

A CONVENIENT PROCEDURE FOR THE SYNTHESIS OF 2,3-DIHYDRO-1,4-DITHIAPHENANTHRENE DERIVATIVES

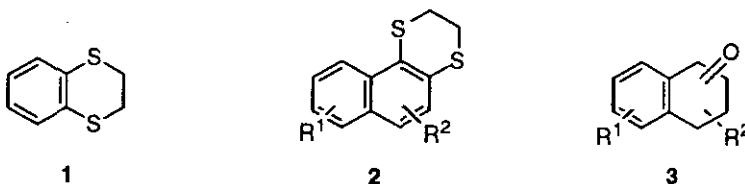
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Abstract- A convenient method for the synthesis of 2,3-dihydro-1,4-dithiaphenanthrene derivatives starting from *S,S*-acetals of tetralones is described. A feasible mechanism for this transformation is also proposed.

In contrast with the chemistry of cyclic sulfides,¹ the chemistry of cyclic disulfides has received few attention with exception of the 1,3-dithiane ring system.² In the case of benzofused 1,4-dithiane derivatives (**1**) there are only small numbers of general methods for the synthesis of this heterocyclic ring system.³⁻⁶ To the best of our knowledge, cyclization of the disodium salt of *ortho*-dimercaptobenzene with 1,2-dibromomethane,³ the reaction of 7-oxanorbornenone with ethanedithiol in presence of BF₃·OEt₂,⁴ and the ring aromatization of *S,S*-acetals of cyclohexanone using halogens in chlorinated solvents,⁵ have been used for the preparation of the parent compound and some derivatives.⁶

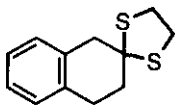
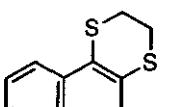
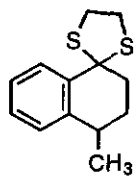
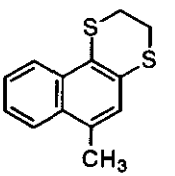
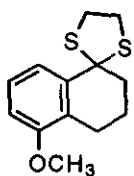
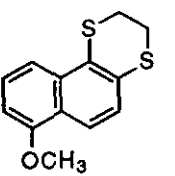
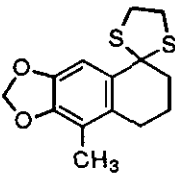
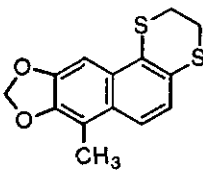
On the other hand, fused 1,4-benzodithianes of general structure (**2**), carrying substituents on the benzenoides rings have, to the best of our knowledge, never been prepared, with exception of the unsubstituted compound (R₁=R₂=H).⁵



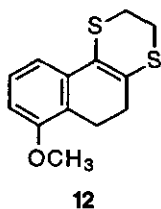
In this paper we wish to report a convenient, general method for the synthesis of these compounds starting from readily available *S,S*-acetals of the related ketones (**3**) by treatment with NBS in CCl₄.⁷ This method constitutes a modification of the procedure indicated in reference 5, avoiding undesired side reactions such as the bromination in the benzenoid ring. Furthermore, a feasible mechanistic pathway for the transformation of **3** to **2** is reported.

The reactions of the appropriate ketones with 1,2-ethanedithiol in the presence of BF₃·OEt₂ affords almost quantitatively the related *S,S*-acetals (**4-7**). Treatment of these compounds with NBS in CCl₄ at 25°C gave dithianes (**8-11**). Isolated yields are indicated in **Table 1**.

Table 1. Reactions of *S,S*-diacetals (4-7) with NBS in CCl₄ at 25°C.

Starting material	Product	Isolated yield(%) ^{a)}
 4	 8	74
 5	 9	80
 6	 10	98
 7	 11	90

^{a)} Compound (8) was purified by distillation and some loss of material was observed during this process. The remaining products were purified by chromatography (compounds (9) and (10)) or recrystallization (compound (11)). For details, see **Experimental Section**.

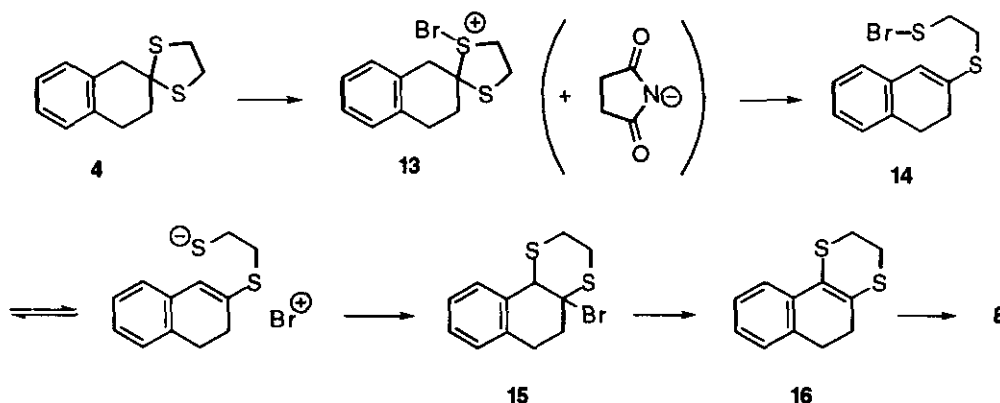


The reaction times in all cases were 20-25 h. Observation of TLC allowed us the presence of an intermediate which, in the case of the transformation of 6 to 10, could be isolated and identified as dithiane (12) (75% isolated yield).

In the remaining cases, a mixture of dithiane intermediate and the final product was observed (NMR).

At longer reaction times, compounds (4-7) evolve to the final products (8-11).

A reasonable reaction pathway for this transformation can be formulated as follows (**Scheme 1**) using compound (4) as an example. In the first step, the reaction of 4 with NBS affords the sulfonium salt (13).⁸ In the presence of succinimide ion a β -elimination occurs to give sulfinyl halide (14) which, by intramolecular deprotonation⁹ followed by Pummerer like displacement affords (15).¹⁰ Dehydrohalogenation gives dithiane (16), the observed intermediate. Final spontaneous aromatization of 16 affords 8.



Scheme 1

In summary, we report here a convenient method for the transformation of substituted tetralones in 2,3-dihydro-1,4-dithiaphenanthrene derivatives in two steps with good overall yields.

EXPERIMENTAL SECTION

General. IR spectra were recorded on a Perkin-Elmer 297 spectrophotometer. ¹H NMR and ¹³C NMR were obtained on Varian XL-300, Bruker AM-250 and Bruker AM-300 spectrometers. Chemical shifts (δ) are reported in ppm from internal (CH₃)₄Si. Silica gel Merck 60 (230-400 mesh) and Merck 60F₂₅₄ plates were used for purification and analytical (TLC) chromatography, respectively. Melting points were determined on a Gallenkamp instrument and are uncorrected. Dichloromethane and BF₃·OEt₂ were distilled over CaH₂ and NBS was recrystallized from water before use. 5-Methyl-6,7-methylenedioxy-1-tetralone was prepared in our laboratory using an intramolecular Friedel-Crafts cyclization from the appropriate 4-arylbutanoic acid. The remaining 1-tetralones were commercially available and were recrystallized before use.

General Procedure for the Synthesis of the 1,3-Dithianes (4-7). 1,2-Ethanedithiol (0.376 g, 4

mmol) and a few drops of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ were added dropwise to a solution of the appropriate tetralone (1 mmol) in CH_2Cl_2 (5 mL). The resulting mixture was refluxed until total consumption of the starting material (TLC) and then cooled at rt. The solution was washed with aqueous 5% NaOH, water and brine, dried (MgSO_4) and concentrated *in vacuo*. The corresponding 1,3-dithianes were obtained after purification by recrystallization in the indicated solvents.

Spiro[2,5-dithiacyclopentane-1,2'-(1',2',3',4'-tetrahydronaphthalene)] (4). From 2-tetralone after 20 h of reaction and purification by recrystallization from ethanol a pale yellow solid (97%) was obtained. mp: 78-79°C. ^1H NMR (CDCl_3 , 300 MHz): δ 2.32 (t, CH_2 , 2H, $J = 6.5$ Hz), 3.04 (t, CH_2 , 2H, $J = 6.5$ Hz), 3.29-3.45 (m, $\text{SCH}_2\text{CH}_2\text{S}$, 4H), 3.37 (s, CH_2 , 2H), 6.94-7.17 (m, ArH, 4H). ^{13}C NMR (CDCl_3 , 75 MHz): δ 29.3, 39.0, 39.1 (2C), 46.4, 66.0, 126.0, 126.5, 129.0 (2C), 134.6, 135.4. IR (KBr): ν 3020, 2930, 2830, 1580, 780, 755 cm^{-1} . Anal. Calcd for $\text{C}_{12}\text{H}_{14}\text{S}_2$: C, 64.82; H, 6.35. Found: C, 64.89; H, 6.28.

Spiro[2,5-dithiacyclopentane-1,1'-(4'-methyl-1',2',3',4'-tetrahydronaphthalene)] (5). From 4-methyl-1-tetralone after 25 h of reaction a yellow oil which solidified at low temperature was obtained (98%). This compound was used without further purification. mp: 33-35°C. ^1H NMR (CDCl_3 , 300 MHz): δ 1.30 (d, CH_3 , 3H, $J = 7.0$ Hz), 1.68-2.20 (m, CH_2 , 2H), 2.88-3.00 (m, CH, 1H), 3.39-3.67 (m, $\text{SCH}_2\text{CH}_2\text{S}$, 4H), 7.08-7.21 (m, ArH, 3H), 7.94 (d, ArH, 1H, $J = 7.0$ Hz). ^{13}C NMR (CDCl_3 , 300 MHz): δ 22.8, 30.8, 32.4, 40.8, 40.9, 41.1, 69.2, 126.1, 127.5, 127.9, 130.9, 138.6, 142.3. IR (KBr): ν 3060, 3020, 2925, 2850, 1485, 1445, 760, 745 cm^{-1} . Anal. Calcd for $\text{C}_{13}\text{H}_{16}\text{S}_2$: C, 66.05; H, 6.82. Found: C, 66.00; H, 6.91.

Spiro[2,5-dithiacyclopentane-1,1'-(5'-methoxy-1',2',3',4'-tetrahydronaphthalene)] (6). From 5-methoxy-1-tetralone after 16 h of reaction and recrystallization from ethanol a yellow solid was obtained (87%). mp: 104-105°C. ^1H NMR (CDCl_3 , 300 MHz): δ 1.96-2.04 (m, CH_2 , 2H), 2.35-2.39 (m, CH_2 , 2H), 2.68 (t, CH_2 , 2H, $J = 6.4$ Hz), 3.41-3.64 (m, $\text{SCH}_2\text{CH}_2\text{S}$, 4H), 3.79 (s, OCH_3 , 3H), 6.67 (dd, ArH, 1H, $J = 8.1, 0.7$ Hz), 7.16 (t, ArH, 1H, $J = 8.1$ Hz), 7.58 (dd, ArH, 1H, $J = 8.7, 0.7$ Hz). ^{13}C NMR (CDCl_3 , 75 MHz): δ 22.0, 22.9, 40.8 (2C), 43.2, 55.3, 68.6, 107.8, 122.4, 125.9, 126.7, 140.2, 156.2. IR (KBr): ν 2940, 2840, 1435, 1255, 1240, 765, cm^{-1} . Anal. Calcd for $\text{C}_{13}\text{H}_{16}\text{OS}_2$: C, 61.87; H, 6.39. Found: C, 61.44; H, 6.30.

Spiro[2,5-dithiacyclopentane-1,1'-(5'-methyl-6',7'-methylenedioxy-1',2',3',4'-tetrahydronaphthalene)] (7). From 5-methyl-6,7-methylenedioxy-1-tetralone after 50 h of reaction and recrystallization from AcOEt a pale brown solid was obtained (88%). mp: 188-189°C. ^1H NMR (CDCl_3 , 300 MHz): δ 1.94-2.02 (m, CH_2 , 2H), 2.04 (s, CH_3 , 3H), 2.33 (m, CH_2 , 2H), 2.53 (t, CH_2 , 2H, $J = 6.8$ Hz), 3.36-3.59 (m, $\text{SCH}_2\text{CH}_2\text{S}$, 4H), 5.87 (s, OCH_2O , 2H), 7.32 (s, ArH, 1H). ^{13}C NMR (CDCl_3 , 300 MHz): δ 11.5, 22.5, 26.2, 40.7 (2C), 43.3, 69.8, 100.4, 107.7, 115.8, 130.2, 131.6, 144.7, 145.3. IR (KBr): ν 3000, 2950, 2920, 1500, 950, 860, 840, 750, 580 cm^{-1} . Anal. Calcd for $\text{C}_{14}\text{H}_{16}\text{O}_2\text{S}_2$: C,

H, 5.75. Found: C, 59.79; H, 5.55.

General Procedure for the Synthesis of 2,4-Dithiaphenanthrene Derivatives (8-12). NBS (0.178 g (1 mmol) for **6** and **7**, 0.267 g (1.5 mmol) for **4** and **5**) was added to a solution of the 1,3-dithiane (1 mmol) in CCl₄ (10 mL). After stirring the resulting mixture at rt until complete disappearance of the starting material (TLC), water (5 mL) was added. The organic layer was washed with 5% aqueous NaHSO₃, water and brine and dried (MgSO₄). After concentrating under reduced pressure, the product was purified by chromatography and/or recrystallization.

2,3-Dihydro-1,4-dithiaphenanthrene (8). After 20 h of reaction and distillation under reduced pressure a yellow liquid was obtained (74%) from **4**. bp : 170-172°C/1 mm Hg. ¹H NMR: 3.26-3.37 (m, SCH₂CH₂S, 4H), 7.17 (d, ArH, 1H, *J* = 9.0 Hz), 7.38 (ddd, ArH, 1H, *J* = 8.1, 6.9, 1.2 Hz), 7.45 (d, ArH, 1H, *J* = 9.0 Hz), 7.48 (ddd, ArH, 1H, *J* = 8.4, 6.9, 1.2 Hz), 7.70 (dd, ArH, 1H, *J* = 8.4, 0.9 Hz), 8.11 (dd, ArH, 1H, *J* = 8.1, 0.9 Hz). ¹³C NMR (CDCl₃, 75 MHz): δ 28.8, 30.1, 122.6, 125.2, 125.5, 126.7, 127.0, 127.2, 128.6, 129.1, 131.6, 132.2. IR (neat): ν 3050, 2920, 1615, 1590, 815, 770 cm⁻¹. Anal. Calcd for C₁₂H₁₀S₂: C, 66.02; H, 4.62. Found: C, 66.11; H, 4.57.

2,3-Dihydro-1,4-dithia-6-methylphenanthrene (9). From **5** after 20 h of reaction and purification by column chromatography (Hexane/benzene 4:1) a yellow oil was obtained (80%). ¹H NMR (CDCl₃, 300 MHz): δ 2.57 (s, CH₃, 3H), 3.27-3.40 (m, SCH₂CH₂S, 4H), 7.06 (s, ArH, 1H), 7.42-7.54 (m, ArH, 2H), 7.88 (dd, ArH, 1H, *J* = 7.2, 1.4 Hz), 8.16 (d, ArH, 1H, *J* = 8.1 Hz). ¹³C NMR (CDCl₃, 75 MHz): δ 19.2, 28.7, 30.2, 123.1, 124.8, 124.9, 125.3, 126.4, 127.4, 128.0, 131.1, 131.6, 132.3. IR (neat): ν 3060, 2920, 2860, 1555, 1445, 1360, 845 cm⁻¹. Anal. Calcd for C₁₃H₁₂S₂: C, 67.20; H, 5.21. Found: C, 66.97; H, 5.28.

2,3-Dihydro-1,4-dithia-7-methoxyphenanthrene (10). From **6** after 25 h of reaction and purification by column chromatography (Hexane/CH₂Cl₂ 1:1) a pale brown oil was obtained (98%). ¹H NMR (CDCl₃, 300 MHz): δ 3.24-3.34 (m, SCH₂CH₂S, 4H), 3.91 (s, OCH₃, 3H), 6.73 (d, ArH, 1H, *J* = 7.5 Hz), 7.17 (d, ArH, 1H, *J* = 9.0 Hz), 7.37 (dd, ArH, 1H, *J* = 8.7, 7.5 Hz), 7.69 (d, ArH, 1H, *J* = 8.7 Hz), 7.91 (d, ArH, 1H, *J* = 9.0 Hz). ¹³C NMR (CDCl₃, 75 MHz): δ 28.6, 29.8, 55.5, 103.6, 114.7, 118.9, 123.3, 125.9, 126.6, 129.56, 132.7, 132.9, 155.6. IR (neat): ν 3070, 3010, 2965, 2925, 2860, 2840, 1590, 1455, 1260, 1020, 795 cm⁻¹. Anal. Calcd for C₁₃H₁₂OS₂: C, 62.87; H, 4.87. Found: C, 62.96; H, 4.59.

2,3-Dihydro-1,4-dithia-7-methyl-8,9-methylenedioxyphenanthrene (11). From **7** after 22 h of reaction and recrystallization from ethanol a yellow solid was obtained (90%). mp 145-146°C. ¹H NMR (CDCl₃, 300 MHz): δ 2.41 (s, CH₃, 3H), 3.22-3.36 (m, SCH₂CH₂S, 4H), 5.99 (s, OCH₂O, 2H), 7.13 (d, ArH, 1H, *J* = 8.9 Hz), 7.42 (d, ArH, 1H, *J* = 0.5 Hz), 7.44 (dd, ArH, 1H, *J* = 8.9, 0.5 Hz). ¹³C NMR (CDCl₃, 75 MHz): δ 11.1, 29.4, 30.3, 97.9, 100.8, 112.0, 120.4, 125.0, 127.5, 127.8, 128.1,

129.6, 145.0, 147.4. IR (KBr): ν 2910, 1465, 925, 870, 840, 810, 775, 745 cm^{-1} . Anal. Calcd for $\text{C}_{14}\text{H}_{12}\text{O}_2\text{S}_2$: C, 60.84; H, 4.38. Found: C, 61.07; H, 4.11.

1,4-Dithia-7-methoxy-2,3,5,6-tetrahydrophenanthrene (12). From **6** after 2.5 h of reaction a brown oil was obtained (75%) without further purification. ^1H NMR (CDCl_3 , 300 MHz): δ 2.34 (t, CH_2 , 2H, $J = 7.7$ Hz), 2.81 (t, CH_2 , 2H, $J = 7.7$ Hz), 3.24-3.35 (m, $\text{SCH}_2\text{CH}_2\text{S}$, 4H), 3.83 (s, OCH_3 , 3H), 6.76 (dd, ArH, 1H, $J = 8.1, 1.1$ Hz), 7.10 (dd, ArH, 1H, $J = 8.1, 1.1$ Hz), 7.14 (t, ArH, 1H, $J = 8.1$ Hz). ^{13}C NMR (CDCl_3 , 75 MHz): δ 20.1, 27.7, 30.0, 31.1, 55.6, 109.2, 114.7, 119.0, 122.6, 126.2, 126.7, 135.3, 155.8. IR (neat): ν 3070, 2920, 2840, 1470, 1115, 785, 745, 710 cm^{-1} . Anal. Calcd for $\text{C}_{13}\text{H}_{14}\text{OS}_2$: C, 62.36; H, 5.64. Found: C, 62.53; H, 5.48.

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REFERENCES AND NOTES

1. For a review on the chemistry of cyclic sulfides, see E. Vedejs and G. A. Krafft, *Tetrahedron*, 1982, **38**, 2857. For a general revision of six membered rings with more than one oxygen or sulfur heteroatom, see K. J. Cook, 'Comprehensive Heterocyclic Chemistry,' Vol. 3, ed. by A. R. Katritzky and Ch. W. Rees, Pergamon Press, Oxford, 1984, pp. 943-993.
2. For a general account on the synthetic utility of 1,3-dithianes, see J. March, in 'Advanced Organic Chemistry. Reactions, Mechanisms and Structure,' 4th Edition, John Wiley and Sons, Inc., New York, 1992, pp. 474-479 and references therein.
3. J. H. Verheijen and H. Kloosterziel, *Synthesis*, 1975, 451.
4. B. Alcaide, J. Plumet, and I. M. Rodríguez-Campos, *Heterocycles*, 1986, **24**, 141.
5. R. Caputo, C. Ferreri, G. Palumbo, and F. Russo, *Tetrahedron*, 1991, **47**, 4187 and references therein. See also: R. Caputo, M. De Nisco, G. Palumbo, C. Adamo, and V. Barone, *Tetrahedron*, 1993, **49**, 11383. R. Caputo, C. Ferreri, G. Palumbo, S. Pedatella, and F. Russo, *Heterocycles*, 1993, **36**, 281.
6. Dihydro-1,4-dithiin fused with carbocyclic systems have been prepared by ring expansion reactions of cyclic sulfoxides. See: C. H. Chen and B. A. Donatelli, *J. Org. Chem.*, 1976, **41**, 3053. J. W. A. M. Janssen and H. Kwart, *J. Org. Chem.*, 1977, **42**, 1530.

7. It should be pointed out that *N*-halosuccinimide reagents cleaved 1,3-dithiane ring systems in solvents such as aqueous acetone or acetonitrile. See E. J. Corey and B. W. Erickson, *J. Org. Chem.*, 1971, **36**, 3553 and references therein.
8. Formation of halosulfonium salts from sulfides and NBS is a well documented process. For a review, see G. E. Wilson, Jr., *Tetrahedron*, 1982, **38**, 2597.
9. The deprotonation in bromosulfonium salts derived from 1,2-disulfides has been previously considered. See G. E. Wilson, Jr., and M. G. Huang, *J. Org. Chem.*, 1970, **35**, 3002.
10. For Pummerer rearrangements in halosulfonium salts, see ref. 8, pp. 2603-2612.

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