# Synthesis of the 1*H*,5*H*-Naphtho[1,8-*ef*][1,3]dithiocin System

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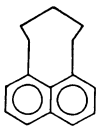
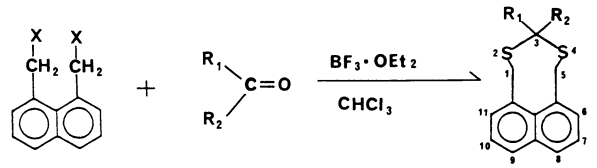
**Synopsis.** The titled new pericyclized naphthalene system has been prepared in four steps from 1,8-naphthalenedicarboxylic anhydride in an overall yield of 35—78%. The key step in the synthesis employed a dithioacetal-cyclization reaction of 1,8-bis(mercaptomethyl)naphthalene with carbonyl compounds using boron trifluoride etherate as a catalyst.

Previously, we reported the synthesis of the 8,9,10,11-tetrahydro-7*H*-cycloocta[*de*]naphthalene system (**1**).[1,2] The successful synthesis of the carbocyclic ring of the eight-membered pericyclized naphthalene system has led us to investigate further the synthesis of heterocyclic analogs of this family of molecules. In this paper, a synthesis of new peri ring system, 1*H*,5*H*-naphtho[1,8-*ef*][1,3]dithiocin (**2**) is reported.



**1**

Lithium aluminum hydride reduction of the commercially available 1,8-naphthalenedicarboxylic anhydride readily gave 1,8-bis(hydroxymethyl)naphthalene (**3**) (85% yield).[2] Bromination of **3** with phosphorus tribromide in dioxane produced the dibromide **4** (94% yield), which, on treatment with thiourea, was converted to the dithiol **5** (99% yield).[3] Our approach to synthesis of the 1*H*,5*H*-naphtho[1,8-*ef*][1,3]dithiocin system then utilized a dithioacetal-cyclization reaction between **5** and carbonyl compounds. The reactions were carried out with a variety of aldehydes and ketones in chloroform using boron trifluoride etherate as a catalyst. Thus, treatment of **5** with paraformaldehyde (**6a**) yielded 1*H*,5*H*-naphtho[1,8-*ef*][1,3]dithiocin (**2a**) (44% yield) with the desired 1,3-dithiocin peri ring. Similarly, from paraldehyde (**6b**) and benzaldehyde (**6c**) were obtained 3-monosubstituted derivatives of **2a**—i.e., 3-methyl- (**2b**) (69% yield) and 3-phenyl- (**2c**) (97% yield) 1*H*,5*H*-naphtho[1,8-*ef*]dithiocins, respectively. Furthermore, ketones also underwent a ready dithioacetalization reaction on treatment with **5** to give rise to 3,3-disubtituted derivatives of **2a**—i.e., from acetone (**6d**), 2-butanone (**6e**), and acetophenone (**6f**) were obtained 3,3-dimethyl- (**2d**) (70% yield), 3-ethyl-3-methyl- (**2e**) (81% yield), and 3-methyl-3-phenyl- (**2f**) (60% yield) 1*H*,5*H*-naphtho[1,8-*ef*][1,3]dithiocins, respectively.




**3**; X = OH
**4**; X = Br
**5**; X = SH

**6a—f**

**2a—f**

**a**; $R_1 = R_2 = H$
**b**; $R_1 = CH_3$, $R_2 = H$
**c**; $R_1 = C_6H_5$, $R_2 = H$
**d**; $R_1 = R_2 = CH_3$
**e**; $R_1 = C_2H_5$, $R_2 = CH_3$
**f**; $R_1 = CH_3$, $R_2 = C_6H_5$

All the products obtained (**2a—f**) are listed in Table 1. Each of these new compounds gave elemental analysis and spectra (IR, NMR, MS) identical with its structure. (See Experimental).

## Experimental

**General.** Melting points were taken on a microscopic hot-stage melting-point apparatus and are uncorrected. The $R_f$ values were obtained on Merck Silica gel $60F_{254}$ (0.2 mm) with benzene as a solvent. The IR spectra were measured with a JASCO IR-G spectrometer using Nujol mulls calibrated with polystyrene. The $^1H$ NMR spectra were determined on a JEOL C-60 spectrometer (at 60 MHz) using chloroform-*d* as a solvent (ca. 10% solution) and tetramethylsilane as an internal standard. Mass spectra were obtained with a JEOL-01SG-2 instrument with a direct-inlet system operating at 75 eV.

**1,8-Bis(hydroxymethyl)naphthalene (3).** This was prepared from 1,8-naphthalenedicarboxylic anhydride in 85% yield as described previously.[2]

**1,8-Bis(bromomethyl)naphthalene (4).** This was ob-

Table 1. Synthesis of 1*H*,5*H*-Naphtho[1,8-*ef*][1,3]dithiocins (**2a—f**) from 1,8-Bis(mercaptomethyl)naphthalene (**5**) and Carbonyl Compounds (**6**)

| Carbonyl compound (**6**) | $R_1$ | $R_2$ | Product (**2**) | Yield/% |
|---|---|---|---|---|
| Paraformaldehyde (**6a**) | H | H | **2a** | 44 |
| Paraldehyde (**6b**) | $CH_3$ | H | **2b** | 69 |
| Benzaldehyde (**6c**) | $C_6H_5$ | H | **2c** | 97 |
| Acetone (**6d**) | $CH_3$ | $CH_3$ | **2d** | 70 |
| 2-Butanone (**6e**) | $C_2H_5$ | $CH_3$ | **2e** | 81 |
| Acetophenone (**6f**) | $CH_3$ | $C_6H_5$ | **2f** | 60 |

tained in a more excellent yield than that reported[4] by using the procedure described below.

To a stirred suspension of the diol **3** (20.435 g) in dioxane (100 ml) was slowly added phosphorus tribromide (30 ml) at room temperature. After 25 h, water (300 ml) was added under cooling to decompose the excess reagent, and the resulting mixture, after further addition of water (1200 ml), was stirred at room temperature for an additional 1 h. The solid precipitated was then collected by filtration and crystallized from benzene to give the dibromide **4** (35 g, 94%) as colorless crystals; mp 131.5—132 °C (lit,[4] mp 130—131.5 °C); MS, *m/z* 314 ($M^+$=$C_{12}H_{10}Br^{79}Br^{81}$).

**1,8-Bis(mercaptomethyl)naphthalene (5).** This was prepared by a modification of the procedure previously reported.[3]

A mixture of the dibromide **4** (34.54 g) and thiourea (17.6 g) in 95% ethanol (580 ml) was boiled under reflux over a period of 4 h. After cooling the white precipitate of bis(isothiouronium) salt was collected. The salt was then added to a nitrogen-degassed solution of potassium hydroxide (180 g) in water (350 ml) and refluxed under nitrogen atmosphere for 1 h. After cooling and washing with benzene, the aqueous alkaline solution was slowly added with ice-cooling to a nitrogen-degassed 6 M-aqueous hydrochloric acid (1 M=1 mol $dm^{-3}$). The resulting cloudy solution was stirred for 30 min at room temperature. The white solid precipitated was collected by filtration to provide the dithiol **5** (23.8 g, 99%); mp 79—81 °C (lit,[3] mp 80—80.5 °C); IR (Nujol) 2557 $cm^{-1}$ (S-H); $^1$H NMR ($CDCl_3$) $\delta$=1.84 (2H, t, $J$=6.1 Hz, SH), 4.42 (4H, d, $J$=6.1 Hz, $ArCH_2SH$), 7.36—7.91 (6H, m, ArH); MS, *m/z* 220 ($M^+$). This was shown (by IR, $^1$H NMR, TLC) to be pure enough and employed without further purification for the following reactions.

**Preparation of 1*H*,5*H*-Naphtho[1,8-*ef*][1,3]dithiocins (2a—f) by Reaction of the Dithiol 5 with Paraformaldehyde (6a), Paraldehyde (6b), Benzaldehyde (6c), Acetone (6d), 2-Butanone (6e), and Acetophenone (6f). General Procedure.** To a stirred and cooled (0 °C) solution of the dithiol **5** (0.5 mmol) and aldehyde or ketone **6** (0.5 mmol) in chloroform (10 ml) there was added boron trifluoride etherate (2 mmol) under nitrogen atmosphere. After the mixture had been stirred at 0 °C for 2 h, it was allowed to warm to room temperature and was stirred for an additional 18 h. Water was then added and the mixture was extracted with ether. The ether layer was washed successively with 10% aqueous sodium hydroxide solution and water, and was evaporated after drying over magnesium sulfate. The resulting solid was purified by recrystallization from ethanol to afford the pure dithioacetal **2.**

**1*H*,5*H*-Naphtho[1,8-*ef*][1,3]dithiocin (2a);** colorless needles; mp 180.5—181 °C; $R_f$ 0.51 ($SiO_2$/benzene); IR (Nujol) 3025, 1600, 1510, 835, 780, 770 $cm^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$=3.55 (2H, s, $C_9$-$CH_2$), 4.69 (4H, broad signal, $ArCH_2$), 7.41—7.94 (6H, m, ArH); MS, *m/z* (relative intensity), 232 ($M^+$, 69), 186 (36), 185 ($M^+$—$CH_3S$, 100), 172 (96), 171 (61), 153 (70), 152 (51); Found: C, 67.29; H, 5.02%. Calcd for $C_{13}H_{12}S_2$: C, 67.19; H, 5.21%.

**3-Methyl-1*H*,5*H*-naphtho[1,8-*ef*][1,3]dithiocin (2b);** colorless microcrystals; mp 133.5—137 °C; $R_f$ 0.52 ($SiO_2$/benzene); IR (Nujol) 3040, 1600, 1510, 830, 770 $cm^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$=1.36 (3H, d, $J$=7.1 Hz, $CH_3$), 3.92 (2H, ABd, $J$=14.3 Hz, $ArCH_2$), 4.10 (1H, q, $J$=7.1 Hz, $C_9$-H), 5.53 (2H, ABd, $J$=14.3 Hz, $ArCH_2$), 7.40—7.93 (6H, m, ArH); MS, *m/z* (relative intensity), 246 ($M^+$, 65), 186 (49), 185 ($M^+$—$C_2H_5S$, 100), 172 (61), 171 (53), 153 (67), 152 (43), 74 (22). Found: C, 68.30; H, 5.91%. Calcd for $C_{14}H_{14}S_2$: C, 68.24; H, 5.73%.

**3-Phenyl-1*H*,5*H*-naphtho[1,8-*ef*][1,3]dithiocin (2c);** colorless microcrystals; mp 192.5—193.5 °C; $R_f$ 0.53 ($SiO_2$/benzene); IR (Nujol) 3050, 1600, 1495, 835, 770, 725, 695 $cm^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$=4.03 (2H, ABd, $J$=14.6 Hz, $ArCH_2$), 5.17 (1H, s, $C_9$-H), 5.68 (2H, ABd, $J$=14.6 Hz, $ArCH_2$), 7.26 (5H, s, Phenyl H), 7.45—7.98 (6H, m, Naphthalene H); MS, *m/z* (relative intensity), 308 ($M^+$, 40), 186 ($M^+$—$C_7H_6S$, 100), 185 (94), 171 (37), 153 (65), 136 (36), 135 (35). Found: C, 73.75; H, 5.40%. Calcd for $C_{19}H_{16}S_2$: C, 73.98; H, 5.23%.

**3,3-Dimethyl-1*H*,5*H*-naphtho[1,8-*ef*][1,3]dithiocin (2d);** colorless microcrystals; mp 152—152.5 °C; $R_f$ 0.42 ($SiO_2$/benzene); IR (Nujol) 3030, 1600, 1505, 825, 770, 765 $cm^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$=1.80 (6H, s, $CH_3$), 4.43 (4H, s, $ArCH_2$), 7.25—7.87 (6H, m, ArH); MS, *m/z* (relative intensity), 260 ($M^+$, 48), 186 (73), 185 ($M^+$—$C_3H_6S$, 100), 171 (47), 153 (82), 152 (55), 88 (81). Found: C, 69.31; H, 6.00%. Calcd for $C_{15}H_{16}S_2$: C, 69.18; H, 6.19%.

**3-Ethyl-3-methyl-1*H*,5*H*-naphtho[1,8-*ef*][1,3]dithiocin (2e);** colorless crystals; mp 154—155 °C; $R_f$ 0.49 ($SiO_2$/benzene); IR (Nujol) 3020, 1605, 1510, 825, 775, 765 $cm^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$=1.10 (3H, t, $J$=7.0 Hz, ethyl-$CH_3$), 1.65 (3H, s, $CH_3$), 2.10 (2H, q, ethyl-$CH_2$), 4.43 (4H, s, $ArCH_2$), 7.29—7.95 (6H, m, ArH); MS, *m/z* (relative intensity), 274 ($M^+$, 27), 186 ($M^+$—$C_4H_8S$, 100), 185 (92), 171 (51), 153 (88), 152 (61), 102 (51). Found: C, 69.85; H, 6.85%. Calcd for $C_{16}H_{18}S_2$: C, 70.02; H, 6.61%.

**3-Methyl-3-phenyl-1*H*,5*H*-naphtho[1,8-*ef*][1,3]dithiocin (2f);** colorless microcrystals; mp 182.5—184.5 °C; $R_f$ 0.54 ($SiO_2$/benzene); IR (Nujol) 3050, 1600, 1510, 825, 770, 760, 695 $cm^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$=1.81 (3H, s, $CH_3$), 4.23 (4H, s, $ArCH_2$), 7.28—8.22 (11H, m, ArH); MS, *m/z* (relative intensity), 322 ($M^+$, 46), 186 (98), 185 ($M^+$—$C_8H_9S$, 100), 171 (45), 153 (84), 152 (55), 150 (73), 149 (60). Found: C, 74.59; H, 5.40%. Calcd for $C_{20}H_{18}S_2$: C, 74.49; H, 5.63%.

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