes with MCPBA are now well established,[6-8] and the in situ produced thiol **3** undergoes intramolecular nucleophilic attack by the thiol or thiolate sulfur to give **4**. The C-7 attack is more favorable than the C-6 attack by the geometrical constraint as suggested

Scheme I



by examination of molecular models[11] and also by strain energies of the corresponding carbocycles.[12] The 4-thiahomoadamantane skeleton of **4** was confirmed in the following manner. Treatment of **4** with thionyl chloride gave the corresponding *exo*-chloride **5** (98%), which was reduced with lithium aluminum hydride to afford 4 thiahomoadamantane (**6**) (82%) as a sublimable camphor-smelling solid. The ^{13}C NMR spectrum of **6** revealed seven lines (three doublets and four triplets), which attested to the inherent *C* symmetry of **4**. The skeletal integrity during the above conversions was supported by alternative conversion of **4** to **6** via **9**. In order to obtain the ketone **9**, oxidation of **4** was examined under several conditions. The PCC (pyridinium chlorochromate) oxidation[13] of **4** in

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(11) The S–C–O arrangement at the transition state is more favorable, i.e., more linear for the C-7 attack than the C-6 attack. Cf. also: Kirk, D. N.; Hartshorn, M. P. "Steroid Reaction Mechanisms", Elsvier: Amsterdam, 1969; p 112.

(12) The carbocyclic homoadamantane ring system is ca. 4 kcal/mol less strained than the tricyclo[5.3.1.$0^{4,9}$]undecane system. Cf.: Ōsawa, E.; Aigami, Y.; Takaishi, N.; Inamoto, Y.; Fujikura, Y.; Majerski, Z.; Schleyer, P. v. R.; Engler, E. M.; Farcasiu, M. *J. Am. Chem. Soc.* **1977**, *99*, 5361 and references cited therein.

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dichloromethane at 25 °C for 1 h afforded ketone **9** in 48% yield, while PDC (pyridinium dichromate)[14] oxidation in the presence of pyridinium trifluoroacetate at 25 °C for 2 h and Swern oxidation with $Me_2SO(COCl)_2$[15] gave **9** in 30 and 26% yields, respectively, but both Moffatt oxidation with Me_2SODCC[16] and Jones oxidation[17] in acetone yielded only a trace of **9**. The PCC oxidation under ice cooling afforded **9** and also an olefinic product **10** in 14% yield, as discussed below. The Wolff–Kishner reduction[18] of **9** afforded **6** (38%). Lithium aluminum hydride reduction of **9** yielded exclusively **11**, the C-2 epimer of **4**. Such stereoselective reduction is also reported for the 4-oxahomoadamantan-2-one system by Goff and Murray.[8a] In ^1H NMR spectra, the exo isomer **4** revealed a characteristic broad singlet at δ 4.10 for the proton at C-2, while the endo isomer **11** exhibited an unsymmetrical double triplet at δ 3.83 (J = 2.0 and 4.5 Hz) for the C-2 proton, supporting the assigned stereochemistry.[19] MCPBA oxidation of **4** and **6** gave somewhat less sublimable corresponding sulfones **8** and **7**, respectively.

The olefinic product **10** from the PCC oxidation of **4** was characterized as 3-thiatricyclo[5.3.1.$0^{4,9}$]undec-5-ene by the following spectral and chemical evidences. The ^1H NMR spectrum had characteristic signals at δ 6.18 (dd), 5.48 (dd), and 3.70 (dd) for the protons at C-6, C-5, and C-4, respectively, and the ^{13}C NMR spectrum exhibited ten lines, including three doublets at δ 133.3, 125.6, and 40.3, supporting the given structure of **10**.[20] Diimide reduction[21] of **10** afforded 3-thiatricyclo[5.3.1.$0^{4,9}$]undecane (or trivial 3-thia-2-homoprotoadamantane or 3-thiadihydronoriceane) (**12**) as a sublimable solid (60%). The formation of the olefin **10** in the oxidation of **4** deserves comment; such olefinic products are not observed in oxidation of the aza and oxa analogues.[7,8a] As explained in Scheme II, an episulfonium ion intermediate **13** may be produced via the corresponding chromate ester from **4** and deprotonation (**14**) provides the olefin **10**. Supporting this scheme, oxidation of *endo*-alcohol **11** under the similar conditions afforded exclusively the ketone **9**, and no trace of **10** was detected (GLC). Furthermore, attempted rearrangement of **4** with 60% sulfuric acid (60 °C, 1 h), or with 85% phosphoric acid (100 °C, 6 days) resulted in the recovery of **4**. Treatment of **4** with HMPT[22] (reflux, 10 h) gave a small amount of **10** among other uncharacterized products (GLC), indicating that **10** could be produced only under nonnucleophilic conditions. Several attempts to increase the yields of **10** were not successful.

Experimental Section[23]

3-*endo*-((Tosyloxy)methyl)-6,7-*exo*-epoxybicyclo[3.3.1]nonane (2). To a stirred ice-cooled solution of 98% MCPBA (880 mg, 5.10 mmol) in benzene–*n*-hexane (15 + 3 mL) was added dropwise 3-*endo*-((tosyloxy)methyl)bicyclo[3.3.1]non-6-ene[9] (**1**) (1.20 g, 3.92 mmol) in benzene (4 mL). The mixture was stirred overnight and allowed to warm to room temperature. Resulted precipitates were filtered and washed with benzene (4 mL). The combined filtrate and washings were treated with 5% $NaHSO_3$ (10 mL) followed by washing with 5% $NaHCO_3$ (3 × 30 mL) and water (10 mL). The organic layer was dried (Na_2SO_4) and evaporated under water aspirator pressure on a rotary evaporator to afford the epoxide **2** as a colorless solid (1.13 g, 90.0%): mp 83–85 °C; IR (KBr) 2940, 1600, 1450, 1360, 1185, 1100, 955, 840, 660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.0–7.2 (AB type m, 4 H), 4.00 (d, J = 7.2 Hz, 2 H), 3.0–2.7 (m, 2 H), 2.45 (s, 3 H), 2.5–0.9 (complex m, 11 H).

Anal. Calcd for $C_{17}H_{22}O_4S$: C, 63.33; H, 6.87. Found: C, 63.27; H, 6.92.

2-*exo*-Hydroxy-4-thiahomoadamantane (4). Method A. A mixture of the epoxide **2** (1.13 g, 3.54 mmol) and sodium sulfide nonahydrate (2.00 g, 8.30 mmol) in Me_2SO (18 mL) and water (2 mL) was stirred at 60 °C for 6 h. The cooled mixture was diluted with water (30 mL), extracted with benzene (3 × 40 mL), and dried (Na_2SO_4). Removal of the solvent under reduced pressure gave a semicrystalline residue which was dissolved in CH_2Cl_2 and filtered through a short silica gel column to afford **4** as a colorless solid (526 mg, 81.0%). An analytical sample was obtained after one sublimation (90 °C, 0.1 torr): mp 217–219 °C; IR (KBr) 3400–3100 (broad), 2920, 1440, 1010 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.10 (br s, 1 H), 2.92 (unsymmetrical d, J = 4.5 Hz, 2 H), 2.80 (br s, 1 H), 2.75–2.35 (m, 2 H), 2.35–1.00 (m, 10 H including D_2O exchangeable OH); ^{13}C NMR ($CDCl_3$) δ 79.3 (d), 44.0 (d), 39.5 (t), 37.8 (t), 36.5 (t), 33.5 (d), 32.4 (t), 31.9 (d), 27.6 (t), 21.5 (d) for each 1 C; MS, m/e (%) 185 (11), 184 (M^+, 46), 168 (35), 166 (68), 150 (23), 119 (35), 105 (35), 93 (41), 91 (100), 71 (37), 69 (66), 67 (69), 65 (43).

Anal. Calcd for $C_{10}H_{16}OS$: C, 65.17; H, 8.75. Found: C, 65.20; H, 8.68.

Method B. A solution of **2** (94 mg, 0.30 mmol) in benzene (10 mL) was added to a vigorously stirred mixture of sodium sulfide nonahydrate (670 mg, 2.80 mmol) and Aliquat 336 (Aldrich) (0.1 mL) in water (25 mL) at 55–60 °C. After the stirring was continued for 5 h, the cooled mixture was diluted with water (30 mL) and extracted with benzene (4 × 30 mL). The combined extracts were washed with water and dried (Na_2SO_4). After removal of the solvent, a solid residue was sublimed to give **4** as a colorless solid (15 mg, 27%).

2-*exo*-Chloro-4-thiahomoadamantane (5). A mixture of the *exo*-hydroxy derivative **4** (190 mg, 1.03 mmol) and thionyl chloride (1 mL) in *n*-hexane (2 mL) was heated at 60 °C for 2 h. After cooling, the solvent and excess thionyl chloride were removed under reduced pressure to give a solid residue, which was sublimed (80 °C, 0.1 torr) to afford the chloride **5** as a colorless solid (205 mg, 98%): mp 186–189 °C; IR (KBr) 2920, 1445, 1295, 1210, 1195, 1025, 755, 735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.50 (br s, 1 H), 3.20 (d, J = 7.5 Hz, 1 H), 2.93 (d, J = 4.0 Hz, 2 H), 2.8–1.1 (m, 11 H).

Anal. Calcd for $C_{10}H_{15}SCl$: C, 59.24; H, 7.46. Found: C, 59.36; H, 7.34.

4-Thiahomoadamantane (6). A. From 5. To a stirred ice-cooled mixture of $LiAlH_4$ (200 mg, 5.27 mmol) in anhydrous THF (15 mL) was added the chloride **5** (205 mg, 1.01 mmol) in THF (5 mL). The mixture was allowed to warm to room temperature and heated at 50 °C for 3 h. The cooled mixture was

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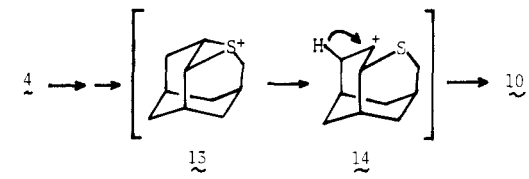
(23) Melting points were taken in a sealed tube on a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were obtained on a JASCO IRA-1 spectrometer. ^1H NMR and ^{13}C NMR spectra were recorded on a JEOL JNM-C-60HL instrument at 60 MHz and a JEOL JNM-FX-60FT NMR spectrometer at 15.04 MHz, respectively. Chemical shifts are reported in parts per million (δ) relative to Me_4Si as an internal standard. Mass spectra were obtained with a JEOL JMS-D10 mass spectrometer at 75 eV. Microanalyses were performed with a Perkin-Elmer 240B elemental analyzer. GLC analyses were carried out by using a JEOL JGC-20K gas chromatograph on 1- or 2-m silicone SE-30 columns.

Scheme II



quenched with solid $Na_2SO_4 \cdot 10H_2O$ until gas evolution ceased. The mixture was filtered and the residue was washed with THF. The combined filtrate and washings were dried (Na_2SO_4) and evaporated under reduced pressure to give a solid residue, which was sublimed (70 °C, 20 torr) to afford **6** as a colorless camphor-smelling solid (140 mg, 82%): mp 235–238 °C; IR (KBr) 2920, 1440, 1260, 1220, 1105, 1035 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.0–2.4 (m, 3 H), 2.4–1.3 (m, 13 H); ^{13}C NMR ($CDCl_3$) δ 41.8 (t, 2 C), 39.3 (t, 1 C), 39.1 (d, 1 C), 36.9 (t, 2 C), 34.7 (t, 1 C), 33.2 (d, 1 C), 26.9 (d, 2 C); MS, *m/e* (%) 170 (6), 169 (11), 168 (M^+, 100), 135 (28), 93 (18), 92 (19), 79 (24).

Anal. Calcd for $C_{10}H_{16}S$: C, 71.37; H, 9.58. Found: C, 71.29; H, 9.66.

B. From the Ketone 9. To the ketone **9** (30 mg, 0.16 mmol) in diethylene glycol (5 mL) was added hydrazine hydrate (1 mL of 100% reagent, 20 mmol) and 85% KOH (500 mg), the mixture was heated at 160–170 °C for 3 h, and then the reaction temperature was raised to 210–220 °C. After 1 h, the cooled mixture was diluted with water (10 mL) and extracted with *n*-pentane (2 × 10 mL). The distillate and some sublimed solid in the condenser was rinsed with *n*-pentane (10 mL). The combined extracts and the washings were washed with water and saturated NaCl solutin and dried (Na_2SO_4). Removal of the solvent gave a solid which was sublimed to give **6** as a colorless solid (10 mg, 38%).

4-Thiahomoadamantane 4,4-Dioxide (7). To a stirred ice-cooled mixture of 98% MCPBA (42 mg, 0.24 mmol) in ether (5 mL) was added **6** (20 mg, 0.12 mmol) in ether (5 mL). After the stirring was continued for 12 h at room temperature, the mixture was washed with 10% sodium thiosulfate solution (3 mL), 5% $NaHCO_3$ solution (2 × 3 mL), and saturated NaCl solution (5 mL) successively, and dried (Na_2SO_4). Removal of the solvent gave a solid, which was sublimed (100 °C, 0.1 torr) to afford the sulfone **7** as a colorless solid (13 mg, 54%): mp 270–273 °C; IR (KBr) 2940, 1450, 1315, 1285, 1220, 1175, 1110 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.45 (unsymmetrical d, J = 3.1 Hz, 2 H), 3.3–3.0 (m, 1 H), 2.6–1.3 (m, 13 H); MS, *m/e* (%) 200 (M^+, 11), 136 (25), 135 (100), 93 (69), 79 (54), 67 (40).

Anal. Calcd for $C_{10}H_{16}O_2S$: C, 59.97; H, 8.05. Found: C, 59.84; H, 8.18.

2-*exo*-Hydroxy-4-thiahomoadamantane 4,4-Dioxide (8). This sulfone was obtained similarly by oxidation of **4** (50 mg, 0.27 mmol) with 98% MCPBA (100 mg, 0.55 mmol) in benzene (4 mL) and *n*-hexane (0.4 mL) for 12 h at room temperature. The workup and sublimation (100 °C, 0.1 torr) gave the sulfone **8** as a colorless solid (21 mg, 36%): mp >300 °C; IR (KBr) 3450 (broad), 2920, 1450, 1280, 1110, 1020, 760 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.61 (s, 1 H), 3.45 (d, J = 4.0 Hz, 2 H), 3.3–3.0 (m, 1 H), 2.60 (br s, 1 H, exchanges in D_2O), 2.6–1.2 (m, 11 H); MS, *m/e* (%) 151 (M^+ – 65, 100), 133 (24), 109 (20), 107 (32), 105 (22), 95 (30), 93 (41), 92 (25), 91 (76), 86 (60), 84 (90), 81 (36), 78 (53), 77 (26), 67 (34), 55 (30), 51 (34), 49 (99).

Anal. Calcd for $C_{10}H_{16}O_3S$: C, 55.53; H, 7.46. Found: C, 55.25; H, 7.74.

4-Thiahomoadamantan-2-one (9). A. By PCC Oxidation. To a stirred solution of PCC[13] (90 mg, 0.42 mmol) in anhydrous CH_2Cl_2 (2 mL) was added **4** (50 mg, 0.27 mmol) at room temperature. After the stirring was continued for 1 h, the solvent was removed under reduced pressure and the residue was extracted with ether (2 × 5 mL). The combined extracts were evaporated to give crude ketone which was purified on a silica gel column (CH_2Cl_2) to afford **9** as a colorless solid after one sublimation (100 °C, 0.1 torr) (23 mg, 48%): mp 280–283 °C; IR (KBr) 2945, 1700, 1450, 1270, 1215, 1110, 1030, 750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.38 (d, J = 8.0 Hz, 1 H), 3.0 (unsymmetrical d, J = 4.5 Hz, 2 H), 3.0–1.1 (m, 11 H); ^{13}C NMR ($CDCl_3$) δ 209.1 (s), 47.9 (d), 43.9 (d), 39.3 (t), 38.3 (t), 37.9 (t), 34.5 (t), 30.5 (d), 29.9 (d), 25.8 (d) for each 1 C; MS, *m/e* (%) 182 (M^+, 100), 111 (32), 107 (27), 99 (38), 93 (38), 79 (64), 77 (48), 67 (26).

Anal. Calcd for $C_{10}H_{14}OS$: C, 65.89; H, 7.74. Found: C, 65.82; H, 7.88.

B. By PDC Oxidation. To a stirred mixture of PDC[14] (160 mg, 0.43 mmol) and pyridinium trifluoroacetate (20 mg, 0.10 mmol) in dry CH_2Cl_2 (2 mL) was added **4** (50 mg, 0.27 mmol) at room temperature. After the stirring was continued for 2 h, the solvent was removed and the residue was purified as above to give **9** (15 mg, 30%).

C. By Swern Oxidation.[15] To a stirred mixture of oxalyl chloride (0.3 mL, 0.3 mmol) and Me_2SO (0.05 mL, 0.7 mmol) in dry CH_2Cl_2 (3 mL) was added **4** (50 mg, 0.27 mmol) under nitrogen at −50 °C. After 15 min, triethylamine (0.19 mL) was added to the mixture, the stirring was continued for 5 min at −50 °C, and then the reaction temperature was allowed to warm to 10 °C. The mixture was diluted with water (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined extracts were washed with saturated NaCl solution and dried (Na_2SO_4). Removal of the solvent gave crude ketone, which was purified as above to afford **9** (13 mg, 26%).

3-Thiatricyclo[5.3.1.0^{4,9}]undec-5-ene (10). To a stirred ice-cooled solution of PCC (700 mg, 3.25 mmol) in dry CH_2Cl (15 mL) was added **4** (300 mg, 1.63 mmol) in CH_2Cl_2 (2 mL). The mixture was stirred for 2 h, during which the reaction temperature was allowed to warm gradually to room temperature. The solvent was removed under reduced pressure and the residue was extracted with ether (2 × 10 mL). The combined extracts were washed with water, dried (Na_2SO_4), and evaporated to give crude product, which was chromatographed (silica gel, CH_2Cl_2) to afford the ketone **9** (72 mg, 25%) and the olefin **10** as a colorless solid after one sublimation (90 °C, 15 torr) (40 mg, 14%): mp 193–195 °C; IR (KBr) 3040, 2920, 1640, 1440, 1355, 1230, 1020, 800, 765 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.18 (dd, J = 9.5 and 7.5 Hz, 1 H), 5.48 (dd, J = 9.5 and 4.5 Hz, 1 H), 3.70 (dd, J = 4.5 and 10.0 Hz, 1 H), 2.9–2.7 (m, 2 H), 2.6–1.1 (m, 9 H); ^{13}C NMR ($CDCl_3$) δ 133.3 (d), 125.6 (d), 40.3 (d), 36.9 (t), 35.5 (t), 31.9 (t), 30.4 (t), 28.6 (d), 26.3 (d), 25.3 (d) for each 1 C; MS, *m/e* (%) 168 (31), 167 (20), 166 (M^+, 53), 123 (38), 119 (57), 117 (57), 105 (25), 97 (51), 91 (100), 86 (78), 77 (34), 56 (34).

Anal. Calcd for $C_{10}H_{14}S$: C, 72.23; H, 8.49. Found: C, 72.49; H, 8.60.

The oxidation of the endo-derivative **11** with PCC under the same conditions gave no trace of **10** but only the ketone **9** (37%). Heating **4** in HMPA for 10 h under reflux, followed by dilution with water and extraction with *n*-hexane gave a complex mixture of uncharacterized products, among which a small amount (ca. 5%) of **10** was detected on GLC analysis.

2-*endo*-Hydroxy-4-thiahomoadamantane (11). To a stirred ice-cooled mixture of $LiAlH_4$ (25 mg, 0.66 mmol) in anhydrous THF (4 mL) was added the ketone **9** (59 mg, 0.32 mmol) in THF (1 mL). The mixture was allowed to warm to room temperature, the stirring was continued for 12 h, and then the reaction was quenched with solid $Na_2SO_4 \cdot 10H_2O$. The mixture was filtered and the residue was washed with THF. The combined filtrate and washings were dried (Na_2SO_4) and evaporated to give a solid which was sublimed (90 °C; 0.1 torr) to afford the endo-alcohol **11** as a colorless solid (50 mg, 84%): mp 208–210 °C; IR (KBr) 3470 (broad), 2940, 1450, 1400, 1225, 1075, 760 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.83 (dt, J = 2.0 and 4.5 Hz, 1 H), 3.45 (br s, 1 H, exchangeable in D_2O), 3.20 (dt, J = 2.0 and 6.0 Hz, 1 H), 2.75 (unsymmetrical d, J = 3.0 Hz, 2 H), 2.8–1.2 (m, 11 H); ^{13}C NMR ($CDCl_3$) δ 72.0 (d), 48.0 (d), 39.1 (t), 38.7 (t), 38.5 (t), 34.9 (d), 33.7 (t), 32.5 (d), 28.0 (t), 26.0 (d), for each 1 C; MS, *m/e* (%) 184 (M^+, 52), 134 (100), 91 (14), 86 (17), 77 (32), 67 (26), 53 (20).

Anal. Calcd for $C_{10}H_{16}OS$: C, 65.19; H, 8.75. Found: C, 65.18; H, 8.74.

3-Thiatricyclo[5.3.1.0^{4,9}]undecane (12). To a stirred mixture of the olefin **10** (42 mg, 0.25 mmol), hydrazine hydrate (0.13 mL, 2.6 mmol), and $CuSO_4$ (10 mg) in MeOH (4 mL) was bubbled oxygen for 4 h at room temperature according to the known procedure.[21] The resulting precipitates were filtered and washed with MeOH (10 mL). The combined filtrate and washings were diluted with water (10 mL) and extracted with *n*-pentane (2 × 10 mL). The extract was washed with saturated NaCl solution and dried (Na_2SO_4). Removal of the solvent gave a solid which was purified by chromatography (silica gel, CH_2Cl_2) and subli-

mation (80 °C, 20 torr) to afford **12** as a colorless solid (26 mg, 60%): mp 267–269 °C; IR (KBr) 2920, 1465, 1435, 1265, 1120, 1020, 865, 825, 765 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.6–2.9 (m, 3 H), 2.7–0.8 (m, 13 H); MS, *m/e* (%) 169 (16), 168 (M^+, 61), 167 (33), 135 (23), 93 (44), 92 (23), 91 (50), 81 (28), 79 (64), 77 (33), 87 (39), 58 (40), 57 (33), 55 (28), 44 (44), 43 (100), 41 (56).

Anal. Calcd for $C_{10}H_{16}S$: C, 71.37; H, 9.58. Found: C, 71.16; H, 9.39.

Registry No. **1**, 30860-11-8; **2**, 87114-49-6; **4**, 87114-50-9; **5**, 87114-51-0; **6**, 87114-52-1; **7**, 87114-53-2; **8**, 87114-54-3; **9**, 87114-55-4; **10**, 87114-56-5; **11**, 87172-12-1; **12**, 87114-57-6.

2,2′:5′,2″-Terthiophene-5-carboxylic Acid and 2,2′:5′,2″-Terthiophene-5,5″-dicarboxylic Acid

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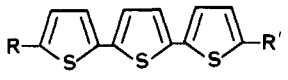
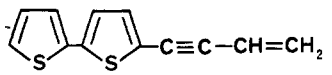
Received April 4, 1983

2,2′:5′,2″-Terthiophene-5-carboxylic acid was obtained in excellent yield by treating 2,2′:5′,2″-terthiophene with lithium diisopropylamide, followed by carboxylation of the lithium salt with solid carbon dioxide. The 5,5″-dicarboxylic acid was obtained similarly, when 2 equiv of base were used. Attempted syntheses of the monoacid, based on the oxidation of the corresponding aldehyde or the acetyl derivative, were unsuccessful. Both the monoacid and the 5,5′-diacid sensitized the hemolysis of human erythrocytes in the presence of ultraviolet light.

The unknown 2,2′:5′,2″-terthiophene-5-carboxylic acid (**1**) was of interest for some photosensitization experiments.



1, R = H; R′ = COOH
2, R = R′ = H
3, R = R′ = COOH
4, R = H; R′ = $COOCH_3$
5, R = R′ = $COOCH_3$
6, R = H; R′ = CHO
7, R = H; R′ = $COCH_3$



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2,2′-Bithiophene had been successfully converted into its 5-carboxylic acid by treatment with phenyllithium in ether, followed by carboxylation of the lithium salt,[1] but several attempts with the terthiophene **2** under identical conditions met with failure, and success was achieved only when lithium diisopropylamide (LDA) in tetrahydrofuran was substituted for phenyllithium in ether. The experimental conditions were critical. When **2** was reacted with 1 equiv of LDA and solid carbon dioxide was added, a solid material was obtained. Its time-resolved mass spectrometric analysis revealed a mixture of two components, identified as the desired carboxylic acid **1** and its dicarboxylic acid homologue **3**.

This result suggested that proton transfer between 2 mol of the monoanion of **2** had occurred, favoring a mixture of the dianion with an equivalent amount of unreacted starting material. In principle, this equilibrium should be repressed by maintaining a relatively high concentration of **2** in the mixture. Indeed, a good yield of the monocarboxylic acid **1** was obtained when only 0.5 equiv of LDA was used and the lithium derivative treated with solid carbon dioxide without delay.

As anticipated from the original observations, the treatment of **2** with 2 equiv of LDA, followed by carbon dioxide, led to the production of the diacid **3** almost quantitatively.

The structural assignments are based on mass spectral and elemental analyses, infrared spectra, and conversion with diazomethane into the methyl esters **4** and **5**, which had satisfactory NMR, mass spectra, and elemental analyses. These results left no doubt about the presence and the number of the carboxyl groups attached to the terthiophene system in each case. Their assignment to the 5 and 5,5″ positions, respectively, is supported by the following arguments: (a) the acidity of the thiophene hydrogens is greater in the α than in the β positions,[1] (b) the NMR spectra of the methyl esters **4** and **5** did not show any ring protons without vicinal coupling, required if any β-carboxylation of **4** had occurred, and (c) the reduction with Raney nickel of **1** and **3** yielded the unbranched tridecanoic acid and 1,12-dodecanedicarboxylic acids, respectively. The former was shown to be identical with an authentic sample by direct comparison (IR, NMR, melting point, mixture melting point). The latter was characterized not only on the basis of the melting point and mass spectrum but also by its NMR data. For any carboxylation which occurred at one β-position in **2**, one α-position would have remained unsubstituted, and thus converted into a methyl group in the reductive degradation with Raney nickel. The NMR showed no such methyls in the product obtained.

Both carboxylic acids **1** and **3** were surprisingly insoluble in organic solvents and in base. While the former could be recrystallized from ethanol and the latter from dimethylformamide, only 1 mg of **1** dissolved when a 7-mg sample was treated with 10 mL of 1 N NaOH solution at room temperature for 24 h. Under exactly the same conditions, 0.5 mg of **3** could be dissolved. The solid recovered from these experiments was the unreacted acid in each case. In similar experiments, the solubility of **1** in pure ethanol was found to be 0.3 g per liter at room temperature, and that of **3** was 0.1 g/L.

The very slow and limited solubility of **1** in base perhaps explains the difficulties that were encountered in early attempts to oxidize the aldehyde **6** with the following reagents: chromium trioxide,[2] silver oxide, either alone[3]

(1) Wynberg, H.; Bentjes, A. *J. Am. Chem. Soc.* **1960**, *82*, 1447.

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