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 α,β -Unsaturated Sulfides. The Reaction of Thiophenol with Certain Ketones¹BY E. CAMPAIGNE AND JOSEPH R. LEAL²

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The reaction between thiophenol and certain ketones, under the conditions which would be expected to form mercaptals, has been found to yield unsaturated sulfides. Of the ketones investigated, 5,5-dimethyl-1,3-cyclohexanedione, propiophenone, desoxybenzoin and isobutyrophenone gave unsaturated sulfides, while acetophenone and ethyl benzoylacetate gave mercaptals. Pivalophenone did not react with thiophenol. Benzyl mercaptan and 2-methyl-1-indanone yielded benzyl 2-methyl-3-indenyl sulfide. A reaction mechanism is discussed.

Introduction

The reaction between a ketone and a thiol in the presence of an acid catalyst generally leads to the formation of a mercaptal,³ although scattered reports in the literature indicate that certain cyclic ketones yield unsaturated sulfides (enol thioethers) rather than the expected mercaptals. Thus 4-cholesten-3-one⁴ and other 3-ketosteroids unsaturated at position 4 are reported⁵ to give α,β -unsaturated sulfides when reacting with excess thiol in the presence of anhydrous sodium sulfate and zinc chloride. A similar behavior is claimed for 1,3-cyclohexanediones⁶ which form 3-alkylthio-2-cyclohexanones when treated with thiols in the presence of hydrogen chloride. Finally, it was observed⁷ that 2-methyl-1-indanone and 2-methyl-1-tetralone react with thiophenol under the conditions of the mercaptal reaction to produce phenyl 2-methyl-3-indenyl sulfide and phenyl 2-methyl-3,4-dihydro-1-naphthyl sulfide, respectively, and not the corresponding mercaptals.

Inasmuch as the cases cited above represent exceptions to a general reaction of very wide scope and few reported limitations, an investigation of the mercaptal reaction was initiated with the object of exploring the extent to which the anomalous unsaturated sulfide product occurs as well as to determine some of the factors which influence the formation of the unsaturated sulfides over that of the mercaptals.

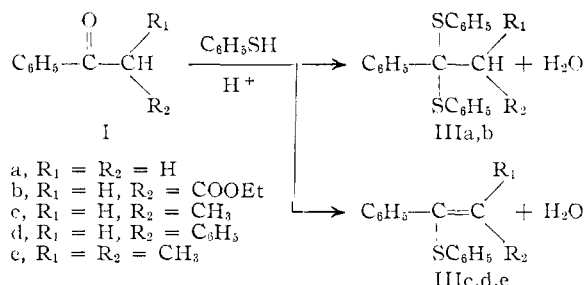
Discussion

In order to determine whether the formation of the unsaturated sulfides observed previously⁷ was the result of the unstable nature of the mercaptals initially formed or of the low reactivity of the thiol used, 2-methyl-1-indanone was treated with benzyl mercaptan.⁸ In this case, the nature of the thiol did not appear to be the only factor involved in the formation of the α,β -unsaturated sulfide since benzyl 2-methyl-3-indenyl sulfide was obtained. Further support for this assumption was found in the fact that 5,5-dimethyl-1,3-cyclohexanedione formed

unsaturated sulfides with ethanethiol⁶ as well as with thiophenol. In other cases, however, the thiol apparently influences the course of the reaction. For example, benzyl mercaptan and 1,2-ethanedithiol yield mercaptals with 4-cholesten-3-one,⁹ whereas thiophenol yields an unsaturated sulfide.⁴

With respect to the nature of the ketone, it can be postulated that steric hindrance about the carbonyl function is the factor responsible for the new course of the mercaptal reactions.¹⁰ On the other hand, although 2-methyl-1-indanone formed unsaturated sulfides with thiophenol and benzyl mercaptan, 2,3-diphenyl-1-indenone is reported to form the dibenzyl mercaptal,¹¹ and fluorenone the diphenyl mercaptal.¹² On the basis of steric hindrance alone, these compounds might be expected to form only hemimercaptals or not react at all.

In order to elucidate the role of the ketone in the mercaptal reaction, a series of phenones I reacted with thiophenol under conditions which usually lead to mercaptal formation. In this series acetophenone (Ia) and ethyl benzoylacetate (Ib) gave the corresponding diphenyl mercaptals (IIa,b) while propiophenone (Ic), desoxybenzoin (Id) and isobutyrophenone (Ie) furnished unsaturated sulfides III.



Pivalophenone did not react with thiophenol. Construction of a Fisher-Hirschfelder model of pivalophenone suggested that although a hemimercaptal of pivalophenone could possibly be formed, the introduction of a second phenylthio group was highly unlikely.

The fact that ethyl benzoylacetate formed a mercaptal with thiophenol is in agreement with the results obtained with ethyl acetoacetate and other β -keto esters.^{13,14} Hydrolysis of the mercaptal es-

(1) Taken from a portion of the thesis submitted by Joseph R. Leal in partial fulfillment of the requirements for the degree Doctor of Philosophy, at Indiana University, February, 1953.

(2) Frederick Gardner Cottrell Fellow in Chemistry, 1951-1952.

(3) E. Baumann, *Ber.*, **18**, 883 (1885).

(4) S. Bernstein and L. Dorfman, *THIS JOURNAL*, **68**, 1152 (1946).

(5) G. Rosenkranz, S. Kaufmann and J. Romo, *ibid.*, **71**, 3689 (1949).

(6) J. D. Kendall and F. P. Doyle, British Patent 595,783, Dec. 16, 1947 (*C. A.*, **42**, 4764 (1948)).

(7) E. Campaigne and R. D. Moss, *THIS JOURNAL*, **76**, 1269 (1954).

(8) Thiophenol represents the least reactive of the thiols in the formation of mercaptals and forms the least stable mercaptals, benzyl mercaptan represents the most reactive thiol, forming the most stable mercaptals. Cf. T. Posner, *Ber.*, **34**, 2643 (1901).

(9) H. Hauptmann, *THIS JOURNAL*, **69**, 562 (1947).

(10) Such an explanation has been suggested for the failure of 11-keto steroids to react with thiols, H. Hauptmann and M. Campos, *ibid.*, **74**, 3179 (1952).

(11) A. Schönberg and O. Schütz, *Ber.*, **60**, 2344 (1927).

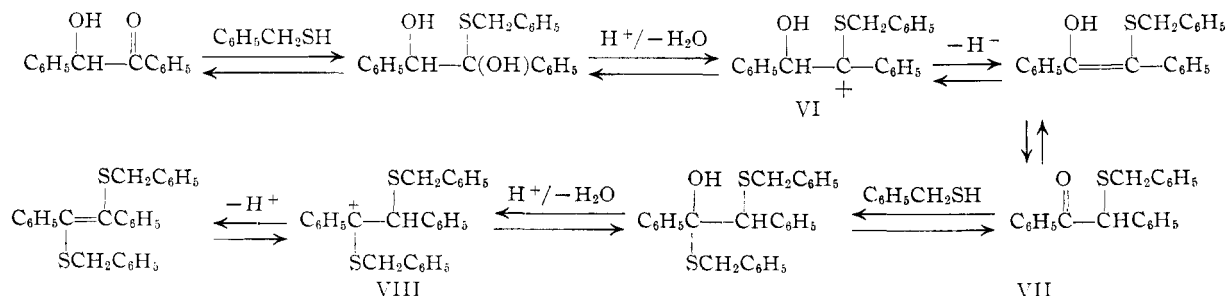
(12) A. Schönberg and T. Stolpp, *Ann.*, **483**, 90 (1930).

(13) R. Escales and E. Baumann, *Ber.*, **19**, 1787 (1886).

(14) T. Posner, *ibid.*, **32**, 2801 (1899).

mediate carbonium ion while steric hindrance prevented the normal mercaptal reaction.

The same mechanism may be extended to explain the abnormal reaction of ethanethiol and benzyl mercaptan with benzoin to form 1,2-dithiostilbene derivatives.²¹ In contrast to Posner's mechanism,^{21a} which involved the formation of the normal mercaptal followed by replacement of the hydroxyl group by a third molecule of thiol to form an unstable intermediate trisulfide which then lost a molecule of thiol, the reaction may be more simply represented as



The tendency for the intermediate carbonium ions VI and VIII to become stabilized by electron shifts, rather than coordination with another molecule of thiol, would be expected to be high, since such stabilization leads to structures which allow for resonance with the phenyl groups. The fact that 2-methoxy-5-chlorothiophenol forms α -(2-methoxy-5-chlorophenylthio)-desoxybenzoin with benzoin²² also agrees with the same mechanism. When the intermediate corresponding to VII is reached, the reaction proceeds no further, due to steric hindrance.

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Experimental²³

Materials.—Commercial samples of 5,5-dimethyl-1,3-cyclohexanedione, acetophenone, propiophenone, ethyl benzoylacetate and thiophenol were used without further purification. 2-Methyl-1-indanone and 2-methyl-1-tetralone were prepared by T. Bowen and R. D. Moss in this Laboratory. Benzyl mercaptan was prepared from benzyl chloride via the isothiuronium salt according to known procedures.^{24,25} Isobutyrophenone and desoxybenzoin²⁶ were synthesized by a Friedel-Crafts reaction with the corresponding acid chlorides.²⁷ Pivalophenone resulted from the alkylation of isobutyrophenone with methyl iodide.²⁸ Ethyl β -phenylthiocinnamate was prepared in a 9.4% yield by the addition of thiophenol to ethyl phenylpropionate according to the procedure of Ruhemann and Stapleton.¹⁶ Hydrolysis of ethyl β -phenylthiocinnamate in ethanolic potassium hydroxide¹⁵

yielded yellow crystals of β -phenylthiocinnamic acid, melting at 160–163° dec.

Benzyl 2-Methyl-3-indenyl Sulfide.—Anhydrous hydrogen chloride was passed into a mixture consisting of 6.6 g. (0.045 mole) of 2-methyl-1-indanone and 11 g. (0.09 mole) of benzyl mercaptan in 50 ml. of absolute ethyl alcohol. After 15 minutes, 20 g. of freshly fused zinc chloride was added to the reaction mixture and the flask shaken for 30 minutes. The reaction mixture was shaken intermittently but frequently for 2 hours, and then poured over ice, extracted with ether and the ether solution washed successively with water, aqueous sodium carbonate and water. Upon distillation of the dried ether solution, 9 g. (80%) of an oil, b.p. 165–170° at 1.5 mm., was obtained which finally solidified after refrigeration and trituration with cold ethyl

alcohol. Recrystallization from methanol yielded 6 g. of benzyl 2-methyl-3-indenyl sulfide, which melted at 73–74°.

Anal. Calcd. for $\text{C}_{17}\text{H}_{16}\text{S}$: S, 12.68. Found: S, 12.45.

Oxidation of Benzyl 2-Methyl-3-indenyl Sulfide.—Oxidation of 0.5 g. of uncrystallized benzyl 2-methyl-3-indenyl sulfide with 1.2 ml. of 30% hydrogen peroxide according to the method of Pomerantz and Connor²⁹ gave 0.11 g. (20%) of benzyl 2-methyl-3-indenyl sulfone, m.p. 135–137°, which after recrystallization from methanol melted at 138–139°.

Anal. Calcd. for $\text{C}_{17}\text{H}_{16}\text{O}_2\text{S}$: S, 11.27. Found: S, 11.14.

5,5-Dimethyl-3-phenylthio-2-cyclohexenone.—A mixture consisting of 7 g. (0.05 mole) of 5,5-dimethyl-1,3-cyclohexanedione and 11 g. (0.1 mole) of thiophenol in 75 ml. of absolute ethyl alcohol was saturated with anhydrous hydrogen chloride. After standing at room temperature for 36 hours, the reaction mixture was taken up in ether and washed successively with water, aqueous sodium carbonate and water. Upon evaporation of the dried ether solution, a viscous yellow oil remained which deposited 3 g. (26%) of pale yellow crystals, m.p. 45–50°, which after recrystallization from methanol gave 2 g. (17%) of 5,5-dimethyl-3-phenylthio-2-cyclohexenone, m.p. 50–51°.

Anal. Calcd. for $\text{C}_{14}\text{H}_{16}\text{OS}$: S, 13.79. Found: S, 14.02.

Acetophenone Diphenyl Mercaptal (IIa).—A current of hydrogen chloride was passed into a mixture of 6 g. (0.05 mole) of acetophenone and 11 g. (0.1 mole) of thiophenol until the mixture froze to a mass of crystals weighing 14.5 g. and melting at 45–51°. Recrystallization from ethyl alcohol yielded 13.5 g. (84%) of acetophenone diphenyl mercaptal, m.p. 54.5–55°.

Anal. Calcd. for $\text{C}_{20}\text{H}_{16}\text{S}_2$: S, 19.87. Found: S, 20.07.

The compound was unstable to moisture, readily decomposing in air, but a sample stored in a vacuum desiccator over calcium sulfate remained crystalline for three months.

Phenyl 1-Phenyl-1-propenyl Sulfide (IIIc).—A mixture of 6.7 g. (0.05 mole) of propiophenone and 11 g. of thiophenol was saturated with hydrogen chloride and allowed to stand at room temperature overnight. The following day, the reaction mixture was taken up in ether and the ether solution washed successively with water, aqueous sodium carbonate and water. Upon evaporation of the dried ether extract, 9.5 g. (84%) of a brown viscous oil remained. Distillation of the oil yielded a light yellow oil, b.p. 121–125° at 0.8 mm., which finally solidified after refrigeration and trituration with cold methanol. Recrystallization from methanol gave colorless crystals of phenyl 1-phenyl-1-propenyl sulfide, m.p. 42–42.5°.

Anal. Calcd. for $\text{C}_{15}\text{H}_{14}\text{S}$: S, 14.16. Found: S, 13.97.

(29) A. Pomerantz and R. Connor, *THIS JOURNAL*, **61**, 3386 (1939).

(21) (a) T. Posner, *Ber.*, **35**, 506 (1902); (b) M. Romero and J. Romo, *Bol. Inst. Quim. (Mex.)*, **IV**, 3 (1952).

(22) W. A. Mitchell and S. Smiles, *J. Chem. Soc.*, 1529 (1933).

(23) Melting points and boiling points are uncorrected.

(24) A. I. Vogel, "A Textbook of Practical Organic Chemistry," Longmans Green and Co., London, 1948, p. 840.

(25) A. J. Speziale, *Org. Syntheses*, **30**, 35 (1950).

(26) A. H. Blatt, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 156.

(27) The over-all yields were found to be greatly improved by using the crude acid chlorides, made with thionyl chloride, instead of isolating and purifying them prior to the acylation step.

(28) A. Haller and E. Bauer, *Compt. rend.*, **148**, 70 (1909).

The crystalline material readily decomposes to a light yellow oil at room temperature but remains unchanged in the refrigerator.

Oxidation of Phenyl 1-Phenyl-1-propenyl Sulfide.—Nineteen grams of the brown viscous crude sulfide, oxidized with potassium permanganate according to the method of Bost, Turner and Norton³⁰ furnished mainly benzoic acid and benzenesulfonic acid along with 1.5 g. (7%) of phenyl 1-phenyl-1-propenyl sulfone, m.p. 90–92°.

Anal. Calcd. for $C_{15}H_{14}O_2S$: S, 12.41. Found: S, 12.53.

Phenylthiostilbene (IIIId).—A solution of 9.8 g. (0.05 mole) of desoxybenzoin and 11 g. of thiophenol in 100 ml. of absolute ethyl alcohol was saturated with hydrogen chloride. After standing 1 hour, the reaction mixture was poured into water, extracted with ether and the ether extract washed successively with water, 2% sodium hydroxide solution and water, dried and distilled. The distillate yielded 1.3 g. of desoxybenzoin and the residue amounted to 11 g. (76%) of a viscous yellow oil which solidified, upon cooling, to a nearly colorless solid, m.p. 35–42°. Recrystallization from methanol gave two fractions: (1) 8 g., m.p. 48–54°, and (2) 2 g., m.p. 50–60°. After repeated fractional recrystallizations from methanol, fraction 1 gave 3.7 g. of phenylthiostilbene, melting at 49–50°.

Anal. Calcd. for $C_{20}H_{16}S$: S, 11.11. Found: S, 10.94.

Repeated fractional recrystallizations of fraction 2 from methanol finally yielded 0.31 g. of an isomer of phenylthiostilbene, m.p. 63–64°.

Anal. Calcd. for $C_{20}H_{16}S$: S, 11.11. Found: S, 11.18.

Ethyl β,β -Bis-(phenylthio)-hydrocinnamate (IIb).—A mixture of 19.2 g. (0.1 mole) of ethyl benzoylacetate, 22 g. (0.2 mole) of thiophenol and 20 g. of freshly fused zinc chloride was saturated with hydrogen chloride. After saturation, the reaction flask was tightly stoppered and shaken vigorously for about 10 minutes while the contents gradually solidified. The solid material was dissolved in ether and the ether solution washed successively with water, aqueous sodium carbonate and water. Evaporation of the dried ether solution deposited a light yellow solid which after washing with cold methanol amounted to 15 g. (38%) of colorless crystals, which melted at 87–90°. Recrystallization from methanol yielded 13 g. (33%) of ethyl β,β -bis-(phenylthio)-hydrocinnamate, melting at 92–93°. This melting point was depressed by admixture with ethyl β -phenylthiocinnamate.

Anal. Calcd. for $C_{23}H_{22}O_2S_2$: S, 16.20. Found: S, 16.16.

Oxidation of Ethyl β,β -Bis-(phenylthio)-hydrocinnamate.—Oxidation of 3.9 g. (0.01 mole) of IIb with 30 ml. of 30% hydrogen peroxide according to the method of Pomerantz and Connor²⁹ yielded mostly benzoic acid along with 0.06 g. (2%) of colorless needles, m.p. 104–105°, which analyzed correctly for ethyl β -phenylsulfinylnicinnamate.

Anal. Calcd. for $C_{17}H_{16}O_3S$: S, 10.68. Found: S, 10.73.

Hydrolysis of Ethyl β,β -Bis-(phenylthio)-hydrocinnamate.—Refluxing of a solution of 5.7 g. (0.014 mole) of IIb and 3 g. of potassium hydroxide in 50 ml. of ethyl alcohol for one hour, followed by evaporation of the reaction mixture to dryness furnished a yellow paste which was taken up in a small volume of water and set aside overnight. The next day, a crop of colorless platelets was filtered off and dissolved in water. Acidification of the aqueous solution liberated 1.5 g. (28%) of β -phenylthiocinnamic acid, which after recrystallization from dilute ethanol melted at 192–193° dec.

Anal. Calcd. for $C_{15}H_{12}O_3S$: S, 12.46. Found: S, 12.35.

When the acid was heated, decomposition, accompanied by gas evolution, occurred with the formation of yellow oil which precipitated acetophenone 2,4-dinitrophenylhydrazones, m.p. 247°,³¹ when treated with acidic 2,4-dinitrophenylhydrazine reagent. The melting point of this acid was depressed by admixture with the β -phenylthiocinnamic acid, m.p. 160–163° dec., obtained by the hydrolysis of ethyl β -phenylthiocinnamate.

Phenyl 1-Phenyl-2-methyl-1-propenyl Sulfide (IVe).—A mixture of 14.8 g. (0.1 mole) of isobutyrophenone, 22 g. (0.2 mole) of thiophenol and 25 g. of freshly fused zinc chloride in 20 ml. of absolute ethyl alcohol was saturated with hydrogen chloride, and allowed to stand overnight. Two layers separated in the reaction mixture, the lower one of which contained a solid. From the lower layer, 2 g. of colorless crystals, m.p. 36–37°, were isolated which after several recrystallizations from methanol melted at 38–38.5°. The identity of this product was not established, but its elemental analysis indicated a composition approximating that required for $C_{23}H_{26}-2S_3$.

Anal. Calcd. for $C_{23}H_{26}-2S_3$: C, 73.33–73.00; H, 5.69–6.13; S, 20.98–20.87. Found: C, 73.29, 73.04; H, 6.17, 6.20; S, 21.19, 21.42.

From the upper layer, 20 g. (83%) of a light yellow oil was obtained which after fractional distillation yielded 15 g. of distillate, boiling at 128–132° at 1 mm. Upon cooling, both the distillate and the residue solidified, and melted at 31–36°. Recrystallization from cold methanol gave 8 g. of phenyl 1-phenyl-2-methyl-1-propenyl sulfide, m.p. 35–36°.

Anal. Calcd. for $C_{16}H_{16}S$: S, 13.34. Found: S, 13.12.

Reaction of Thiophenol with Pivalophenone.—From the reaction of 8.1 g. (0.05 mole) of pivalophenone, 11 g. of thiophenol and 10 g. of freshly fused zinc chloride in 25 ml. of absolute ethyl alcohol, treated in the same manner as described above, 6 g. of starting ketone was recovered along with 1 g. of diphenyl disulfide, m.p. 58–59°.

Anal. Calcd. for $C_{12}H_{10}S_2$: S, 29.32. Found: S, 29.48.

The melting point of this substance was not depressed by admixture with an authentic sample of diphenyl disulfide, obtained by the air oxidation of thiophenol in ammoniacal ethanol solution.

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(30) R. W. Bost, J. Turner and R. D. Norton, *THIS JOURNAL*, **54**, 1986 (1932).

(31) R. L. Shriner and R. C. Fuson, "Identification of Organic Compounds," 3rd ed., John Wiley and Sons, Inc., New York, N. Y., 1948 p. 263.