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Thiation Reactions of Some Active Carbonyl Compounds with Sulfur Transfer Reagents

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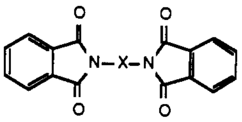
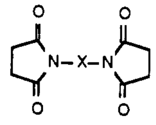
Anthrone reacts with the sulfur transfer reagents dithiobisphthalimide and dithiobissuccinimide in the presence of pyridine to provide a simple synthesis of monothioanthraquinone. Products of a different nature, derived from two molecules of ketone, were obtained from acenaphthenone and from a variety of β-diketones. A unified mechanism for the formation of all of the observed products, based upon the generation of transient thione intermediates, is proposed and supported by trapping experiments.

Thiobisphthalimide (1) and dithiobisphthalimide (2) have been investigated as sulfur transfer agents in reactions with a variety of thiols, alcohols, and amines.[1,2] The reaction of carbanions with reagents of this type does not appear to have been described.[3] We now report the results of a study of the action of a number of stabilized keto-carbanions on dithiobisphthalimide and, to a lesser extent, its alicylic analogue dithiobissuccinimide (3). We shall refer to reagents 2 and 3 as DBP and DBS, respectively.



1 X=S
2 X=S-S (DBP)

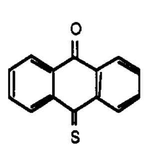


3 X=S-S (DBS)

Results

Reagent DBP is a high-melting, stable crystalline compound that has been prepared previously by the reaction of sulfur monochloride with potassium phthalimide in a petroleum ether suspension.[4] In our hands, this procedure gave erratic results. However, DBP (2) was readily available by the reaction of sulfur monochloride on dry, *recrystallized* phthalimide in tetrahydrofuran in the presence of triethylamine. The related succinimide reagent 3 was also easily available by the same procedure. It was previously synthesized only by more indirect routes.[5,6]

Monothioanthraquinone (4) has been synthesized only by the reaction of elemental sulfur with diazoanthrone in a hot DMF solution.[7] In the course of searching for an alternate route to this unusual thione, we found that it could be readily prepared by briefly warming a solution of anthrone and either DBP or DBS in dimethylformamide containing pyridine. The yield was only fair, but the pure product crystallized directly as olive-green needles on cooling the reaction mixture.



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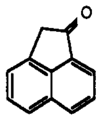

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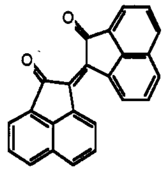

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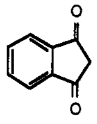

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The successful direct thiation of anthrone prompted us to try to extend this reaction to the synthesis of a number of unknown keto thiones. In none of these cases could we isolate a product of this type.

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(1) Harpp, D. N.; Back, T. G. *Tetrahedron Lett.* **1972**, 1481.

(2) Harpp, D. N.; Ash, D. K. *Int. J. Sulfur Chem.* **1971**, *57*, 211.

(3) For reactions of carbanions with monoimido sulfides, see: (a) Mukaiyama, T.; Kobayashi, S.; Kumamoto, T. *Tetrahedron Lett.* **1970**, 5115. (b) Grossert, J. S.; Dubey, P. K. *J. Chem. Soc., Chem. Commun.* **1982**, 1183.

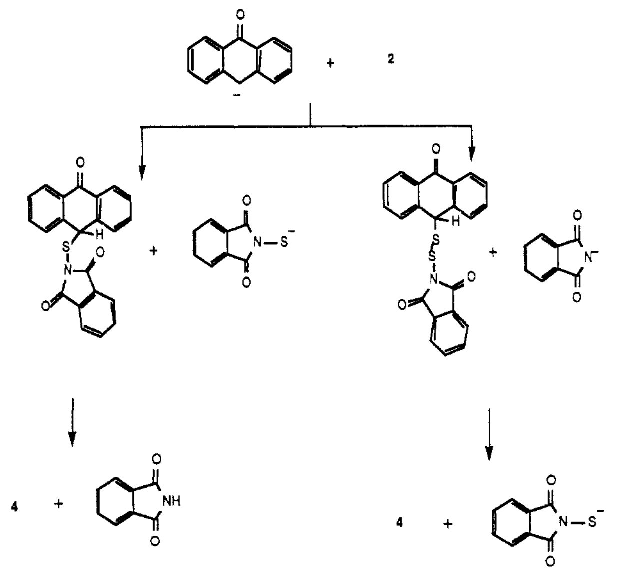
(4) Kalnins, M. V. *Can. J. Chem.* **1966**, *44*, 2111. See also ref 6 for an improved procedure.

(5) Haque, M.-U.; Behforouz, M. *J. Chem. Soc., Perkin Trans. 2* **1974**, 1459.

(6) Harpp, D. N.; Steliou, K.; Chan, T. H. *J. Am. Chem. Soc.* **1978**, *100*, 1222.

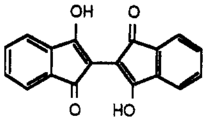
(7) Raasch, M. S. *J. Org. Chem.* **1979**, *44*, 632.

Scheme I



Acenaphthenone (**5**) reacted with DBP in DMF-pyridine to give bright orange needles, which were identified as biacenaphthylidenedione (**6**). Indan-1,3-dione (**7**) underwent a somewhat similar reaction to afford black crystals of the enolic coupling product **8**.

Products of a different type were obtained from several other cyclic β-diketones. Thus, cyclohexane-1,3-dione (**9**), 5,5-dimethylcyclohexane-1,3-dione (**10**), and dibenzo-β-tropolone (**11**) gave monosulfides (**12**, **13**, and **14**, respectively) derived from two molecules of the diketone.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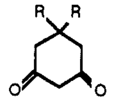
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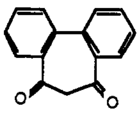
10 R=Me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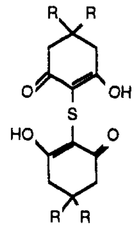
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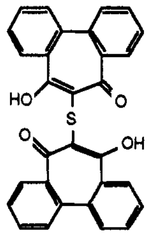
13 R=Me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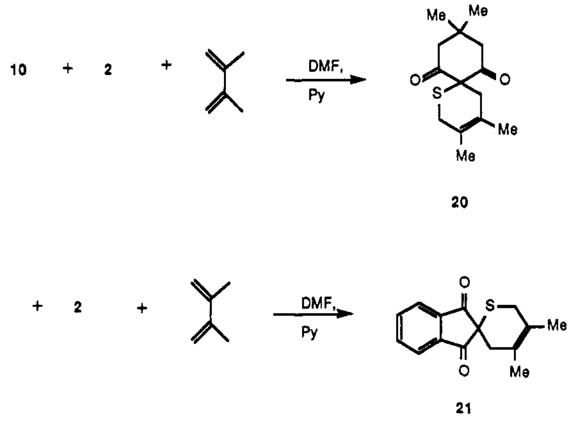
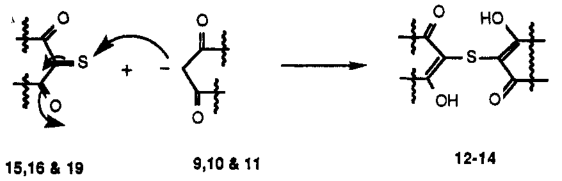
Discussion

The mechanism of the conversion of anthrone to monothioanthraquinone (**4**) clearly involves, as the first step, a nucleophilic attack of the anthrone anion on one of the sulfur atoms of the disulfide reagent, as shown in Scheme I. Ejection of an imidothiolate ion affords an intermediary imidosulfide, which then undergoes a facile base-catalyzed imide elimination to give the observed thione. The initial nucleophilic attack on the reagent may, of course, alternatively result in N-S cleavage with the formation of an imido disulfide intermediate that could equally well afford the thione **4** (Scheme I). We believe that other ketones which we have studied also afford the corresponding thiones (**15**-**19**), but that these thiones are too reactive to survive the reaction conditions and are converted to secondary products.

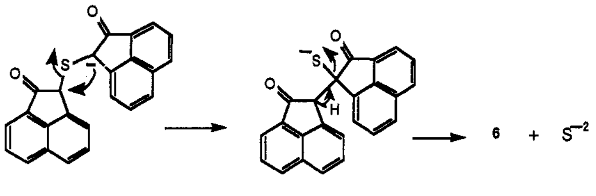
Scheme II



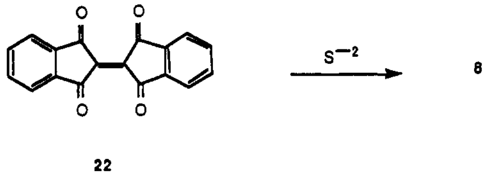
Scheme III



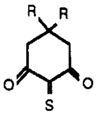
Scheme IV



Scheme V



Since monothioanthraquinone is known to readily afford a 4 + 2 adduct with 2,3-dimethylbutadiene,[6] we carried out the reaction of several of the substrate ketones with the thiation reagent in the presence of this diene. Indeed, the diketo thione intermediates **16** and **17** could be trapped, albeit with only modest efficiency, to give the corresponding stable crystalline adducts **20** and **21**, as shown in Scheme II.[8]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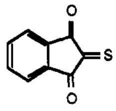
16 R=Me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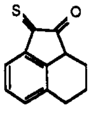
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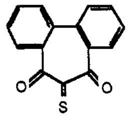
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The elusive thione intermediates **15**-**19** are apparently efficiently scavenged as they are produced, by a reaction involving a thiophilic attack by the anion of the precursor ketone, as shown in Scheme III. Enolization of both

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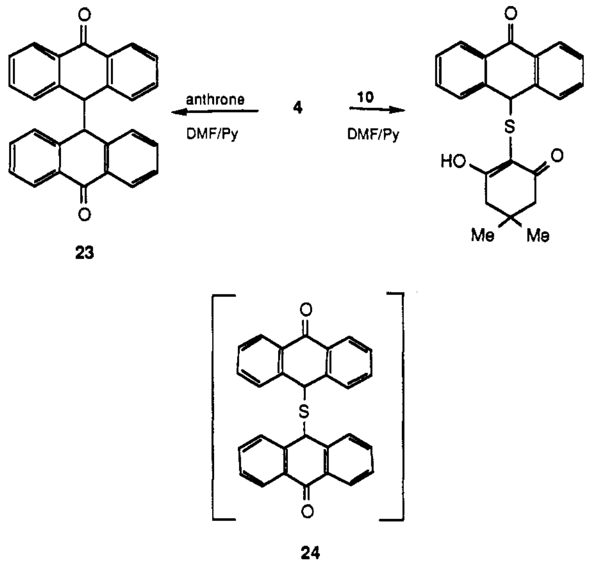
[8] The presence of sp^2 carbons in both the dimedone and the dihydrothiopyran moieties of adduct **20** coupled with its spiro nature appears to confer a high degree of conformational rigidity to the molecule; molecular models indicate that in the pseudochair conformation the -CH$_2$ protons in the dimedone moiety experience different magnetic environments due to the anisotropy of the C=O group leading to the observed chemical shifts at 3.34 and 2.28, (J_{gem} = 13.57 and 12.83 Hz, respectively).

Scheme VI

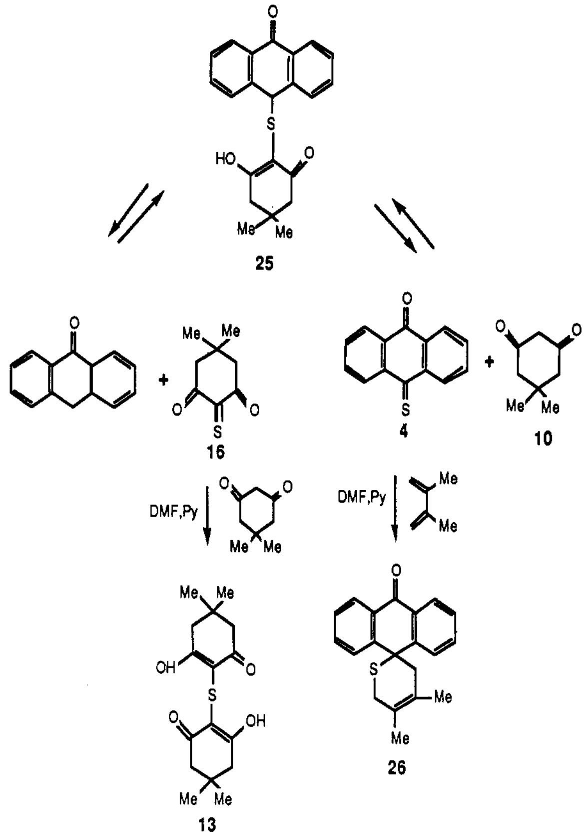


diketonic moieties results in the formation of the stable sulfide products **12–14**. If a sulfide formed in this way is largely or even appreciably ketonized in the reaction medium, intramolecular elimination of sulfide ion may occur, as illustrated in Scheme IV. This process would explain the formation of the unsaturated dione **6** from acenaphthenone. In the case of indane-1,3-dione, the expected enetetraone **22** is apparently reduced in situ by the sulfide ion liberated in the elimination step. (Scheme V).

The yield of monothioanthraquinone from anthrone never exceeded 55% under a variety of experimental conditions. In the course of attempts to maximize the yield of this compound, we found that like the transient thiones **15–19**, it is susceptible to thiophilic attack by a carbanion. The major byproduct in the preparation of thioquinone **4** proved to be bianthrone (**23**) and, indeed, bianthrone was obtained when **4** was warmed with anthrone in a DMF–pyridine mixture until the green color of the thione disappeared. Under similar conditions, but in the absence of added anthrone, thione **4** was recovered unchanged. The presumed precursor of bianthrone is dianthronyl sulfide (**24**). Although it was not possible to isolate this compound, indirect evidence for its intermediacy was obtained by the facile reaction of **4** with dimedone in the presence of pyridine to give the mixed anthrone–dimedone sulfide **25** (Scheme VI).

Sulfide **25** was quite labile in the presence of a base catalyst; on warming its solution in methanol containing a little pyridine, the green color of thione **4** soon became evident. Base-catalyzed cleavage of sulfide **25** could conceivably give not only its experimental precursors (**4** and dimedone) but also the product pair anthrone and thione intermediate **16**. In order to obtain evidence for the preferred cleavage pathway, **25** was decomposed by warming in DMF containing dimedone, pyridine, and a large excess of 2,3-dimethylbutadiene. The diene served as a potential trap for thione **16**. This reaction afforded a good yield of the known adduct **26** of monothioanthraquinone; products derived from thione **16** were not detected. When the decomposition of **25** was carried out in the same way, but in the absence of dimethylbutadiene, the major reaction product was the sulfide **13**, derived from dimedone and its thiono derivative **16**; anthrone as well as bianthrone were also isolated. These observations indicate that the base-catalyzed cleavage of the mixed sulfide **25** preferentially regenerates monothioanthraquinone and dimedone, as indicated by the experiment in which the thione was trapped as generated by the diene. In the absence of a diene, however, these cleavage products will be in equilibrium with the mixed sulfide **25**, which can also cleave, albeit more slowly, to generate anthrone and the highly reactive diketo thione **16**. The latter thione can, of course, react with the anthrone anion to regenerate sulfide **25**, but it can also be trapped *irreversibly* by the added dimedone anion to give the bisdimedone sulfide **13** (Scheme VII).

Scheme VII



Experimental Section

General. All melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. Elemental analyses were carried out by Atlantic Microlabs, Atlanta. Infrared, ultraviolet, NMR, and mass spectra were determined on Perkin-Elmer 781, Perkin-Elmer λ4, Nicolet NB-200, and Finnigan spectrometers, respectively. All chemical shifts ($CDCl_3$) are reported in δ values downfield from Me_4Si.

Dithiobisphthalimide (2). To a cooled mixture (ice bath) of recrystallized phthalimide (29 g) and triethylamine (27 mL) in THF dried over molecular sieves (200 mL) was added a solution of sulfur monochloride (Aldrich; 8 mL) in portions with vigorous swirling. The mixture was allowed to stand 45 min. Cold water (700 mL) was added. The white precipitate was filtered, washed with more water, and dried (rubber dam) under suction. The precipitate was stirred with ether, filtered, and dried (31 g). Recrystallization from chloroform–methanol (300 mL:125 mL) gave pure **2** as heavy prisms (20 g, 56.3%): mp 225 °C (lit.[4] mp 226–229 °C). From the mother liquor of crystallization a second crop (4 g) could be obtained.

Dithiobissuccinimide (3). To a mixture of succinimide (19.85) and triethylamine (20.2 g) in dry THF (250 mL) was added sulfur monochloride (8 mL) at room temperature. After being stirred 1 h at room temperature, the mixture was refluxed for 1 h. The cooled THF solution was filtered free of $Et_3N\cdot HCl$. The solvent was removed in vacuo; the residual white solid was washed with *ice-cold* water, filtered, and dried. (Note: Imido sulfide **3** is very sensitive to water and this operation has to be carried out very quickly.) The dried material from two batches was crystallized from CH_2Cl_2–hexane to give **3** (15 g; 57.7%) as white crystals: mp 187–190 °C (lit.[6] mp 189–190 °C).

Monothioanthraquinone (4). (i) A mixture of anthrone (6 g) and imido disulfide 2 (10.5 g) in *N,N'*-dimethylacetamide (100 mL) (or DMF) was warmed to effect dissolution. Pyridine (dried over sieves; 6 mL) was added and the solution was heated with stirring for *15 min* on a hot plate (temperature of mixture was 80 °C). Upon cooling green crystals of 4 separated. These were filtered and washed with methanol and dried (2.6 g; 37.5%): mp 209 °C (lit.[1] mp 214 °C). It was pure as determined by MS and NMR spectroscopy. (ii) A mixture of anthrone (0.97 g), imido disulfide 3 (0.13 g), and pyridine (0.1 g) in dry DMF (8 mL) was heated at 60–70 °C (internal temperature) for 15 min. The dark green solution upon cooling gave thioanthraquinone (4) (0.87 g). Recrystallization from $CHCl_3$ yielded pure product (0.61 g; 54.5%).

Biacenaphthylidenedione (6). A mixture of acenaphthenone (0.42 g), dithiophthalimide 2 (0.89 g), and pyridine (0.2 g) in DMF (10 mL) was heated at 80–90 °C for 45 min. The mixture turned deep orange and orange crystals separated. These were filtered (0.18 g). Recrystallization from DMF gave pure 6 (0.17 g; 41%): mp >250 °C dec, identical with an authentic sample (mp, IR spectrum, and mass spectrum).[9]

Tetraketone Monosulfide 12. A mixture of 1,3-cyclohexanedione (0.45 g), imido sulfide 2 (1.42 g), and pyridine (0.1 g) in dry DMF (10 mL) was heated at 90 °C for 3 h. The solvent was removed. The residue was stirred with CH_2Cl_2, freed from phthalimide, and evaporated. Chromatography of the reaction product (SiO_2/3:1 hexane:EtOAc) yielded as the major product, sulfide 12 as a white crystalline solid. Recrystallization from THF–hexane gave white crystals (0.33 g; 64%): mp 138–142 °C; infrared spectrum (KBr) 1615 cm^{-1}; NMR spectrum 1.94 (quintet, J = 6.03 Hz, 4 H), 2.52 (t, J = 6.03 Hz, 8 H), 4.67 (br s, 2 H, OH); mass spectrum, m/e (relative intensity) 256 ($M^+ + 2$, 11.3), 255 ($M^+ + 1$, 23.9), 254 (M^+, 98.9), 144 ($M^+ - 110$, 100), 112 ($M^+ - 142$, 31); UV spectrum (MeOH) λ_{max} 249 nm (ϵ 22 525). Anal. Calcd for $C_{12}H_{14}O_4S$: C, 56.69; H, 5.51; S, 12.60. Found: C, 56.76; H, 5.58; S, 12.53.

Tetraketone Monosulfide 13. The reaction was carried out as described above using dimedone (0.28 g), 2 (0.356 g), and pyridine (0.1 g) in DMF (5 mL). At the end of 3 h at 80–90 °C, the product (13) crystallized from the clear solution. It was filtered and washed with hexane to give white needles (0.245; 76.9%): mp 227–230 °C (lit.[10] mp 224–230 °C); mass spectrum, m/e (relative intensity) 310 (M^+, 53.9), 172 (26.7), 83 (100); ultraviolet spectrum (MeOH) λ_{max} 255 nm (ϵ 15 310).

Thiobis(dibenzo-β-tropolone) (14). Dibenzo-β-tropolone (0.44 g), disulfide 2 (0.356 g), and pyridine (0.15 g) in dry DMF (5 mL) were heated for 1 h on the steam bath. The light yellow reaction mixture was diluted with water (30 mL). The precipitate was filtered and washed with methanol. The insoluble pale yellow residue was crystallized from DMF to give 14 (0.31 g, 65.4%): mp 268–270 °C; infrared spectrum (KBr) 1605, 1590 cm^{-1}; NMR spectrum 7.43–8.20 (m, Ar), 12.7 (br s, OH); mass spectrum, m/e (relative intensity) 474 (M^+, 7.0), 222 (49), 180 (100); UV spectrum ($CHCl_3$) λ_{max} 255 nm (ϵ 21 250), 270 (21 975). Anal. Calcd for $C_{30}H_{18}O_4S$: C, 75.95; H, 3.80; S, 6.75. Found: C, 75.89; H, 3.85; S, 7.17.

Enolic Coupling Product from Indandione (8). A mixture of 1,3-indandione (150 mg) and imido disulfide 2 (200 mg) in DMF (4 mL) at room temperature was treated with pyridine (1 mL) in portions. Initially a bright purple-red color appeared and was quickly replaced by a dull brown color. At this stage, the mixture was heated on the steam bath for 20 min when long black needles of the coupled product 8 separated. This was separated, washed with ether, and dried (0.07 g; 47%), mp >250 °C dec. It was identical (mp, IR spectrum, TLC, and mass spectrum) with an authentic sample.[11]

2,3-Dimethylbutadiene Adduct of Diketo Thione 16 (20). A mixture of dimedone (10; 0.84 g), imido disulfide 3 (0.78 g), 2,3-dimethylbutadiene (1 mL), and pyridine (0.15 g) in dry DMF (5 mL) was heated at 60 °C for 3 h. After cooling, the insoluble white precipitate (identified to be recovered dimedone; 0.29 g) was filtered, and the filtrate was diluted with water (40 mL). The pale yellow precipitate (0.32 g) was separated, washed, and dried; chromatography (SiO_2/2:1 hexane:EtOAc followed by 10:1 CH_2Cl_2/hexane) yielded tetraketo sulfide 13 (0.18 g) and the adduct 20, which after crystallization from CH_2Cl_2–hexane formed white leaflets; mp 96–99 °C (5.3%). When the above reaction was carried out at 45–50 °C for 12 h, the yield of adduct 20 rose to 0.15 g (10%): infrared spectrum (KBr) 1725, 1700 cm^{-1}; NMR spectrum 0.80 (s, 3 H), 1.16 (s, 3 H), 1.71 (s, 3 H), 1.78 (s, 3 H), 2.28 (d, J = 13.57 Hz, 2 H), 2.49 (s, 2 H), 2.97 (s, 2 H) and 3.34 (d, J = 12.83 Hz, 2 H); mass spectrum, m/e (relative intensity) 254 ($M^+ + 2$, 5.3), 253 ($M^+ + 1$, 14.2), 252 (M^+, 77.0), 237 (38.9), 205 (27) 83 (100). Anal. Calcd for $C_{14}H_{20}O_2S$: C, 66.67; H, 7.94; S, 12.70. Found: C, 66.73; H, 8.00; S, 12.68.

2,3-Dimethylbutadiene Adduct of Diketo Thione 17 (21). Indandione (7; 0.29 g), imido disulfide 3 (0.26 g), and 2,3-dimethylbutadiene (0.82 g) were stirred in DMF (4 mL) containing pyridine (0.15 g) for 12 h. Dilution of the reaction mixture followed by filtration and crystallization from CH_2Cl_2–hexane yielded 0.15 g of yellow crystals. Chromatography of this material (SiO_2/2:1 hexane:EtOAc) gave light yellow crystals of 21: mp 144–145 °C; infrared spectrum (KBr) 1728 cm^{-1}; NMR spectrum 1.78 (s, 3 H), 1.85 (s, 3 H), 2.51 (s, 2 H), 3.28 (s, 2 H), 7.81–8.00 (m, 4 H); mass spectrum, m/e (relative intensity) 260 ($M^+ + 2$, 7.7), 259 ($M^+ + 1$, 20.6), 258 (M^+, 89.7), 225 (100), 104 (91.6). Anal. Calcd for $C_{15}H_{14}O_2S$: C, 69.71; H, 5.43; S, 12.40; Found: C, 69.82; H, 5.46; S, 12.45.

Under the same reaction conditions, but in the absence of the diene, the coupled product 8 was isolated in 48.3% yield.

Bianthrone (23). A mixture of thioquinone 4 (0.1 g), anthrone (0.1 g), and pyridine (0.1 g) in DMF (5 mL) was heated on the steam bath for 0.5 h. The reaction mixture was cooled in ice, and the yellow crystals that separated were filtered, washed with water, and dried (0.14 g). Several recrystallizations yielded 23 as white crystals (0.1 g): mp 268 °C dec; infrared spectrum (KBr) 1600, 1468, 1320, 935, 790, and 700 cm^{-1}; NMR spectrum 4.78 (s, 2 H), 6.87 (m, 4 H), 7.43 (m, 8 H), and 7.95 (m, 4 H). Anal. Calcd for $C_{28}H_{18}O_2$: C, 87.04; H, 4.66. Found: C, 87.01; H, 4.71.

Anthrone–Dimedone Sulfide 25. A mixture of thioquinone 4 (0.22 g), dimedone (10, 0.21 g), and pyridine (0.1 mL) in $CHCl_3$ (10 mL) was stirred at room temperature for 1 h. The resulting pale yellow solution was concentrated in vacuo; the residue was washed with cold methanol (1 mL). Mixed sulfide 25 remained on the filter (0.26 g; 72%) and was crystallized from CH_2Cl_2 to yield pale yellow crystals: mp 139–141 °C; infrared spectrum (KBr) 1655, 1570 cm^{-1}; NMR spectrum 0.99 (s, 6 H) 2.20 (s, 4 H), 5.50 (s, 1 H), 6.86 (br s, 1 H), 7.34–7.72 (m, 6 H), and 8.18 (d, J = 6.4 Hz, 2 H). Anal. Calcd for $C_{22}H_{20}O_3S$: C, 72.53; H, 5.49; S, 8.79. Found: C, 72.42; H, 5.56; S, 8.74.

Base-Catalyzed Cleavage of Sulfide 25. (i) In the Presence of 10 and 2,3-Dimethylbutadiene. A mixture of mixed sulfide 25 (0.12 g), dimedone (10, 0.069 g), and pyridine (0.04 g) in DMF (2 mL) was treated with 2,3-dimethylbutadiene (0.27 g) at room temperature. The cloudy mixture was warmed at 50–60 °C for 13 h. The volatiles were removed in vacuo and the residue (0.18 g) was washed with aqueous sodium hydroxide (5 mL; 5%). The insoluble pale yellow solid (0.07 g; 69%), mp 137–140 °C, was identical with an authentic sample of adduct 26 by mp, TLC, and NMR spectrum.[6]

(ii) In the Presence of Dimedone Alone. A solution of mixed sulfide 25 (0.12 g), dimedone (10, 0.069 g), and pyridine (0.05 g) in DMF (1.5 mL) was heated on the steam bath for 0.5 h. Upon cooling the mixture, thiobisdimedone 13 (0.083 g; 81%) separated. From the filtrate, by evaporation and chromatographic workup anthrone (0.04 g, 62.5%) and bianthrone (23, 0.018 g, 25.8%) was obtained.

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