^{1}H NMR (300 MHz) δ 0.91 (t, J = 6 Hz, 3 H), 1.16 (d, J = 7 Hz, 3 H), 1.20–1.57 (m, 8 H), 1.70 (s, 2 H exchanged with D_2O), 3.60–3.68 (m, 1 H), 3.77–3.88 (m, 1 H); $[\alpha]^{25}_J$ = +19° (c 0.05 $CHCl_3$) (lit.[17] $[\alpha]^{18}_D$ = +22°); ee 99%.

Reduction of 3 by *B. sulfurescens*. *B. sulfurescens* (ATCC 7159) was grown in 500-mL conical flasks containing 100 mL of the following medium: glucose, 30 g/L; peptone, 10 g/L; K_2HSO_4, 1 g/L; $MgSO_4$, 0.5 g/L; KCl, 0.5 g/L; $ZnSO_4$, 0.3 g/L; $FeSO_4 \cdot 7H_2O$, 0.01 g/L in tap water. After 24-h cultivation on a rotary shaker at 27 °C, the mycelium was harvested by filtration, washed four times with saline (8 g/L), and compressed with suction for 10 min. Parts of wet mycelium (5 g) were resuspended in 500-mL conical flasks containing 50 mL of distilled water and 0.050 g of octane-2,3-dione (3). The reaction was carried out at 27 °C with stirring.

A. Twenty-four-Hour Incubation. After 24 h, the contents of 10 flasks were filtered and the filtrate was continuously extracted with ether overnight. The crude extract contained solely (2*S*,3*S*)-octane-2,3-diol (2), which was easily purified by silica gel column chromatography using eluent II. The yield determined with an internal standard (1-hexen-5-one) was 80%.

(−)-(2*S*,3*S*)-Octane-2,3-diol (2): 0.350 g (70%); R_f 0.30 (eluent II); GC retention time 20.9 min; ^{1}H NMR (300 MHz) δ 0.91 (t, J = 6 Hz, 3 H), 1.21 (d, J = 7 Hz, 3 H), 1.20–2.10 (m, 8 H), 1.64, 2 H, exchanged with D_2O), 3.32–3.41 (m, 1 H), 3.56–3.69 (m, 1 H); $[\alpha]^{25}_J$ = −16° (c 0.03, $CHCl_3$) (lit.[14b] $[\alpha]^{20}_D$ = −18.5°); ee 99%.

B. One-Hour Incubation. After 1 h, the crude extract was composed of octane-2,3 dione (3) (13%), (3*S*)-3-hydroxyoctan-2-one (4) (67%), and (2*S*,3*S*)-octane-2,3-diol (2) (20%) as shown by GC analysis. The compounds were purified by silica gel column chromatography using successively eluent I and eluent II, and ketol 4 was obtained pure.

(+)-(3*S*)-3-Hydroxyoctan-2-one (4): 0.200 g (40% yield); R_f 0.70 (eluent I); GC retention time 14.4 min; ^{1}H NMR (300 MHz) δ 0.9 (t, J = 6 Hz, 3 H), 1.20–1.60 (m, 6 H), 1.75–1.90 (m, 2 H), 2.20 (s, 3 H), 3.47 (s, 1 H exchanged with D_2O), 4.15–4.24 (m, 1 H); $[\alpha]^{25}_J$ = +92° (c 0.03, $CHCl_3$); ee 90%.

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Registry No. 1, 84435-13-2; 2, 84518-30-9; 3, 585-25-1; 4, 86838-20-2; 5, 66007-44-1; 3-oximido-2-octanone, 584-92-9.

An Unusual Dimer of 2-Mercaptothiophene

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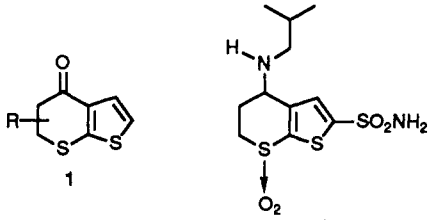
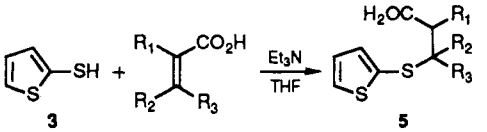
In previous communications,[1,2] we described the synthesis of various 5,6-dihydro-4*H*-4-oxothieno[2,3-*b*]thiopyrans (1). Recently, interest has increased in the preparation of derivatives of this ring system due to the pharmacology[3] associated with 5,6-dihydro-4*H*-4-[(2-methylpropyl)amino]thieno[2,3-*b*]thiopyran-2-sulfonamide 7,7-dioxide (2) (MK-927) as a carbonic anhydrase inhibitor (CAI) useful in the treatment of glaucoma.[4] Reaction of 2-mercaptothiophene (3) with substituted acrylic acids followed by Friedel–Crafts cyclization provides a facile entry into the synthesis of a large variety of thieno[2,3-*b*]thiopyrans.[2] Since 2-mercaptothiophene[5] is an essential starting material in these synthetic strategies, we report on an unusual dimerization reaction observed for 3.



1 2 (MK-927)

Interestingly, 2-mercaptothiophene (3) slowly solidifies on standing. HPLC analysis[6] of a sample of 3 that was stored in a refrigerator for several months under a blanket of nitrogen indicated that the mixture consisted of approximately 7% 3, 93% of an unidentified compound, and a trace amount of a third component (<0.5%). Conversion of 3 to the disulfide 4 by air oxidation[7] was the most obvious concern. However, reaction of this mixture with acrylic acids, as previously described,[2] gave nearly quantitative yields of 3-(2-mercaptothiopheneyl)-substituted propionic acids 5. This result indicated that the major product was not the disulfide 4. The third component was subsequently identified as the disulfide 4[7] by HPLC comparison with authentic material.



3 5

Trituration of the solid with hexane gave a yellow compound, which by elemental and mass spectral analyses[8] was found to be a dimer of 3. The mass spectrum showed a major fragment at m/z 116, the ion of 3, as well as the parent ion at 232. Additionally, the structural assignment of this dimer was based on NMR analyses. Three aromatic and five aliphatic protons were found in the ^{1}H NMR spectrum.[9] Further inspection of the proton couplings showed that the structure of the dimer must be 6. Results

(1) Ponticello, G. S.; Freedman, M. B.; Habecker, C. N.; Lyle, P. A.; Schwam, H.; Varga, S. L.; Christy, M. E.; Randall, W. C.; Baldwin, J. J. *J. Med. Chem.* **1987**, *30*, 591.

(2) Ponticello, G. S.; Freedman, M. B.; Habecker, C. N.; Holloway, M. K.; Amato, J. S.; Conn, R. S.; Baldwin, J. J. *J. Org. Chem.* **1988**, *53*, 9.

(3) Sugrue, M. F.; Gautheron, P.; Grove, J.; Mallorga, P.; Schwam, H.; Viader, M. P.; Baldwin, J. J.; Ponticello, G. S. *ARVO*, Sarasota, FL, May 1–6, 1988.

(4) Hennekes, R.; Pfeiffer, N.; Lippa, E.; Garus, H.; Grehn, F.; Jaeger, A. *ARVO*, Sarasota, FL, May 1–6, 1988.

(5) Compound 3 was obtained from Trans World Chemicals, Inc., Rockville, MD.

(6) HPLC's were run on a Spectra-Physics 8700XR equipped with a variable wavelength detector set at 210 nm and a Waters C-18 μ-Bondapak column using a flow rate of 3.0 mL/min. The column was run at 35 °C using gradient elution with 95% 0.1% H_3PO_4 and 5% CH_3CN to 5% 0.1% H_3PO_4 and 95% CH_3CN over 30 min. Under these conditions, 3 was eluted in 12.6 min, 6 in 18.9 min, and 4 in 21.2 min.

(7) Challenger, F.; Miller, S. A.; Gibson, G. M. *J. Chem. Soc.* **1948**, 769. In this report the authors also claim that 2-mercaptothiophene (3) is easily oxidized by air to the disulfide and, therefore, stored under nitrogen. In direct contrast, samples of 3 stored in air do not produce large amounts of disulfide 4, but, instead, are converted mainly to dimer 6. The sample of disulfide was not a solid as reported by Challenger; however, 4 was adequately characterized by mass spectral analysis. Noteworthy, the dimer 6 may be considered as a protected form of 3 which is resistant to air oxidation.

(8) Mp 34–36 °C (*n*-BuCl). Anal. Calcd for $C_8H_8S_4$: C, 41.34; H, 3.47. Found: C, 41.13; H, 3.31. The mass spectrum was taken on a VG MMZAB-HB spectrometer at an ionizing energy of 70 eV and the data was processed by a VG 11-250 data acquisition system.

(9) The proton NMR spectrum was obtained at 360 MHz (Nicolet NT-360) in $CDCl_3$. Chemical shifts are referenced to tetramethylsilane. Chemical shift in ppm (splittings in hertz, assignment): 3.01 (17.9, 9.5, H-3a), 3.35 (18.0, 6.2, 0.4, H-3b), 3.97 (9.5, 8.7, 6.1, 6.1, H-4), 3.67 (11.5, 8.7, H-5a), 3.74 (11.5, 6.0, H-5b), 7.23 (3.5, 1.3, H-8), 7.06 (5.4, 3.6, H-9), and 7.47 (5.4, 1.3, H-10).

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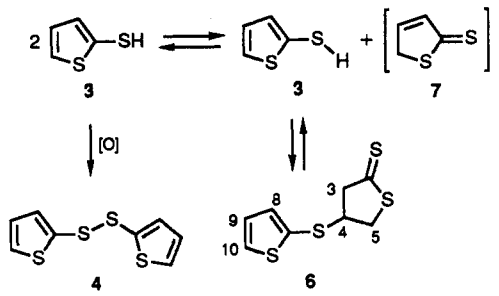
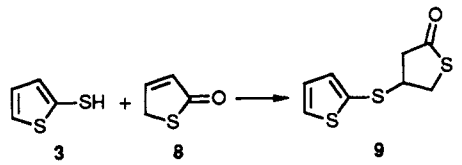
from ^{13}C NMR spectroscopy[10] are also in complete accord with structure **6**.

On investigating the chemical properties of **6**, it was discovered that the dimer is readily converted to the monomer **3** (bp_{15} 59–60 °C; lit.[11] bp_5 54 °C). Alternatively, treatment of **6** with Et_3N in THF in the absence of an acrylic acid also transforms **6** to **3** as evidenced by HPLC and ^1H NMR analysis. Thus, these studies demonstrate that the dimer reaction is easily reversed to regenerate usable 2-mercaptothiophene (**3**).

The behavior of **3** toward dimerization may be rationalized in terms of a slow tautomerization of **3** to 2,5-dihydro-2*H*-2-thioxothiophene (**7**) followed by a rapid Michael addition of 2-mercaptothiophene onto the acceptor **7** to yield **6**. Based on the isolation and characterization of the dimer as **6**, the existence of this highly reactive intermediate **7** appears mechanistically reasonable in spite of the fact that **7** was not detected by ^1H NMR spectroscopy.



Since 2-hydroxythiophene is known to exist predominately as 2,5-dihydro-2*H*-2-oxothiophene (**8**),[12] the Michael addition of **3** onto **8** (neat, 18 h, 25 °C) was next examined. From this reaction, a quantitative yield of **9** was isolated, and the compound was analogous to dimer **6**. The structural assignment of **9** was based on ^1H NMR and mass spectral analyses.[13] Thus, this result further substantiates the existence of intermediate **7** in the above sequence.



Acknowledgment. We thank Dr. John J. Baldwin and Professor Samuel J. Danishefsky for helpful discussions, Dr. Harri G. Ramjit for mass spectral analysis, and Vera W. Finley for preparation of the manuscript. In addition, we wish to thank Dr. Thomas J. Blacklock of Process Research for a sample of disulfide **4**.[7]

Registry No. **3**, 7774-74-5; **4**, 6911-51-9; **6**, 120665-65-8; **8**, 3354-32-3; **9**, 120638-04-2.

(10) Carbon NMR spectra were obtained at 75 MHz (Varian XL-300) in $CDCl_3$. Chemical shifts are referenced to the $CDCl_3$ triplet at 77.0 ppm. The carbon resonances were assigned with the aid of a carbon–proton correlation experiment (HETCOR). The assignments for C-8 and C-10 are based on the observation that $^1J_{CH}$ couplings for thiophene α-carbons are generally larger than for the corresponding β-carbons. Chemical shift in ppm (assignment): 241.1 (C-2), 59.57 (C-3), 50.97 (C-4), 44.17 (C-5), 129.3 (C-7), 136.8 (C-8), 128.1 (C-9), and 131.7 (C-10).

(11) Houff, W. H.; Schuetz, R. D. *J. Am. Chem. Soc.* **1953**, *75*, 6316.

(12) Frisell, C.; Lawesson, S. O. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. V, p 642 and references cited therein.

(13) The HPLC was run as described in ref 6 and under these conditions, **8** was eluted in 3.12 min and **9** in 15.35 min. The mass spectrum calculated for $C_8H_8OS_3$ 215.9737, found 215.9756. Chemical shift in ppm (splittings in hertz, assignment): 2.58 (16.8, 9.9, H-3a), 2.83 (17.0, 7.1, 0.7, H-3b), 3.77 (10.0, 8.8, 6.4, 5.9, H-4), 3.43 (11.5, 8.8, H-5a), 3.56 (11.2, 5.6, 0.7, H-5b), 7.22 (3.6, 1.3, H-8), 7.06 (5.3, 3.5, H-9), and 7.48 (5.4, 1.2, H-10).

Bromination of α-Substituted Alkylbenzenes: Synthesis of (*p*-Bromophenyl)acetylene

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Introduction

Ring halogenation of α-substituted alkyl aromatic compounds in presence of Lewis acid catalysts is practically impossible due to competing alkylation, which usually leads to polymerization and tar formation. Benzyl derivatives like bromide, chloride, alcohol, or acetate cannot be halogenated in the presence of iron or aluminum salts. It is also well-known that benzyl chloride cannot even be distilled in the presence of traces of iron due to excessive tar formation.

We have recently reported that quaternary ammonium salts can function as an alternative Friedel–Crafts aromatic bromination catalysts.[1] This group of catalysts, despite being less active than iron or aluminum salts, are water resistant and can therefore also catalyze oxybromination of aromatic compounds in presence of aqueous hydrogen peroxide as an oxidant.[1]

Results

We have now examined the bromination of benzyl derivatives in the presence of e.g. aliquat 336 (tricaprylmethylammonium chloride) catalyst. It was found that in the presence of 10 mol % catalyst, upon the gradual addition of 1 equiv of bromine at 60 °C, benzyl bromide was completely converted to *o*- and *p*-bromobenzyl bromide in the ratio of 9:11, respectively. The two isomers were separated by gas chromatography and identified by comparison with authentic samples. No alkylation or polymerization were observed.

When the same procedure was applied to benzyl chloride, nuclear bromination took place as well, but facile halogen exchange of the benzylic chlorine occurred simultaneously; 10 mol % excess of bromine is required in this experiment for complete conversion of the substrate. This phenomenon was utilized for the preparation of *o*- and *p*-bromobenzyl bromides directly from benzyl chloride. The isomer distribution is essentially the same as in the bromination of benzyl bromide.

More complicated were our attempts to brominate benzyl alcohol under the same conditions. Although some ring bromination was observed, at least 25% of the alcohol was oxidized by the bromine to benzaldehyde,[2] which is inert to bromination. In addition, some meta bromination (up to 5 mol %) of the alcohol took place simultaneously with 36% and 24% ortho and para bromination, respectively. No attempt was made to isolate these products.

Of particular interest to us was the bromination of (1-bromoethyl)benzene (BEB). This compound is an important raw material for various substituted styrenes, but, unfortunately, it cannot be halogenated under traditional conditions. We have examined the bromination of BEB in the presence of quaternary ammonium catalysts and were surprised to learn that the reaction took an unexpected route of simultaneous dehydrobromination–bromination (eq 1).

(1) Dakka, J.; Sasson, Y. *J. Chem. Soc., Chem. Commun.* **1987**, 1421.
(2) Dakka, J.; Sasson, Y. *Bull. Soc. Chim. Fr.* **1988**, 756.

0022-3263/89/1954-3224$01.50/0