over sodium sulfate. The crude mixture was purified by flash chromatography (benzene) to give 232 mg (74%) of **8b** as an oil: $^1$H NMR (60 MHz, $CCl_4$) $\delta$ 1.47–1.93 (6 H, m), 2.18 (2 H, br t, $J$ = ~6 Hz), 4.32 (1 H br t), 7.10–7.53 (10 H, m); IR (liquid film) 2960 (m), 2270 (m), 1595 (s), 1035 (s), 750 (s), 695 cm$^{-1}$ (s).

By a similar procedure $\omega,\omega$-bis(phenylthio)nitriles **8c**, **11**, and **14** were prepared starting from the corresponding $\omega$-(phenylthio)alkanol. Yields of products and their spectral data together with those of intermediate $\omega$-(phenylthio)nitriles are summarized below.

**3-Methyl-6,6-bis(phenylthio)hexanenitrile (8c)**: 35% overall yield from the corresponding $\omega$-(phenylthio)alkanol; oil; $^1$H NMR (60 MHz, $CCl_4$) $\delta$ 1.02 (3 H, d, $J$ = 5.8 Hz), 1.53–1.60 (4 H, m), 2.05–2.30 (2 H, m), 4.25 (1 H, br t), 7.17–7.63 (5 H, m); IR (liquid film) 2960 (s), 2275 (m), 1595 (s), 1035 (s), 750 (s), 695 cm$^{-1}$ (s).

**7-(Phenylthio)heptanenitrile**: 76% yield; oil; $^1$H NMR (60 MHz, $CCl_4$) $\delta$ 1.17–1.83 (8 H, m), 2.14 (2 H, br t), 2.80 (2 H, br t), 6.93–7.30 (5 H, m); IR (liquid film) 2985 (s), 2285 (m), 1605 (s), 750 (s), 695 cm$^{-1}$ (s).

**7,7-Bis(phenylthio)heptanenitrile (11)**: 65% yield; bp 220 °C (0.07 mmHg); $^1$H NMR (60 MHz, $CCl_4$) $\delta$ 1.33–1.90 (8 H, m), 2.17 (2 H, br t, $J$ = ~6 Hz), 4.27 (1 H, br t, $J$ = ~6 Hz), 7.13–7.50 (10 H, m); IR (liquid film) 2960 (s), 2240 (s), 740 (s), 690 cm$^{-1}$ (s).

**8-(Phenylthio)octanenitrile**: 80% yield; waxy solid; $^1$H NMR (60 MHz, $CCl_4$) $\delta$ 1.17–1.83 (10 H, m), 2.18 (2 H, br t), 2.83 (2 H, br t), 7.07–7.36 (5 H, m); IR (liquid film) 2940 (s), 2250 (m), 745 (s), 690 cm$^{-1}$ (s).

**8,8-Bis(phenylthio)octanenitrile (14)**: 77% yield; bp 195–205 °C (0.03 mmHg); $^1$H NMR (60 MHz, $CCl_4$) $\delta$ 1.23–1.90 (10 H, m), 2.18 (2 H, br t, $J$ = ~6 Hz), 4.28 (1 H, br t, $J$ = ~6 Hz), 7.13–7.50 (10 H, m); IR (liquid film) 2955 (s), 2260 (m), 1590 (s), 745 (s), 695 cm$^{-1}$ (s).

**General Procedure for the Intramolecular Cyclization Reaction.** To a solution of $\omega,\omega$-bis(phenylthio)nitrile (1.0 mmol) and TMEDA (3.0 mmol) in THF (10 mL) was added *sec*-BuLi (cyclohexane solution, 3 mmol) at −85 °C under a nitrogen atmosphere. The mixture was stirred at this temperature for 1 h, then allowed to warm gradually to a room temperature, and stirred further for 12 h. After aqueous workup, product(s) was isolated by means of flash chromatography (petroleum ether/benzene, gradient). Physical and spectral data of new compounds are as follows.

**3-Methyl-1-(phenylthio)cyclopentene (10)**: oil; $^1$H NMR (60 MHz, $CCl_4$) $\delta$ 1.03 (3 H, d, $J$ = 6.6 Hz), 1.80–2.87 (5 H, m), 5.50 (1 H, m), 7.07–7.47 (5 H, m); IR (liquid film) 2940 (s), 1590 (m), 815 (s), 740 (s), 690 cm$^{-1}$ (s); mass spectrum, $m/e$ (relative intensity) 190 ($M^+$, 33), 175 (22), 147 (11), 110 (12), 81 (100); exact mass calcd for $C_{12}H_{14}S$ 190.0817, found 190.0815.

***trans*- and *cis*-[2-(Phenylthio)cyclopentyl]acetonitrile (13).** This compound was obtained as a 5.5:1 mixture of two isomers. Each isomer was isolated by means of preparative GC. Major isomer: oil; $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 1.62–2.18 (6 H, m), 2.35 (1 H, dd, $J$ = 14.4 and 8.0 Hz), 2.48 (1 H, m), 2.61 (1 H, dd, $J$ = 14.4 and 5.2 Hz), 3.70 (1 H, br q, $J$ = ~6.5 Hz), 7.20–7.40 (5 H, m); IR (liquid film) 2960 (s), 2260 (m), 1595 (s), 745 (s), 695 cm$^{-1}$ (s); mass spectrum, $m/e$ (relative intensity) 217 ($M^+$, 23), 110 (100), 67 (22). Minor isomer: oil; $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 1.58–2.26 (7 H, m), 2.37 (1 H, dd, $J$ = 16.8 and 6.5 Hz), 2.55 (1 H, dd, $J$ = 16.8 and 4.4 Hz), 3.12 (1 H, br q, $J$ = ~8 Hz), 7.19–7.42 (5 H, m); mass spectrum, $m/e$ (relative intensity) 217 ($M^+$, 22), 110 (100), 67 (23); exact mass (mixture of two isomers) calcd for $C_{13}H_{15}NS$ 217.0927, found 217.0909.

***cis*-[2-(Phenylthio)cyclohexyl]acetonitrile (16)**: oil; $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 1.12 (8 H, m), 2.12 (1 H, m), 2.44 (1 H, dd, $J$ = 16.8 and 8.8 Hz), 2.62 (1 H, dd, $J$ = 16.8 and 8.0 Hz), 3.51 (1 H, m, width at half height = ~6 Hz), 7.16–7.48 (5 H, m); IR (liquid film) 2950 (s), 2250 (m), 1590 (s), 1030 (s), 740 (s), 695 cm$^{-1}$ (s); mass spectrum, $m/e$ (relative intensity) 231 ($M^+$, 11.5), 110 (100), 81 (29), 79 (11); exact mass calcd for $C_{14}H_{17}NS$ 231.1083, found 231.1082.

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**Registry No.** **1a**, 100-68-5; **1b**, 622-38-8; **1c**, 874-79-3; **1d**, 1126-80-3; **1e**, 831-91-4; **2a**, 7205-91-6; **2b**, 13557-24-9; **2c**, 87514-10-1; **2d**, 72653-47-5; **2e**, 7693-31-4; **3a**, 7214-53-1; (*E*)-**3b**, 23261-39-4; (*Z*)-**3b**, 41796-43-4; (*E*)-**3c**, 66164-65-6; (*Z*)-**3c**, 66164-53-2; (*E*)-**3d**, 99965-66-9; (*Z*)-**3d**, 99965-71-6; **3e**, 24466-59-9; (*E*)-**3f**, 99965-67-0; (*Z*)-**3f**, 99965-72-7; (*E*)-**3g**, 99965-68-1; (*Z*)-**3g**, 99965-73-8; **3h**, 7594-43-6; **3i**, 99965-69-2; (*E*)-**3j**, 99965-70-5; (*Z*)-**3j**, 99965-74-9; **3k**, 85895-10-9; (±)-**5**, 19657-49-9; *meso*-**5**, 15146-07-3; **8a**, 99965-77-2; **8b**, 99965-78-3; **8c**, 99965-79-4; **9**, 37053-16-0; **10**, 99965-85-2; **11**, 99965-90-9; **12**, 4922-47-8; *trans*-**13**, 99965-86-3; *cis*-**13**, 99965-87-4; **14**, 99965-84-1; **15**, 64741-11-3; **16**, 99965-88-5; $PhCH_2CN$, 140-29-4; $CH_3CN$, 75-05-8; $CH_3CH_2CN$, 107-12-0; $(CH_3)_2CHCN$, 78-82-0; $PhS(CH_2)_3CH(CH_3)CH_2OH$, 99965-80-7; $PhS(CH_2)_6OH$, 99965-82-9; $PhS(CH_2)_7OH$, 99965-89-6; $\alpha$-$naphCH_2CN$, 132-75-2; thiophenol, 108-98-5; 5-(phenylthio)-1-pentanol, 57774-95-5; 5-(phenylthio)-1-pentyl mesylate, 99965-75-0; 6-(phenylthio)hexanenitrile, 99965-76-1; 7-(phenylthio)heptanenitrile, 99965-81-8; 8-(phenylthio)octanenitrile, 99965-83-0.

# Thietane Alkylations. A General Synthesis of 3-Halopropyl Benzyl Sulfides[1]

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Reaction of thietane with benzyl halides yields 3-halopropyl benzyl sulfides in good to excellent yield.

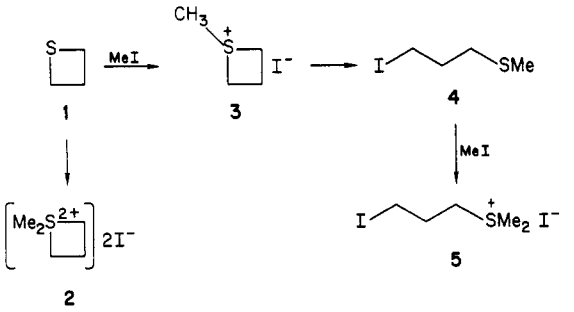
Some 58 years have elapsed since Bennett and Hock demonstrated that the reaction of thietane (**1**) with methyl iodide did not yield 1,1-dimethylthietanediylium diiodide (**2**) as originally proposed, but rather *S,S*-dimethyl-3-(iodopropyl)sulfonium iodide (**5**).[2] They proposed that this compound arose by attack by iodide ion on the initially formed *S*-methylthietanium iodide (**3**) to yield 3-iodopropyl methyl sulfide (**4**), which underwent subsequent alkylation with methyl iodide.[3] Since that time, only a few additional reports have appeared on the reaction of

(1) This work was supported by a grant (RO1 CA28351) to Princeton University from the National Cancer Institute, National Institutes of Health.

(2) Bennett, G. M.; Hock, A. L. *J. Chem. Soc.* **1927**, 2496.

(3) Grischikevitsch-Trochimovski, E. *Zh. Russ. Fiz.-Khim. O-va.* **1916**, *48*, 880.

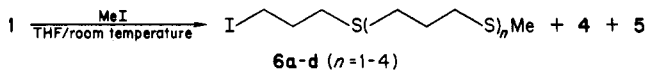
0022-3263/86/1951-0846$01.50/0 



thietanes with alkylating agents;[4,5] the products are reported to be either stable thietanium salts or ring-opened sulfides, according to the nature of the alkylating agent employed and the reaction conditions.[6-10]

As part of a project aimed at the utilization of thietane derivatives in the preparation of potential antitumor agents, we have reexplored the reaction of thietane with various alkylating agents. The results of this investigation, which include a general one-step synthesis of 3-halopropyl benzyl sulfides **7** and **8**, are summarized in this report.

The reaction of thietane with 1 equiv of methyl iodide in THF at room temperature did not cleanly produce 3-iodopropyl methyl sulfide (**4**), as might have been expected. Instead, a complex mixture of polysulfides was obtained (**6a–d**), together with small amounts of **4** and **5**. We



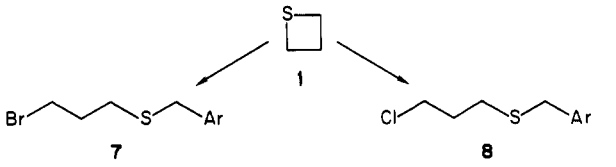
assume that the polymeric sulfides arose as a consequence of sequential reaction of **3** with one, two, three, and four molecules of **1**, respectively, to generate new thietanium salts which, in each case, underwent subsequent ring opening with iodide ion to yield the components of the observed reaction mixture.[11] It was possible to convert thietane smoothly to **5**, however, by reaction of **1** with a ninefold excess of methyl iodide at room temperature.[12]

Markedly different results were obtained upon treatment of **1** with other alkylating agents. For example, there was no reaction whatsoever between **1** and ethyl iodide, either in the absence of solvent at room temperature for prolonged periods of time or upon heating in either THF or acetone. Complex mixtures of polysulfides were obtained upon heating **1** with ethyl iodide in the absence of solvent or at room temperature in acetonitrile as solvent. By contrast, **1** proved to be relatively unreactive toward either 1- or 2-propyl iodide at room temperature or upon heating in THF, acetone, or acetonitrile. Once again, however, complex polysulfides were obtained upon heating **1** with the above alkyl iodides in the absence of solvent. No synthetically useful transformations could be carried out by using a number of different alkyl bromides. We therefore turned our attention to the reaction of thietane with benzylic halides.

We have found that a broad variety of 3-bromopropyl benzyl sulfides (**7**) can be formed in good to excellent yield either by heating equimolar quantities of thietane and the appropriate benzyl bromide in the absence of solvent or by allowing an equimolar mixture of thietane and the appropriate benzyl bromide in acetonitrile as solvent to stand at room temperature. Although benzyl chlorides proved to be totally unreactive under the latter set of reaction conditions, a wide variety of 3-chloropropyl benzyl sulfides (**8**) could be obtained in good yield by heating equimolar amounts of thietane and benzyl chlorides in the absence of solvent. Results are summarized in Table I.

As part of our program for preparing pteridine and deazapteridine analogues of methotrexate we required the unsymmetricaly functionalized isobutyraldehyde acetals **10**, with the objective of ultimately converting the indicated methylene group regiospecifically to an aldehyde by a directed Pummerer rearrangement.[13] These apparently

**Table I. Conversion of Thietane to 3-Halopropyl Benzyl Sulfides**



| compd | R | time, h | yield,[a,b] % | yield,[a,c] % |
|---|---|---|---|---|
| **7a** | *o*-$NO_2$ | 18 | 56 | |
| | | 13 | | 85 |
| **7b** | *p*-$NO_2$ | 18 | 57 | |
| | | 36 | | 84 |
| **7c** | *o*-Me | 30.5 | 76 | |
| | | 18 | | 76 |
| **7d** | *p*-Me | 30.5 | 69 | |
| | | 18 | | 82 |
| **7e** | *p*-OMe | | *d* | |
| | | 24 | | 76 |
| **7f** | *o*-Br | 17 | 78 | |
| | | 18 | | 81 |
| **7g** | *p*-Br | 17 | 81 | |
| | | 18 | | 94 |
| **7h** | *o*-CN | 21 | 84 | |
| | | 22 | | 69 |
| **7i** | H | 13 | 50 | |
| | | 26 | | 88 |
| **8a** | *o*-$NO_2$ | 72 | 44 | |
| | | 120 | | 17 |
| **8b** | *p*-$NO_2$ | 72 | 53 | |
| | | 96 | | 19 |
| **8c** | *o*-OMe | 30 | 75 | |
| | | 21 | | *e* |
| **8d** | *m*-OMe | 72 | 56 | |
| | | 48 | | *e* |
| **8e** | *p*-OMe | 24 | 85 | |
| | | 21 | | 19 |
| **8f** | *o*-Cl | 73 | 47 | |
| | | 107.5 | | *e* |
| **8g** | *p*-Cl | 73 | 53 | |
| | | 107.5 | | *e* |
| **8h** | *m*-F | 77 | 32 | |
| | | 94 | | *e* |
| **8i** | *p*-SMe | 40 | 79 | |

[a] The yields represent isolated products purified by vacuum distillation or column chromatography. [b] Thietane and the benzyl halide were heated at 70–80 °C. [c] Thietane and the benzyl halide were stirred in acetonitrile at room temperature. [d] This reaction was not attempted given the facility with which this benzyl halide polymerized/decomposed. [e] These reactions were attempted but gave mostly recovered benzyl halide.

(4) Etienne, Y.; Soulas, R.; Lumbroso, H. In "Heterocyclic Compounds with Three- and Four-Membered Rings"; Interscience: New York, 1964; p 647.
(5) Sander, M. *Chem. Rev.* **1966**, *66*, 341.
(6) Trost, B. M.; Schinski, W. L.; Mantz, I. B. *J. Am. Chem. Soc.* **1969**, *91*, 4320.
(7) Barbarella, G.; Garbesi, A.; Fava, A. *Helv. Chim. Acta* **1971**, *54*, 2297.
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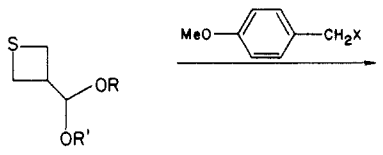
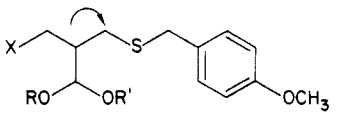
(9) (a) Vedejs, E.; Hagen, J. P. *J. Am. Chem. Soc.* **1975**, *97*, 6878. (b) Vedejs, E.; Hagen, J. P.; Roach, B. L.; Spear, K. L. *J. Org. Chem.* **1978**, *43*, 1185.
(10) Vilsmaier, E.; Schalk, W. *Synthesis* **1971**, 429.
(11) Bannister (Bannister, B. *J. Chem. Soc., Perkin Trans. 1* **1978**, 274) describes attack on a thietanium salt by thietane in the presence of acetic acid to generate a polysulfide with the structure $RS(CH_2)_3S(CH_2)_3OAc$.
(12) Fields, D. L.; Reynolds, D. D. U.S. Patent 3 247 225, 1966.

relatively inaccessible compounds could be conveniently prepared in high yield by application of the above thietane ring-opening reaction. Thus, heating equimolar quantities of **9a,b** with *p*-methoxybenzyl chloride or *p*-methoxybenzyl bromide afforded the ring-opened products **10a–c** in 71–83% purified yield. The utilization of these multifunctional intermediates for the preparation of methotrexate analogues has been described elsewhere.[14]




**9a**, R=R'=Et
**b**, R, R'=$CH_2CH_2$




**10a**, R=R'=Et; X=Cl
**b**, R, R'=$CH_2CH_2$; X=Cl
**c**, R, R'=$CH_2CH_2$; X=Br

## Experimental Section

Boiling points and melting points are uncorrected. Infrared spectra were recorded as thin films on KBr salt plates by using a Perkin-Elmer 467 grating infrared spectrometer. NMR spectra were obtained on a Varian A-60A instrument in $CDCl_3$ and are reported in ppm ($\delta$) from internal $Me_4Si$. Mass spectra were recorded with a VG ZAB mass spectrometer in the field desorption (FD) or chemical ionization (CI, $NH_3$ atmosphere) mode. We are indebted to Robert J. Hale, Tennessee Eastman Co., for these analyses. Column chromatography was performed with E. Merck silica gel 60. Elemental analyses were determined by Eli Lilly and Co., Indianapolis, IN, and Hoffmann-La Roche, Inc., Nutley, NJ.

**3-Iodopropyl Methyl Sulfide.** A filtered solution of 1.85 g (0.025 mol) of **1** in 100 mL of dry acetonitrile was stirred at room temperature while 3.65 g (0.026 mol) of methyl iodide was slowly added. The reaction was conveniently monitored by removal of an aliquot, evaporation, and NMR analysis of the residual oil. After 24 h, the reaction was judged complete. Evaporation of the acetonitrile left an oily semisolid, which was separated by trituration with hexane and cooling at 0 °C. The precipitate was collected by filtration, washed with a small volume of hexane, and air-dried to afford 1.70 g (19%) of **5** as pale yellow needles: mp 97–99 °C; mass spectrum FD, *m/z* 231.

The combined filtrate/washes from **5** were evaporated to leave 2.38 g of a light yellow, vile smelling oil: $^1H$ NMR ($CDCl_3$) $\delta$ 2.00 (m), 2.10 (s), 2.45 (m), 3.10 (t) [consistent with **4**[15] except that the integration ratio of 2:3:2:2 was clearly not observed]; mass spectrum FD, *m/z* 216, 290, 364, 438, 512 [corresponding to the molecular weights of **4** and **6a–d**, respectively].

***S,S*-Dimethyl-3-(iodopropyl)sulfonium Iodide (5).** A mixture of 1.85 g (0.025 mol) of **1** and 13.0 mL (0.209 mol) of methyl iodide was stirred at room temperature for 24 h, during which time a voluminous white solid precipitated. This was collected by filtration, washed with diethyl ether, and recrystallized from absolute ethanol to yield 6.91 g (77%) of **5**: mp 96.5–99.0 °C (lit.[12] mp 97–98 °C); mass spectrum FD, *m/z* 231.

**3-Halopropyl Benzyl Sulfides 7a–i and 8a–i.** Representative procedures for the preparation of **7a–i** and **8a–i**, using acetonitrile as solvent and in the absence of solvent, are described below in detail.

**3-Bromopropyl Benzyl Sulfide (7i).** A mixture of 8.10 g (0.109 mol) of **1** and 17.1 g (0.100 mol) of benzyl bromide in 50 mL of dry acetonitrile was stirred at room temperature for 26 h. The $^1H$ NMR spectrum of an aliquot at 26 h showed only a trace of benzyl bromide remaining. The acetonitrile was evaporated at reduced pressure and the residue distilled in vacuo to yield 21.59 g (88%) of **7i** as a colorless oil: bp 105–107 °C (0.3 mmHg) [lit.[16] bp 147 °C (13.5 mmHg)]; IR (neat) 3050, 3020 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 2.08 (m, 2 H), 2.57 (m, 2 H), 3.47 (t, 2 H), 3.72 (s, 2 H), 7.30 (s, 5 H).

Anal. Calcd for $C_{10}H_{13}BrS$: C, 48.99; H, 5.35; S, 13.08; Br, 32.59. Found: C, 48.71; H, 5.26; S, 12.81; Br, 32.83.

**3-Bromopropyl *o*-Nitrobenzyl Sulfide (7a).** A mixture of 0.81 g (0.011 mol) of **1** and 2.16 g (0.010 mol) of *o*-nitrobenzyl bromide in 5 mL of dry acetonitrile was stirred at room temperature for 13 h. The acetonitrile was evaporated at reduced pressure, and the residual oil was chromatographed on silica gel. Elution with pentane resulted in recovery of a small amount of *o*-nitrobenzyl bromide. Elution with 3:1 pentane/$CH_2Cl_2$ and evaporation gave 2.47 g (85%) of **7a** as a light orange oil: IR (neat) 3050, 1600, 1515, 1335 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 2.13 (m, 2 H), 2.70 (m, 2 H), 3.53 (t, 2 H), 4.15 (s, 2 H), 7.60 (m, 3 H), 8.06 (m, 1 H).

Anal. Calcd for $C_{10}H_{12}BrSNO_2$: C, 41.40; H, 4.17; N, 4.83; S, 11.05; Br, 27.54. Found: C, 41.61; H, 4.37; N, 5.06; S, 10.88; Br, 27.76.

**3-Bromopropyl *p*-Nitrobenzyl Sulfide (7b).** A mixture of 0.81 g (0.011 mol) of **1** and 2.16 g (0.010 mol) of *p*-nitrobenzyl bromide in 8 mL of dry acetonitrile was stirred at room temperature for 36 h. TLC on silica gel with 1:1 $CH_2Cl_2$/pentane showed no benzyl halide remaining after this time. The acetonitrile was evaporated to leave a yellow oil, which was chromatographed on silica gel. Elution with pentane and evaporation gave 2.43 g of **7b** (84%) as a viscous yellow oil: IR (neat) 3100, 3070, 1595, 1510, 1340 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 2.20 (m, 2 H), 2.68 (m, 2 H), 3.55 (t, 2 H), 3.87 (s, 2 H), 7.58 (m, 2 H), 8.28 (m, 2 H).

Anal. Calcd for $C_{10}H_{12}BrNO_2S$: C, 41.40; H, 4.17; N, 4.83; S, 11.05; Br, 27.54. Found: C, 41.15; H, 3.87; N, 4.80; S, 10.91; Br, 27.69.

**3-Bromopropyl *p*-Methoxybenzyl Sulfide (7e).** A mixture of 0.82 g (0.011 mol) of **1** and 2.10 g (0.011 mol) of *p*-methoxybenzyl bromide[17] in 5 mL of acetonitrile was stirred at room temperature for 24 h. TLC on silica gel with pentane showed no remaining benzyl halide. Evaporation of the acetonitrile left an oil, which was chromatographed on silica gel. Elution with pentane and evaporation afforded 2.21 g (76%) of **7e** as a colorless oil: IR (neat) 3040, 3020, 1600, 1500 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 2.15 (m, 2 H), 2.63 (m, 2 H), 3.35 (t, 2 H), 3.73 (s, 2 H), 3.83 (s, 3 H), 6.91 and 7.30 (AB q, 4 H).

Anal. Calcd for $C_{11}H_{15}BrOS$: C, 48.01; H, 5.50; S, 11.65; Br, 29.04. Found: C, 47.80; H, 5.23; S, 11.90; Br, 28.87.

**3-Bromopropyl *o*-Bromobenzyl Sulfide (7f).** A mixture of 0.745 g (0.010 mol) of **1** and 2.50 g (0.010 mol) of *o*-bromobenzyl bromide in 5 mL of dry acetonitrile was stirred at room temperature for 18 h. TLC on silica gel with 1:1 $CH_2Cl_2$/pentane showed no remaining benzyl halide. Evaporation of the acetonitrile left an oil, which was chromatographed on silica gel. Elution with pentane and evaporation gave 2.63 g (81%) of **7f** as a viscous, colorless oil: IR (neat) 3040, 1560, 1460 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 2.12 (m, 2 H), 2.67 (m, 2 H), 3.53 (t, 2 H), 3.92 (s, 2 H), 7.37 (m, 4 H).

Anal. Calcd for $C_{10}H_{12}Br_2S$: C, 37.07; H, 3.73; S, 9.89; Br, 49.32. Found: C, 37.04; H, 3.64; S, 9.55; Br, 49.59.

**3-Bromopropyl *o*-Cyanobenzyl Sulfide (7h).** A mixture of 0.82 g (0.011 mol) of **1** and 1.96 g (0.010 mol) of *o*-cyanobenzyl bromide in 5 mL of acetonitrile was stirred at room temperature for 24 h. TLC on silica gel with pentane showed only a trace of remaining benzyl halide. Evaporation of the acetonitrile left a viscous yellow oil, which was chromatographed on silica gel. Elution with 300 mL of pentane removed a small amount of the benzyl halide. Continued elution with 1:1 pentane/toluene and

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(17) Rzeszotarska, R.; Weber, K. *Org. Prep. Proced. Int.* **1974**, *6*, 211. This extremely reactive benzyl halide should be prepared fresh and used immediately. In our hands, freshly prepared and distilled material, stored in a brown bottle under nitrogen at −10 °C, polymerized vigorously after 6–10 days.

evaporation afforded 1.86 g (69%) of **7h** as a pale yellow viscous oil: IR (neat) 2220 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 2.13 (m, 2 H), 2.68 (m, 2 H), 3.55 (t, 2 H), 3.97 (s, 2 H), 7.60 (m, 4 H).

Anal. Calcd for $C_{11}H_{12}BrNS$: C, 48.91; H, 4.48; N, 5.19; S, 11.87; Br, 29.58. Found: C, 48.80; H, 4.41; N, 4.93; S, 11.69; Br, 29.35.

**3-Bromopropyl *p*-bromobenzyl sulfide (7g)** was obtained in 94% yield as a colorless oil: bp 125–126 °C (0.01 mm); IR (neat) 3040, 1580, 1480 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 2.07 (m, 2 H), 2.60 (m, 2 H), 3.53 (t, 2 H), 3.73 (s, 2 H), 7.28 (m, 2 H), 7.57 (m, 2 H).

Anal. Calcd for $C_{10}H_{12}Br_2S$: C, 37.07; H, 3.73; S, 9.89; Br, 49.32. Found: C, 36.93; H, 3.55; S, 9.80; Br, 49.71.

**3-Bromopropyl *o*-methylbenzyl sulfide (7c)** was obtained in 76% yield as a pale yellow oil: bp 103–105 °C (0.05 mm); IR (neat) 3050, 3010 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 2.06 (m, 2 H), 2.38 (s, 3 H), 2.59 (m, 2 H), 3.45 (t, 2 H), 3.70 (s, 2 H), 7.13 (s, 4 H).

Anal. Calcd for $C_{11}H_{15}BrS$: C, 50.98; H, 5.83; S, 12.37; Br, 30.83. Found: C, 51.23; H, 5.71; S, 12.08; Br, 30.88.

**3-Bromopropyl *p*-methylbenzyl sulfide (7d)** was obtained in 82% yield as a colorless oil: bp 98–100 °C (0.03 mm); IR (neat) 3040, 3010 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 2.02 (m, 2 H), 2.32 (s, 3 H), 2.54 (m, 2 H), 3.45 (t, 2 H), 3.68 (s, 2 H), 7.15 (m, 4 H).

Anal. Calcd for $C_{11}H_{15}BrS$: C, 50.98; H, 5.83; S, 12.37; Br, 30.83. Found: C, 51.07; H, 5.81; S, 12.37; Br, 30.57.

**3-Chloropropyl *p*-Methoxybenzyl Sulfide (8e).** A mixture of 3.7 g (0.05 mol) of **1** and 7.84 g (0.05 mol) of *p*-methoxybenzyl chloride[18] was stirred at 70–80 °C for 47 h. An aliquot of the reaction mixture showed only a trace of benzyl halide remained by NMR. The reaction mixture was vacuum distilled to give 9.78 g (85%) of **8e** as a colorless oil with bp 105–107 °C (0.02 mm): IR (neat) 3050, 3020, 1600, 1500, 1245 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 2.06 (m, 2 H), 2.60 (m, 2 H), 3.58 (t, 2 H), 3.68 (s, 2 H), 3.78 (s, 3 H), 6.81 (m, 2 H), 7.21 (m, 2 H).

Anal. Calcd for $C_{11}H_{15}ClOS$: C, 57.26; H, 6.55; Cl, 15.36; S, 13.89. Found: C, 57.35; H, 6.63; Cl, 15.61; S, 13.61.

**3-Chloropropyl *p*-(Methylthio)benzyl Sulfide (8i).** A mixture of 1.542 g (0.025 mol) of **1** and 3.537 g (0.020 mol) of *p*-(methylthio)benzyl chloride[19] was stirred at 82 °C for 40 h. NMR analysis of an aliquot showed no benzyl halide remained. The reaction mixture was vacuum distilled to afford 3.95 g (79%) of **8i** as a colorless oil with bp 130–132 °C (0.10 mm): IR (neat) 3040, 3020 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 1.90 (m, 2 H), 2.57 (s, 3 H), 2.67 (m, 2 H), 3.67 (s, 2 H), 3.78 (t, 2 H), 7.37 (s, 4 H).

Anal. Calcd for $C_{11}H_{15}ClS_2$: C, 53.53; H, 6.13; Cl, 14.37; S, 25.98. Found: C, 53.96; H, 6.15; Cl, 13.94; S, 25.26.

**3-Chloropropyl *m*-Methoxybenzyl Sulfide (8d).** A mixture of 2.06 g (0.0278 mol) of **1** and 3.94 g (0.0252 mol) of *m*-methoxybenzyl chloride was stirred at 72–75 °C for 72 h. The reaction mixture was distilled in vacuo at 0.015 mmHg. After removal of unreacted *m*-methoxybenzyl chloride (1.124 g, 28.5%), **8d** distilled at 95–97 °C as a colorless oil, 3.23 g (56%): IR (neat) 3050, 3010 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 2.07 (m, 2 H), 2.63 (m, 2 H), 3.67 (t, 2 H), 3.75 (s, 2 H), 3.88 (s, 3 H), 6.93 (m, 3 H), 7.30 (m, 1 H).

Anal. Calcd for $C_{11}H_{15}ClOS$: C, 57.26; H, 6.55; Cl, 15.36; S, 13.89. Found: C, 57.25; H, 6.54; Cl, 14.99; S, 14.11.

**3-Chloropropyl *o*-Methoxybenzyl Sulfide (8c).** A mixture of 0.74 g (0.010 mol) of **1** and 1.98 g (0.010 mol) of *o*-methoxybenzyl chloride[20] was stirred at 70–78 °C for 30 h. NMR analysis of an aliquot showed only a trace of the benzyl halide remained. The reaction mixture was vacuum distilled to yield 1.72 g (75%) of **8c** as a pale yellow oil with bp 98–99 °C (0.03 mm): IR (neat) 3040, 3010, 1580, 1240 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 2.07 (m, 2 H), 2.61 (m, 2 H), 3.64 (t, 2 H), 3.78 (s, 2 H), 3.88 (s, 3 H), 6.93 (m, 2 H), 7.28 (m, 2 H).

Anal. Calcd for $C_{11}H_{15}ClOS$: C, 57.26; H, 6.55; Cl, 15.36; S, 13.89. Found: C, 57.14; H, 6.35; Cl, 15.31; S, 14.09.

**3-Chloropropyl *o*-Nitrobenzyl Sulfide (8a).** A mixture of 0.82 g (0.011 mol) of **1** and 1.72 g (0.010 mol) of *p*-nitrobenzyl chloride was stirred at 70–80 °C for 72 h. An aliquot showed only a trace of benzyl halide by NMR. The reaction mixture was chromatographed on silica gel. Elution with pentane removed a small amount of unreacted benzyl halide. Continued elution with pentane then toluene and evaporation afforded 1.315 g (53%) of **8b** as a pale yellow oil, which crystallized upon standing overnight at −10 °C: mp 30.5–32.0 °C; IR (neat) 3060, 1510, 1340 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 2.08 (m, 2 H), 2.68 (m, 2 H), 3.67 (t, 2 H), 3.88 (s, 2 H), 7.61 (m, 2 H), 8.60 (m, 2 H).

Anal. Calcd for $C_{10}H_{12}ClNO_2S$: C, 48.89; H, 4.92; N, 5.70; S, 13.05; Cl, 14.43. Found: C, 48.81; H, 4.71; N, 5.84; S, 13.07; Cl, 14.32.

**3-Chloropropyl *o*-chlorobenzyl sulfide (8f)** was obtained in 47% yield as a colorless oil: bp 97–98 °C (0.10 mm); IR (neat) 3060 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 2.00 (m, 2 H), 2.65 (m, 2 H), 3.60 (t, 2 H), 3.82 (s, 2 H), 7.26 (m, 4 H).

Anal. Calcd for $C_{10}H_{12}Cl_2S$: C, 51.08; H, 5.14; S, 13.63; Cl, 30.16. Found: C, 50.98; H, 5.17; S, 13.26; Cl, 30.17.

**3-Chloropropyl *p*-chlorobenzyl sulfide (8g)** was obtained in 53% yield as a colorless oil: bp 101–102 °C (0.10 mm); IR (neat) 3020 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 2.00 (m, 2 H), 2.60 (m, 2 H), 3.61 (t, 2 H), 3.68 (s, 2 H), 7.27 (m, 4 H).

Anal. Calcd for $C_{10}H_{12}Cl_2S$: C, 51.08; H, 5.14; S, 13.63; Cl, 30.16. Found: C, 51.00; H, 5.10; S, 13.30; Cl, 30.45.

**3-Chloropropyl *m*-fluorobenzyl sulfide (8h)** was obtained in 32% yield as a colorless oil: bp 77–79 °C (0.010 mm); IR (neat) 3070, 1620, 1590, 1490 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 2.03 (m, 2 H), 2.57 (m, 2 H), 3.60 (t, 2 H), 3.68 (s, 2 H), 7.12 (m, 4 H).

Anal. Calcd for $C_{10}H_{12}ClFS$: C, 54.94; H, 5.53; F, 8.69; Cl, 16.21; S, 14.66. Found: C, 54.68; H, 5.33; F, 8.42; Cl, 16.15; S, 14.66.

**1-Chloro-2-(diethoxymethyl)-3-[(*p*-methoxybenzyl)thio]propane (10a)**: A mixture of 0.895 g (0.0051 mol) of **9a**[14] and 0.805 g (0.0052 mol) of *p*-methoxybenzyl chloride[18] was stirred at 70–80 °C for 24 h. The reaction mixture was evacuated to 0.1 mmHg and held at 50–55 °C for 5 h to remove any unreacted starting materials. The residue was chromatographed on silica gel with methylene chloride as the eluant. Evaporation of the methylene chloride left 1.42 g (83%) of **10a** as a pale yellow oil: IR (neat) 1600, 1500, 1240 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 1.20 (t, 3 H), 1.23 (t, 3 H), 2.20 (m, 1 H), 2.71 (d, $J$ = 6 Hz, 1 H), 2.74 (d, $J$ = 6 Hz, 1 H), 3.55 (m, 6 H), 3.55 (m, 6 H), 3.70 (s, 2 H), 3.82 (s, 3 H), 4.60 (d, $J$ = 6 Hz, 1 H), 6.86 (m, 2 ), 7.29 (m, 2 H).

Anal. Calcd for $C_{16}H_{25}ClO_3S$: C, 57.73; H, 7.57; Cl, 10.65; S, 9.63. Found: C, 57.96; H, 7.43; Cl, 10.41; S, 9.45.

**1-Chloro-2-(1,3-dioxolan-2-yl)-3-[(*p*-methoxybenzyl)thio]propane (10b).** A mixture of 0.735 g (0.005 mol) of **9b**[14] and 0.785 g (0.005 mol) of *p*-methoxybenzyl chloride[18] was stirred at 73–75 °C for 24 h. Unreacted *p*-methoxybenzyl chloride (0.15 g, 19.1%) was recovered by heating the reaction mixture gently at 0.01 mmHg. The residual oil, **10b**, 1.22 g (80%, 100% based on recovered *p*-methoxybenzyl chloride) was pure: IR (neat) 1610, 1510 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 2.10 (m, 1 H), 2.68 and 2.70 (d, $J$ = 6 Hz, 2 H), 3.68 (s, 2 H), 3.75 (m, 2 H), 3.78 (s, 3 H), 3.87 (m, 4 H), 4.98 (d, $J$ = 4 Hz, 1 H), 6.92 and 7.24 (AB q, 4 H).

Anal. Calcd for $C_{14}H_{19}ClO_3S$: C, 55.53; H, 6.33; Cl, 11.71; S, 10.59. Found: C, 55.74; H, 6.24; Cl, 11.85; S, 10.69.

**1-Bromo-2-(1,3-dioxolan-2-yl)-3-[(*p*-methoxybenzyl)thio]propane (10c).** A solution of 5.0 g (0.034 mol) of **9b**[14] and 6.88 g (0.034 mol) of freshly prepared *p*-methoxybenzyl bromide[17] in 50 mL of dry acetonitrile was stirred at room temperature under a nitrogen atmosphere for 16 h. The solvent was removed at reduced pressure to leave 8.42 g (71%) of **10c** as a light yellow oil: IR (neat) 1610, 1590 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 2.08 (m, 1 H), 2.67 and 2.70 (d, $J$ = 6 Hz, 2 H), 3.58 (m, 2 H), 3.67 (s, 2 H), 3.78 (s, 3 H), 3.87 (s, 4 H), 4.95 (d, $J$ = 4 Hz, 1 H), 6.83 and 7.26 (AB q, 4 H).

Anal. Calcd for $C_{14}H_{19}BrO_3S$: C, 48.42; H, 5.52; Br, 23.01; S, 9.23. Found: C, 48.49; H, 5.53; Br, 23.21; S, 8.95.

(18) Adapted from: Fujii, T.; Uneo, Y.; Mitsukuchi, M. *Chem. Pharm. Bull. Jpn.* **1971**, *19*, 1374. *p*-Methoxybenzyl chloride has bp 54–57 °C (0.05 mm): NMR ($CDCl_3$) $\delta$ 3.82 (s, 3 H), 4.58 (s, 2 H), 6.85 (d, 2 H), 7.31 (d, 2 H).

(19) *p*-(Methylthio)benzyl chloride was prepared in 61.3% yield by reaction of *p*-(methylthio)benzyl alcohol (Aldrich) with concentrated HCl at 0 °C: bp 72–74 °C (0.25 mm); NMR ($CDCl_3$) $\delta$ 2.53 (s, 3 H), 4.60 (s, 2 H), 7.33 (s, 4 H).

(20) *o*-Methoxybenzyl chloride was prepared in two steps from *o*-anisaldehyde. Sodium borohydride reduction (Cresp, T. M.; Giles, R. G. F.; Sargent, M. V.; Brown, C.; Smith, D. O. N. *J. Chem. Soc., Perkin Trans. 1* **1974**, 2435) afforded *o*-anisyl alcohol in 95.2% yield. This was converted to *o*-methoxybenzyl chloride in 69.1% yield by using thionyl chloride/benzene as described by: Grice, R.; Owen, L. N. *J. Chem. Soc.* **1963**, 1947. Bp 67–69 °C (0.07 mm); NMR ($CDCl_3$) $\delta$ 3.83 (s, 3 H), 4.68 (s, 2 H), 6.90 (m, 2 H), 7.30 (m, 2 H).

**Registry No.** **1**, 287-27-4; **4**, 93530-08-6; **5**, 99810-16-9; **7a**, 99809-99-1; **7b**, 99810-00-1; **7c**, 99810-01-2; **7d**, 99810-02-3; **7e**, 99810-03-4; **7f**, 99810-04-5; **7g**, 99810-05-6; **7h**, 99810-06-7; **7i**, 88738-51-6; **8a**, 99810-07-8; **8b**, 99810-08-9; **8c**, 99810-09-0; **8d**, 99810-10-3; **8e**, 99810-11-4; **8f**, 99810-12-5; **8g**, 99810-13-6; **8h**, 99810-14-7; **8i**, 99810-15-8; **9a**, 99810-17-0; **9b**, 87373-80-6; **10a**, 99810-18-1; **10b**, 99810-19-2; **10c**, 87373-82-8; *p*-$MeSC_6H_4CH_2OH$, 3446-90-0; *o*-$O_2NC_6H_4CH_2Br$, 3958-60-9; *p*-$O_2NC_6H_4CH_2Br$, 100-11-8; *o*-$CH_3C_6H_4CH_2Br$, 89-92-9; *p*-$CH_3C_6H_4CH_2Br$, 104-81-4; *p*-$CH_3OC_6H_4CH_2Br$, 2746-25-0; *o*-$BrC_6H_4CH_2Br$, 3433-80-5; *p*-$BrC_6H_4CH_2Br$, 589-15-1; *o*-$NCC_6H_4CH_2Br$, 22115-41-9; $C_6H_5CH_2Br$, 100-39-0; *o*-$O_2NC_6H_4CH_2Cl$, 612-23-7; *p*-$O_2NC_6H_4CH_2Cl$, 100-14-1; *o*-$CH_3OC_6H_4CH_2Cl$, 7035-02-1; *m*-$CH_3OC_6H_4CH_2Cl$, 824-98-6; *p*-$CH_3OC_6H_4CH_2Cl$, 824-94-2; *o*-$ClC_6H_4CH_2Cl$, 611-19-8; *p*-$ClC_6H_4CH_2Cl$, 104-83-6; *m*-$FC_6H_4CH_2Cl$, 456-42-8; *p*-$CH_3SC_6H_4CH_2Cl$, 874-87-3.

# Synthesis of Halogenated Terpyridines and Incorporation of the Terpyridine Nucleus into a Polyethereal Macrocycle[1]

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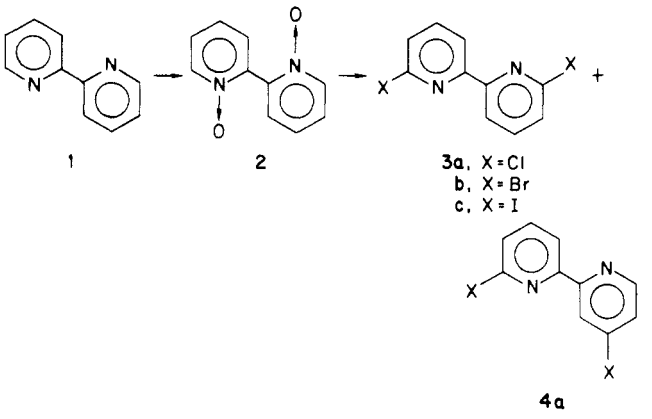
Two synthetic approaches to haloterpyridines are herein described. The first method involved direct halogenation of terpyridine *N*-oxides with $POCl_3$ to generate a mixture of polyhalogenated terpyridines. A more efficient approach to 6,6″-dibromo-2,2′:6′,2″-terpyridine utilized the Kröhnke synthesis to form the terpyridine moiety from appropriately halosubstituted precursors. Direct nucleophilic substitution on terpyridine was found to give low yields of macrocyclic products; however, if 1,5-bis(6-bromo-2-pyridyl)-1,5-dioxopentane was employed, macrocyclization afforded improved yields of the desired terpyridines.

In a systematic study[2-5] dealing with the conformational effects of polypyridino macrocycles and resulting transition-metal complexes, we required efficient synthetic routes to the starting terminal dihalopolypyridines. Historically, 6,6″-dihalo-2,2′:6′,2″-terpyridines have been prepared, albeit in poor overall yields, via vapor-phase halogenation of the unsubstituted terpyridine.[6] We herein report two improved synthetic routes to haloterpyridines, which may provide viable alternatives to the older procedure as well as give entrance to novel terpyridine macrocycles.

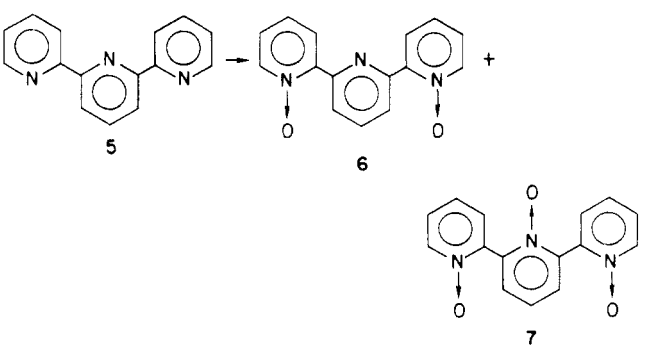
## Results and Discussion

The reaction of 2,2′-dipyridine di-*N*-oxide (**2**) with $POCl_3$ has been demonstrated to give a variable product distribution, which was temperature dependent (Scheme I).[7-9] At 45–50 °C, 6,6′-dichloro-2,2′-dipyridine (**3a**) was generated (40%) along with traces of the 4,6-isomer **4a**; whereas, **3a** and **4a** were formed in 35% and 17% yields, respectively, at 75 °C.[7,10] In view of the inertness of **3a** to transmetalation, the more reactive bromide **3b** and iodide **3c** were prepared (>80%) via treatment of **3a** with HBr or HI in glacial AcOH, respectively.[11]

**Scheme I**




**Scheme II**




Initially the same general approach found successful for the preparation 2,2′-dipyridine (Scheme I) was applied to terpyridine. Attempts to prepare terpyridine di-*N*-oxide (**6**) via partial oxidation of 2,2′:6′,2″-terpyridine (**5**) with $AcO_2H$ gave an inseparable mixture of *N*-oxides (Scheme

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