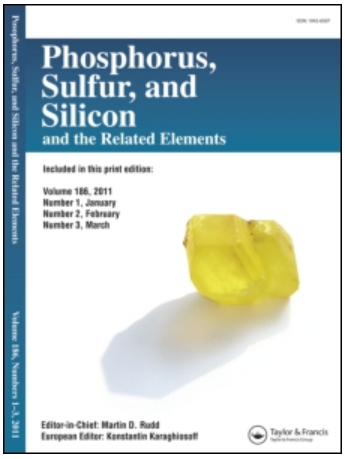

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S-(HYDROXYMETHYL) 4-HYDROXYPHENYL SULFIDES: SYNTHESIS AND SELECTED CHEMISTRY OF SOME STABLE HEMIMERCAPTALS

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S-(HYDROXYMETHYL) 4-HYDROXYPHENYL SULFIDES: SYNTHESIS AND SELECTED CHEMISTRY OF SOME STABLE HEMIMERCAPTALS

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The base-catalyzed reaction of 3,5-di-*tert*-butyl-4-hydroxybenzenethiol (**1a**), 3-*tert*-butyl-4-hydroxy-5-methylbenzenethiol (**1b**), and 4-hydroxybenzenethiol (**1c**) with formaldehyde gave the corresponding hemimercaptal derivatives **2a–c**, respectively. The stable hemimercaptals **2a–c** were characterized by IR, ^{1}H NMR, ^{13}C NMR, MS and elemental analysis. The ester of **2a** with 3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propanoic acid (**3a**) was prepared using triphenylphosphine and diethyl azodicarboxylate (Mitsunobu conditions).

The reversibility of the addition of thiols to aldehydes to form hemimercaptals is well known in the literature.[1] In certain cases the resultant hemimercaptals have been isolated. As early as 1870, for example, Martius and Mendelssohn-Bartholody reported the isolation of stable hemimercaptals from the reaction of chloral with thiols.[2] Interestingly, Levi reported the isolation of some stable hemimercaptals from the reaction of both alkanethiols and arenethiols with formaldehyde.[3] Later Poppelsdorf and Holt described the reaction of these hemimercaptals with activated methylene groups under acidic conditions in a formal sulfur analogue of the Mannich reaction.[4] Except for the IR spectral evidence of Field *et al.*,[5] however, no spectral characterization of stable hemimercaptals has been reported despite their paramount importance in synthetic and mechanistic chemistry as proposed intermediates in the formation of mercaptals.[6] We report herein the isolation and chemistry of some stable hemimercaptals.

RESULTS AND DISCUSSION

The reaction of **1a** with formaldehyde (37% aqueous solution) using a catalytic amount of potassium hydroxide in a methyl alcohol reaction medium gave the hemimercaptal **2a** (69% recrystallized) in a mildly exothermic reaction. The examination of the ^{1}H NMR and TLC of the crude reaction product indicated that the yield of **2a** was essentially quantitative.

The structure of **2a** is based upon the following observations. The ^{1}H NMR spectrum (200 MHz) of **2a** showed a doublet resonance at δ 4.91, whose peak area

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integrated to two protons, which was assigned to the protons of the methylene carbon coupled to the hydroxyl proton with $^3J_{HCOH} = 6$ Hz. Similarly, in the ^{13}C NMR spectrum a resonance was observed at δ 67.9 which was assigned to the methylene carbon atom.

The observation of $^3J_{HCOH}$ coupling between the protons of the methylene carbon atom and the hydroxyl proton in the ^1H NMR spectrum of **2a** clearly indicates that **2a** is *not* in rapid equilibrium with **1a** and formaldehyde. This must be the case since rapid equilibration would result in the loss of the observed coupling.[7,8] Specifically, coupling is lost in an exchanging system when $1/\mathrm{Te} > J$, where Te is the lifetime at a particular site and J is the coupling constant in Hertz.

In the IR spectrum of **2a** absorptions were observed at 3635 and 3585 cm^{-1} assignable to free (non-hydrogen bonded) hydroxyl stretching vibrations. The presence of two distinct free hydroxyl absorbances (3635 and 3585 cm^{-1}, respectively) in the IR spectrum of **2a** and two distinct resonances at δ 2.01 and δ 5.29 in the ^1H NMR spectrum is consistent with the suggestion that **2a** is not in rapid equilibration with **1a** and formaldehyde.

The MS of **2a** displayed a molecular ion at m/z 268. Both the spectral and elemental analyses were fully in accord with structure **2a**.

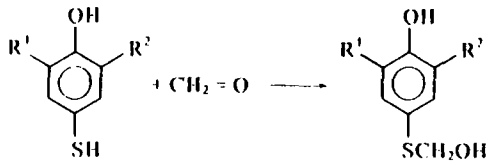
In an analogous manner, the reaction of **1b** and **1c** with formaldehyde gave the hemimercaptals **2b** and **2c**, respectively. The spectral and elemental analysis of both **2b** and **2c** were fully in accord with the hemimercaptal structure. In the ^1H NMR spectrum (200 MHz) of **2b**, $^3J_{HCOH}$ coupling of the methylene carbon protons was observed. In a decoupling experiment, irradiation of the triplet hydroxyl resonance at δ 2.49 led to the collapse of the doublet at δ 4.91 assigned to the methylene protons. As in the case of **2a**, the observation of coupling demonstrates that **2b** is not in rapid equilibration with **1b** and formaldehyde.

In the case of **2c**, no information could be obtained as to whether this hemimercaptal was in rapid equilibration with thiol and formaldehyde due to extensive hydrogen bonding of the hydroxyl protons. Hydrogen bonding, which of course leads to rapid exchange of the hydroxyl protons, necessarily results in the loss of coupling between the hydroxyl proton and the protons of the methylene carbon atom. The similarity of the chemical shifts of the methylene carbon atoms in the ^{13}C NMR spectra of **2a–c**, 69.7, 69.7 and 69.3, respectively, suggests, however, that **2c** is not in rapid equilibrium with **1c** and formaldehyde.

Further structural proof of **2a** was provided by the conversion of **2a** to the ester **4**. Previously, esters of hemimercaptals were prepared by indirect methods, for example, either by a Pummerer rearrangement[9] or by the reaction of an alkanethiolate anion with chloromethyl acetate.[10]

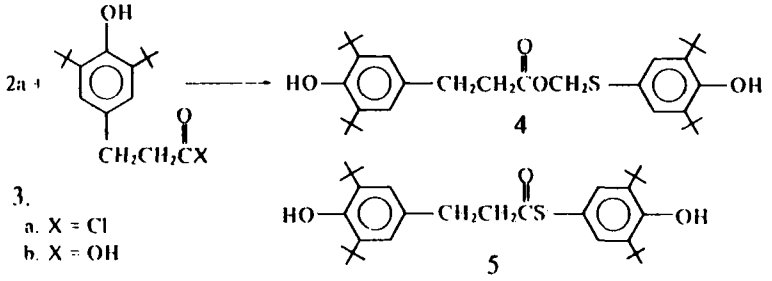
The reaction of the acid chloride **3a** with **2a** using triethylamine as an acid acceptor gave products **4** and **5** in a ratio of 1:2. Presumably the formation of **5** was due to deformylation of **2a** prior to reaction with **3a**. A reasonable explanation of this observation is that **2a** underwent base catalyzed equilibration with **1a** and formaldehyde in the presence of triethylamine. The observed product ratios do *not* necessarily provide, however, any information regarding the position of the equilibrium (Curtin-Hammett Principle).[11]

The reaction of **2a** with **3b** under Mitsunobu conditions (triphenylphosphine: diethyl azodicarboxylate)[12] gave a high yield of **4** (77% chromatographed). The



1.
a. $R^1 = R^2$ = tert-Butyl
b. R^1 = tert-Butyl; R^2 = Methyl
c. $R^1 = R^2 = H$

2.
a. $R^1 = R^2$ = tert-Butyl
b. R^1 = tert-Butyl; R^2 = Methyl
c. $R^1 = R^2 = H$



3.
a. X = Cl
b. X = OH

examination of the crude reaction product prior to flash chromatography by TLC and IR indicated that **4** was the exclusive product under *nonbasic* reaction conditions. Consistent with the proposed structure, a singlet was observed in the ^1H NMR spectrum of **4** at δ 5.32, whose peak area integrated to two protons, which was assigned to the protons of the methylene carbon atom bonded to both sulfur and oxygen.

EXPERIMENTAL

All melting points were determined in open capillary tubes with a Thomas-Hoover melting point apparatus and are uncorrected. ^1H NMR spectra were taken on a Varian Model CFT-20 or XL-200 spectrometer. All ^{13}C and ^1H chemical shifts are reported relative to tetramethylsilane, where a positive sign is downfield from the standard. IR spectra (1% solution; sodium chloride cells) were recorded on a Perkin-Elmer Model 1300 spectrometer. Mass spectra were obtained on a Finnegan Model 8200 mass spectrometer. Merck 9385 silica gel-60 (230-400 mesh) was used for flash chromatography.[13] All solvents were dried prior to use. Reagents were purchased from Aldrich Chemical Company.

4-Hydroxybenzenethiol was purchased from Polysciences, Inc., Warrington, PA. Reactions were carried out in flame-dried apparatus under a dry-nitrogen atmosphere. Elemental analyses were performed by Analytical Research Services, CIBA-GEIGY Corporation.

3,5-Di-tert-Butyl-4-Hydroxybenzenethiol, (**1a**). To a mixture of 140 g (0.295 mol) of bis(3,5-di-*tert*-butyl-4-hydroxylphenyl) disulfide,[14] 250 mL of ethyl alcohol, 500 mL of toluene, and 1870 mL of 3M hydrochloric acid was added in portions 225.6 g (3.45 mol) of zinc dust. The reaction mixture was stirred at room temperature until disappearance of starting disulfide as determined by TLC. The organic phase was separated and it was washed twice with deoxygenated water. The organic phase was dried over anhydrous sodium sulfate and then the solvent was removed *in vacuo* to give 117.6 g (84%) of a white solid: mp 85–87°C;[15] IR (CCl_4) ν 3650 (OH), 2560 (SH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.48 (s, $(CH_3)_3C$, 18 H), 3.43 (s, SH, 1 H), 5.21 (s, OH, 1 H) 7.27 (s, ArH, 2 H). Anal. Calcd. for $C_{14}H_{22}OS$: C, 70.5; H, 9.3. Found: C, 70.5; H, 9.6.

2-tert-Butyl-6-Methyl-4-Thiocyanatophenol. The methodology of Mueller *et al.*[16] was followed using 164.2 g (1.0 mol) of 6-*tert*-butyl-2-methylphenol, 250 g (2.58 mol) of potassium thiocyanate, and 175 g (1.1 mol)

of elemental bromine in 1 L of methyl alcohol. The reaction mixture was poured into 7 L of water and the resultant solid was collected by filtration. The crude product was recrystallized from hexane to give 179 g (81%) of a pale yellow solid: mp 81–84°C (lit[17] 85–87°C); IR (CH_2Cl_2) ν 3600, 3440 (OH), 2160 (SCN) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.41 (s, $(CH_3)_3C$, 9 H), 2.27 (s, CH_3, 3 H) 5.35 (s, OH, 1 H), 7.25 (d, ArH, 1 H), 7.33 (d, ArH, 1 H). Anal. Calcd. for $C_{12}H_{15}NOS$: C, 65.1; H, 6.8. Found: C, 64.8; H, 6.8.

3-tert-Butyl-4-Hydroxy-5-Methylbenzenethiol, (**1b**). To a solution of 243.5 g (6.1 mol) of sodium hydroxide in 1.2 L of deoxygenated distilled water was added 177 g (0.8 mol) of 2-*tert*-butyl-6-methyl-4-thiocyanatophenol. The reaction mixture was heated to 60–65°C and the resultant turbid red-brown reaction mixture was stirred at this temperature for 75 minutes. To the cooled reaction mixture was added 720 g of 50% aqueous sulfuric acid maintaining the reaction temperature between 0–5°C. The reaction mixture was partitioned between 1 L of toluene and water. The organic phase was washed twice with water and it was dried over anhydrous sodium sulfate. The solvent was removed *in vacuo* and the residue was added to a mixture of 850 mL of toluene, 322 mL of ethyl alcohol and 1.72 L of 3M hydrochloric acid in a 5 L Morton flask. To the rapidly stirred mixture was slowly added 43.0 g (0.66 mol) of zinc dust. The reaction mixture was stirred at room temperature for 50 h. The organic phase was separated and was washed with water. The organic phase was dried over anhydrous sodium sulfate and the solvent was removed *in vacuo*. The residue was distilled to give 109.6 g (70%) of a liquid which crystallized upon standing: bp 92–95°C, 0.06 mm (lit 134–135°C,[15b] 5 mm); mp 38–41°C; IR (CH_2Cl_2) ν 3600 (OH), 2570 (SH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.46 (s, $(CH_3)_3C$, 9 H) 2.27 (s, CH_3, 3 H), 3.40 (s, SH, 1 H), 4.71 (s, OH, 1 H), 7.02 (d, ArH, 1 H) 7.14 (d, ArH, 1 H). Anal. Calcd. for $C_{11}H_{16}OS$: C, 67.3; H, 8.2. Found: C, 66.9; H, 8.4

3,5-Di-tert-Butyl-4-Hydroxyphenyl S-(Hydroxymethyl) Sulfide, (**2a**). To a solution of 47.67 g (200 mmol) of **1a** and 16.23 g (200 mmol) of 37% aqueous formaldehyde in 150 mL of methyl alcohol was added dropwise a 0.1 M methanolic potassium hydroxide solution. After the addition of 5 mL of the methanolic potassium hydroxide solution, a mild exotherm was observed. The solvent was removed *in vacuo* and the residue was triturated with heptane to give 37.0 g (69%) of a white solid. The analytical sample was prepared by recrystallization from petroleum ether: mp 79–82°C; IR (CH_2Cl_2) ν 3635, 3585 (OH) cm^{-1}; ^1H NMR ($CDCl_3$) (200 MHz) δ 1.43 (s, $(CH_3)_3C$, 18 H), 2.01 (t, OH, $^3J_{HOCH}$ = 6 Hz, 1 H), 4.91 (d, CH_2, $^3J_{HCOH}$ = 6 Hz, 2 H), 5.29 (s, OH, 1 H), 7.35 (s, ArH, 2H); ^{13}C NMR ($CDCl_3$) δ 29.3 (s), 33.7 (s), 69.7 (s, SCH_2O), 123.3 (s), 130.1 (s), 137.3 (s), 154.5 (s); MS m/z 268 (M^+). Anal. Calcd. for $C_{15}H_{24}O_2S$: C, 67.1; H, 9.0; S, 11.9. Found: C, 66.8; H, 8.6; S, 11.6.

3-tert-Butyl-4-Hydroxy-5-Methylphenyl S-(Hydroxymethyl) Sulfide, (**2b**). By the procedure used to prepare compound **2a**, compound **2b** was prepared from 23.56 g (120 mmol) of **1b**, 9.73 g (120 mmol) of 37% aqueous formaldehyde, and 1 mL (0.1 mmol) of 0.1 M methanolic potassium hydroxide. The residue was triturated with hot petroleum ether to give 26.59 g (98%) of a white solid.

The analytical sample was prepared by recrystallization from a mixture of toluene and heptane: mp 61–73°C; IR (CH_2Cl_2) ν 3600 (OH) cm^{-1}; ^1H NMR ($CDCl_3$) (200 MHz) δ 1.43 (s, $C(CH_3)_3$, 9 H), 2.23 (s, CH_3, 3 H), 2.49 (t, OH, 1 H), 4.91 (d, CH_2, 2 H), 5.11 (s, OH, 1 H), 7.23 (d, ArH, 1 H), 7.33 (d, ArH, 1 H); ^{13}C NMR ($CDCl_3$) δ 15.3 (s), 28.9 (s), 34.1 (s), 69.7 (s, SCH_2O), 123.3 (s), 124.5 (s), 130.1 (s), 133.3 (s), 136.9 (s), 153.3 (s). Anal. Calcd. for $C_{12}H_{18}O_2S$: C, 63.7; H, 8.0; S, 14.2. Found: C, 63.6; H, 8.3; S, 14.2.

4-Hydroxyphenyl S-(Hydroxymethyl) Sulfide, (**2c**). By the procedure used to prepare compound **2a**, compound **2c** was prepared from 15.14 g (120 mmol) of 4-hydroxybenzenethiol, 9.73 g (120 mmol) of 37% aqueous formaldehyde, and 5 mL (0.5 mmol) of 1.0 M methanolic potassium hydroxide. The residue was triturated with a mixture of hot petroleum ether and toluene to give 17.9 g (95%) of a white solid: mp 85–89°C; IR (KBr Pellet) ν 3400 (OH) cm^{-1}; ^1H NMR (d_6-DMSO) δ 4.80 (s, CH_2, 2 H), 6.90 (AB q, ArH, 4 H); ^{13}C NMR (d_6-DMSO) δ 69.3 (s, SCH_2O), 116.9 (s), 124.9 (s), 134.1 (s), 158.1 (s). Anal. Calcd. for $C_7H_8O_2S$: C, 53.9; H, 5.2. Found: C, 53.5; H, 5.3.

3-(3,5-Di-tert-butyl-4-hydroxyphenyl)propanoic acid chloride, (**3a**). To a cooled solution of 13.9 g (0.05 mol) of **3b** in 75 mL of chloroform at 0–5°C was added dropwise 11.9 g (0.1 mol) of thionyl chloride. After the addition was complete, the reaction mixture was heated at 50°C. The progress of the reaction was monitored by IR spectroscopy. When the absorption in the IR spectrum due to the acid (1710 cm^{-1}) had completely disappeared, the entire reaction mixture was concentrated *in vacuo* to give 14.8 g (quantitative yield) of an off white solid:[18] m.p. 66–69°C; IR ($CHCl_3$) ν 1790 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.46 (s, 18 H), 3.04 (m, 4 H), 5.12 (s, 1 H), 6.94 (s, 2 H).

Reaction of **2a** *with* **3a**. To a solution of 13.4 g (50 mmol) of **2a** and 5.1 g (50 mmol) of triethylamine in 50 mL of toluene at −10°C was added dropwise a solution of 14.8 g (50 mmol) of **3a** in 50 mL of

toluene. After the addition was complete, the reaction mixture was allowed to warm to room temperature and was stirred until the reaction was complete as determined by the disappearance of the acid chloride carbonyl absorption in the IR spectrum. (c. 30 min). After the precipitated triethylamine hydrochloride was removed by filtration, the solvent was removed *in vacuo* and the residue was purified by flash chromatography (toluene/heptane eluent) to give two major components.[19]

The lower R_f component was recrystallized from petroleum ether to give 1.6 g (6%) of a white solid **4**: mp 102–104°C; IR (CCl_4) ν 3640 (OH), 1740 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.44 (s, $(CH_3)_3$, 36 H), 2.78 (m, 4 H), 5.04 (s, OH, 1 H), 5.16 (s, OH, 1 H), 5.32 (s, SCH_2O, 2 H), 6.96 (s, ArH, 2 H), 7.30 (s, ArH, 2 H). Anal. Calcd. for $C_{32}H_{48}O_4S$: C, 72.7; H, 9.1; S, 6.1. Found: C, 72.7; H, 9.5; S, 6.3.

The higher R_f component was recrystallized from acetonitrile to give 5.1 g (20%) of a white solid **5**: mp 165–168°C; IR (CCl_4) ν 3640 (OH), 1705 (C=O) cm^{-1}; ^1H NMR (C_6D_6) δ 1.31 (s, $(CH_3)_3C$, 18 H), 1.39 (s, $(CH_3)_3$ 18 H), 2.85 (d, CH_2, $^3J_{HCCH}$ = 7 Hz, 2 H), 2.93 (d, CH_2, $^3J_{HCCH}$ = 7 Hz, 2 H), 4.83 (s, OH, 1 H), 5.07 (s, OH, 1 H) 7.02 (s, ArH, 2 H), 7.44 (s, ArH, 2 H). Anal. Calcd. for $C_{31}H_{46}O_3S$: C, 74.7; H, 9.3; S, 6.4. Found: C, 74.7; 9.6; S, 6.5.

3-(3,5-Di-tert-Butyl-4-Hydroxyphenyl)propanoic acid, l-(3,5-Di-tert-butyl-4-Hydroxyphenylthio)methyl ester, (**4**). To a solution of 2.68 g (10 mmol) of **2a**, 2.78 g (10 mmol) of **3b**, and 2.62 g (10 mmol) of triphenylphosphine in 25 mL of tetrahydrofuran was added a solution of 1.74 g (10 mmol) of diethyl azodicarboxylate in 5 mL of tetrahydrofuran. The reaction mixture was stirred until the disappearance of **3b** as determined by TLC. The reaction mixture was filtered and the solvent was removed *in vacuo*. The residue was purified by flash chromatography (toluene:heptane eluent) to give 4.1 g (77%) of **4** identical in every respect to that prepared by the reaction of **3a** with **2a**.

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