Preparation and Rearrangement Reactions of 2-Methylsulfinylindanedione-1,3. The Mechanism of the New Ninhydrin Synthesis

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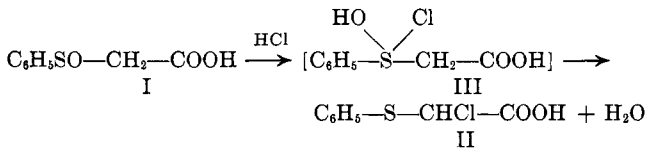
Received December 6, 1963

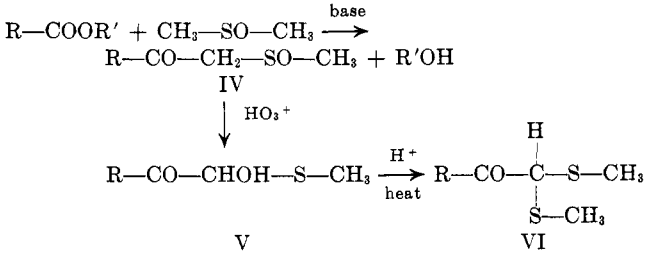
Diethyl phthalate condenses with methylsulfinyl carbanion to give 2-methylsulfinylindanedione-1,3. This new β-keto sulfoxide undergoes acid-catalyzed rearrangement reactions (Pummerer reactions) with various nucleophiles leading to 2-substituted 2-methylmercaptoindanediones. The rearrangement of 2-methylsulfinylindanedione-1,3 into 2-hydroxy-2-methylmercaptoindanedione-1,3 has been followed by ultraviolet spectroscopy. The exhibition of two isosbestic points in the course of the reaction suggests that we are dealing with a true rearrangement rather than with a cleavage and recombination process. A mechanism of probable generality for acid-catalyzed reactions of β-keto sulfoxides is proposed.

The Pummerer Reaction.—Pummerer found that phenylsulfinylacetic acid (I) is cleaved by warm dilute mineral acids to form thiophenol and glyoxylic acid.[1] Combination of the cleavage products can lead to the phenylthioacetal of glyoxylic acid.[2] Treatment of phenylsulfinylacetic acid with gaseous hydrogen chloride yields α-chlorophenylmercaptoacetic acid (II).[1] For its formation, Pummerer assumed an *intramolecular* rearrangement *via* the hypothetical intermediate III.



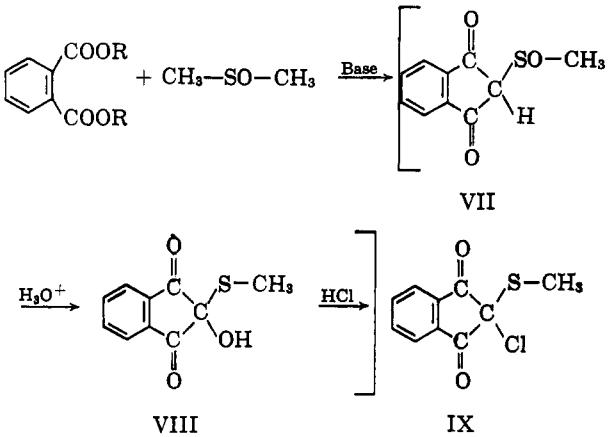
Upon treatment with acetic anhydride, phenylsulfinylacetic acid yields α-acetoxythioglycolic acid.[2] This reaction was later studied by Horner and Kaiser and found to be a general reaction between sulfoxides and acid anhydrides.[3] The mechanism of this reaction has recently been substantiated by means of a tracer study.[4]

Interest in the Pummerer reaction was renewed when β-keto sulfoxides became easily available by base-catalyzed condensation of dimethyl sulfoxide with esters and the observation was made that ω-methylsulfinylacetophenone rearranged smoothly into the hemithioacetal of phenylglyoxal (V) at room tempera-



ture in the presence of acid.[5] No chemical evidence was found that at any time during the reaction the cleavage products, methanethiol and phenylglyoxal, were present. Furthermore, it was found that the methylthioacetal of phenylglyoxal (VI) only resulted from decomposition of the hemithioacetal under drastic conditions. A recently proposed cleavage–recombination mechanism[6] for the Pummerer reaction thus appears rather unlikely.

The base-catalyzed condensation of dimethyl sulfoxide with diethyl phthalate, followed by acidification of the reaction mixture with hydrochloric acid, yields 2-chloro-2-methylmercaptoindanedione-1,3 (IX), which upon hydrolysis gives ninhydrin.[7a] The reaction sequence proposed involved a step in which the OH group in the "normal" rearrangement product VIII would be



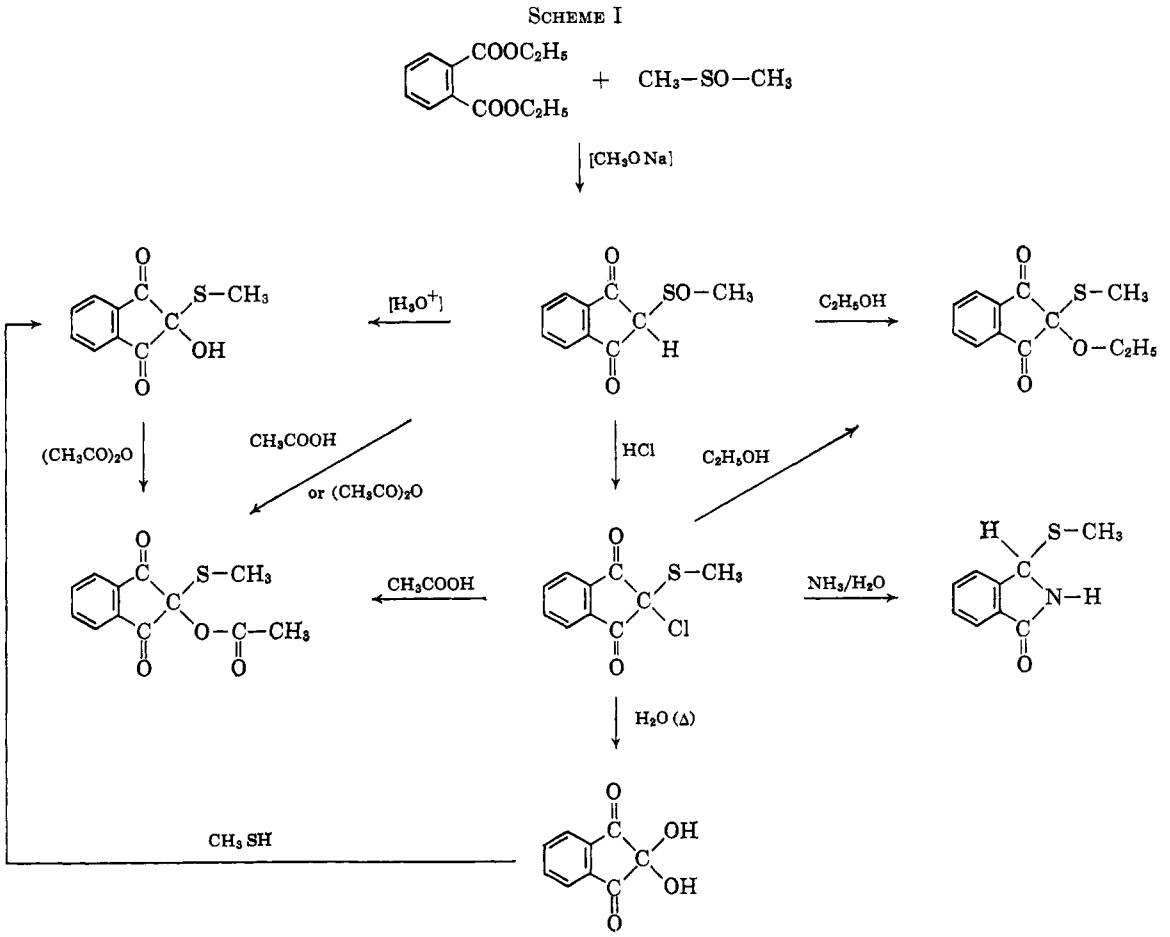
substituted by treatment with hydrochloric acid to yield IX. This appeared at the time reasonable since the conversion of α-hydroxy thioethers into α-chloro thioethers is well known.[8] Attempts to isolate the intermediates VII and VIII had previously been unsuccessful because no information about the chemistry of 2-methylsulfinylindanedione-1,3 (VII) was available. We now wish to report the synthesis of both VII and VIII.

Results[9]

We have finally succeeded in preparing 2-methylsulfinylindanedione-1,3 (VII) by base-catalyzed condensation of dimethyl sulfoxide with diethyl phthalate.[10] In its crystalline state (m.p. 111°) it is stable.

(1) R. Pummerer, *Ber.*, **42**, 2282 (1909).
(2) R. Pummerer, *ibid.*, **43**, 1401 (1910).
(3) L. Horner and P. Kaiser, *Ann.*, **626**, 19 (1959).
(4) S. Oae, T. Kitao, S. Kawamura, and Y. Kitaoka, *Tetrahedron*, **19**, 817 (1963).
(5) H.-D. Becker, G. J. Mikol, and G. A. Russell, *J. Am. Chem. Soc.*, **85**, 3410 (1963).
(6) W. J. Kenney, J. A. Walsh, and D. A. Davenport, *ibid.*, **83**, 4019 (1961).
(7) (a) H.-D. Becker and G. A. Russell, *J. Org. Chem.*, **28**, 1896 (1963); (b) H.-D. Becker and G. A. Russell, *ibid.*, **28**, 1896, 1897 (1963).
(8) See, *e.g.*, A. Schöberl and A. Wagner, "Methoden der Organischen Chemie," Vol. 9, E. Müller, Ed., Houben-Weyl, 1955, p. 204.
(9) See Scheme I.
(10) Base-catalyzed reaction of diethyl phthalate with dimethyl sulfone in dimethyl sulfoxide solution yields the recently described[7b] stable 2-methylsulfonylindanedione-1,3 in 50% yield if sodium methoxide is used as base. Application of potassium *t*-butoxide as base in dimethyl sulfoxide results in the condensation of 2 moles of dimethyl sulfone per mole of diethyl phthalate, yielding a compound, $C_{12}H_{12}O_8S_2$. Details will be published later.

SCHEME I



Its isolation, however, was complicated by the extreme facility with which VII underwent rearrangement in solution. It was found to be a most interesting representative of the group of β-keto sulfoxides since it underwent the Pummerer reaction with a variety of nucleophiles to yield α-substituted thioethers. In dilute aqueous solution, VII is completely ionized. A 10^{-2} *M* solution has a pH of 2; a 10^{-3} *M* solution, a pH of 3. A saturated aqueous solution has a pH of 1.8 which, during a 24-hr. period, changes to pH 2.5. The unidentified high melting product isolated from this reaction possessed a molecular weight suggestive of a trimer, which indicates that VII underwent intermolecular condensation reactions, perhaps with its own anion (VIIa).

We found that treatment of VII with *strong* hydrochloric acid indeed yielded 2-chloro-2-methylmercaptoindanedione-1,3. Acetic anhydride converted VII smoothly into 2-acetoxy-2-methylmercaptoindanedione-1,3. This substance, however, was also formed by treatment of VII with acetic acid. We made this observation originally when we attempted to condense VII with diphenylcarbinol in the presence of acetic acid, a reaction which has been described for 2-nitroindanedione-1,3.[11a,b] In the presence of ethanol, 2-methylsulfinylindanedione-1,3 was converted into 2-ethoxy-2-methylmercaptoindanedione-1,3. The rearrangement products were also obtained by nucleophilic substitution reactions of 2-chloro-2-methylmercaptoindanedione-1,3 with acetic acid and with ethanol, respectively.[12] The product of the reaction of VII with acetic anhydride was shown, furthermore, to be identical with the acetylation product of 2-hydroxy-2-methylmercaptoindanedione.

Treatment of 2-methylsulfinylindanedione-1,3 with *dilute* hydrochloric acid yielded 2-hydroxy-2-methylmercaptoindanedione-1,3 (VIII). We have prepared VIII also by an independent method from triketohydrindene hydrate and methanethiol. *This hemithioketal could not be converted into the 2-chloro-2-methylmercaptoindanedione-1,3 (IX) by treatment with hydrochloric acid.* This clearly indicates that IX must be a direct rearrangement product of 2-methylsulfinylindanedione-1,3 (VII).

We have studied the rearrangement of VII into VIII spectroscopically. This was possible despite the very small differences in the ultraviolet spectra of undissociated VII and VIII, but, since VII is a strong acid, we actually observed the spectrum of its anion (VIIa) in aqueous solution. Addition of 75 ml. of 10^{-2} *N* hydrochloric acid to 25 ml. of a 10^{-4} *M* solution of VII shifted the equilibrium to the side of the undissociated

(11) (a) G. Vanag, "Cyclic β-Diketones" (in Russian), G. Vanag, Ed., Riga, 1961, p. 127. The author is indebted to Dr. Oškaja, Riga, for sending a copy of this book. (b) *Cf.* also Z. Eckstein, K. Oracz, and B. Rudnicka, *Roczniki Chem.*, **37**, 249 (1963).

(12) When we extended our work to the substitution reaction of 2-chloro-2-methylmercaptoindanedione with ammonia, we found that rather drastic changes in the molecule occurred. The formation of 2-arylaminoindanedione-1,3 from 2-halo-2-methylindanedione-1,3 and amines had been described in the literature [G. Ya. Vanag and Ya. Ya. Ozol, *Zh. Obsch. Khim.*, **32**, 1436 (1962)]. Treatment of 2-chloro-2-methylmercaptoindanedione-1,3 with aqueous ammonia did not lead to the 2-amino derivative, but yielded 3-methylmercaptophthalimidine. Its structure is supported by C, H, N, S analysis and infrared and n.m.r. data. Its formation probably involves a decarboxylation reaction, since ring-opening reactions of triketohydrindene hydrate in base are known [see, *e.g.*, D. J. McCaldin, *Chem. Rev.*, **60**, 39 (1960)].

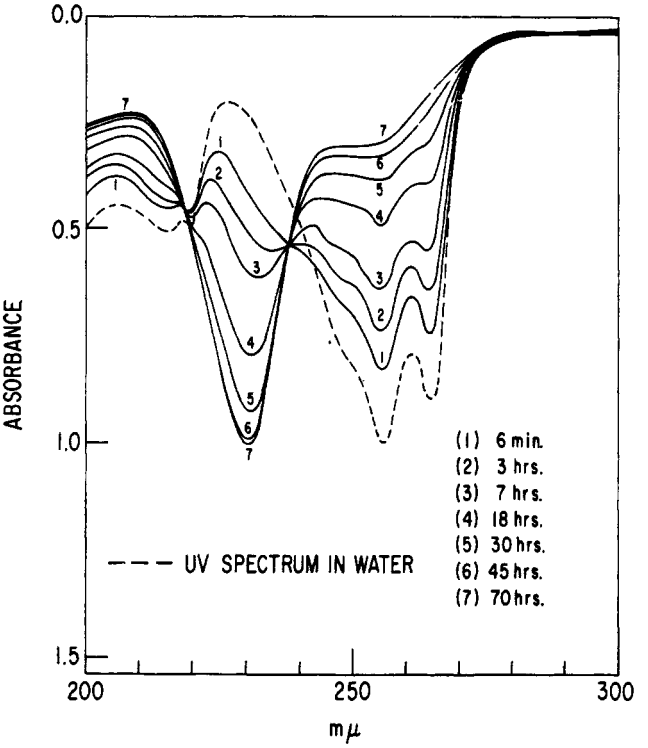


Figure 1.

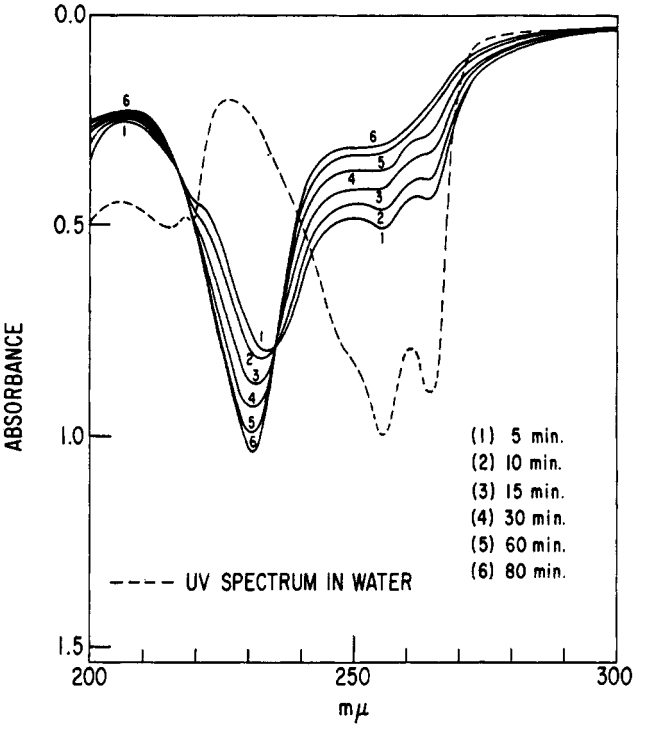
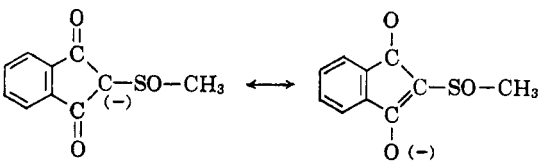


Figure 2.

indanedione derivative, as indicated by the slight change in its spectrum (Fig. 1). The absorbance of the anion at 256 and 265 mμ decreases immediately from 1.0 and 0.9, to 0.85 and 0.75, respectively. Spectroscopic observation over 70 hr. revealed that anion VIIa slowly disappears. The new maximum formed at 231 mμ corresponds to that of a 2.5×10^{-5} *M* solution of 2-hydroxy-2-methylmercaptoindanedione (in hydrochloric acid). Two isosbestic points which are exhibited in the course of the reaction prove that we are

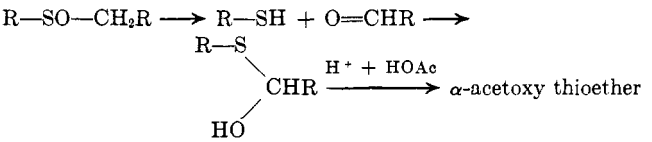


VIIa

dealing with a rearrangement reaction in which only two absorbing species are present in detectable amounts. Since VII is in equilibrium with its anion VIIa, the ultraviolet spectrum of this mixture can be considered as that of one species. When a 10^{-4} *M* solution of VII (25 ml.) was diluted with 75 ml. of 5×10^{-2} *N* hydrochloric acid, absorbance of the anion at 256 mμ (265) dropped from 1.0 (0.9) to0.45 (0.37); a new maximum appeared immediately at 234 mμ (Fig. 2). This originally appeared rather discouraging for the spectroscopic investigation of the rearrangement reaction. However, we noted that the rapid increase of the absorbance of this maximum was connected with a slight shift of the maximum to 231 mμ, and the curves exhibited two isosbestic points. Thus, the maximum at 234 mμ appears to be that of an equilibrium favoring undissociated VII.

Discussion

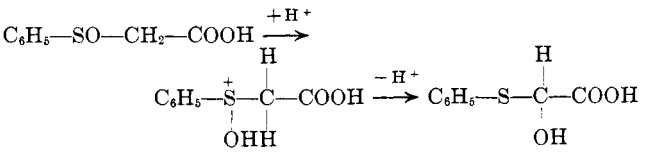
The main feature of a mechanism recently proposed for the Pummerer reaction was the direct cleavage of the sulfinyl compound into a mercaptan and a carbonyl fragment followed by recombination to form the α-substituted thioether.[6] The results were obtained under the rather drastic reaction conditions shown.



Our chemical and spectroscopic results are in disagreement with this mechanism. We did not find it possible to substitute the hydroxy group in the hemithioketal (VIII) under the conditions of reaction.

The cleavage–recombination mechanism appears even less likely by the finding that the rearrangement of sulfoxides of pyrimido[5,4-*b*][1,4]thiazines is subject to acid and base catalysis leading to different α-substituted thioethers.[13] Their formation was explained with the reaction of the nucleophilic media with the easily formed and stable 4,1-azathionium ion.

Recently evidence has been presented for an *intramolecular* mechanism of the rearrangement of phenylsulfinylacetic acid into the hemiphenylmercaptal of glyoxylic acid.[14] We have found that the hemithio-

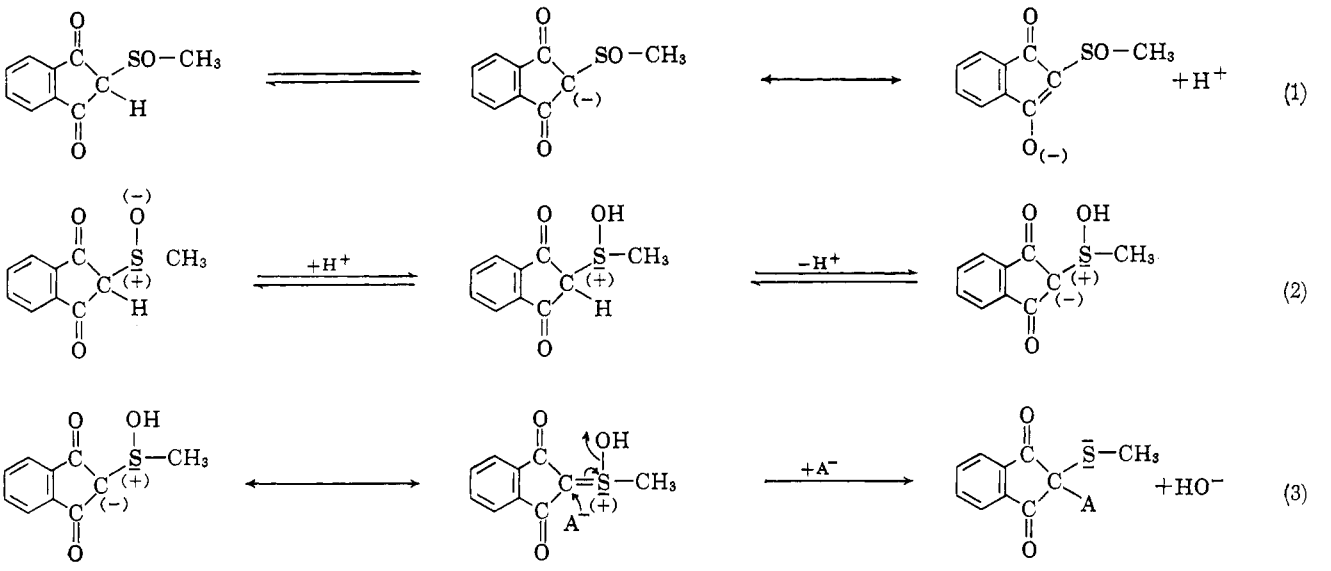


ketal (VIII) is formed in aqueous solution, while other 2-substituted 2-methylmercaptoindanediones are

(13) E. F. Schroeder and R. M. Dodson, *J. Am. Chem. Soc.*, **84**, 1904 (1962).

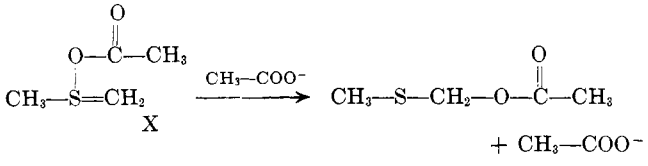
(14) D. Walker and J. Leib, *Can. J. Chem.*, **40**, 1242 (1962).

MECHANISM A



formed in other solvents and are not formed *via* the α-hydroxy thioethers.[15]

Of particular importance for the understanding of the rearrrangement of sulfoxides were the results obtained in an O^{18} tracer investigation recently reported.[4] The earlier proposed[3] cyclic *intramolecular* mechanism for the conversion of dimethyl sulfoxide into α-acetoxymethyl methyl sulfide could not be supported by this study. The new mechanism suggested involves an *intermolecular* nucleophilic attack on an intermediate (X) by acetate ions.



A similar mechanism for the conversion of dimethyl sulfoxide into monochloro dimethyl sulfide has been proposed earlier.[16]

The results obtained in the present investigation show that the acid-catalyzed rearrangement of VII involves a nucleophilic attack of a reactive intermediate by the solvent. As the spectroscopic data of the conversion of VII into VIII reveal, the reaction is higher than first order in hydrogen ions. This indicates that formation of a reactive intermediate requires protonation of the sulfinyl group in VII. Our results cannot be explained, however, by an *intramolecular* rearrangement of this protonated species. Mechanism A which is in agreement with both our chemical and spectroscopic data involves the sequence (eq. 1–3, where A^- = OH^-, Cl^-, CH_3COO^-, or $C_2H_5O^-$), in which protonation of the sulfinyl group is followed by formation of the reactive intermediate which undergoes attack by nucleophiles such as HO^-, Cl^-, CH_3COO^-, or $C_2H_5O^-$, leading to the various 2-substituted 2-methylmercapto-indanediones described in the present work.[17] The mechanism should be applicable to acid-catalyzed rearrangement reactions of β-keto sulfoxides in general. Recent results indicate that sulfinyl compounds other than β-keto-substituted ones can undergo quite different acid-catalyzed rearrangement reactions.[18]

Experimental[19]

Dimethyl sulfoxide was dried over calcium hydride and freshly distilled under vacuum. Sodium methylate was a commercial product.

2-Methylsulfinylindanedione-1,3 (VII).—To a suspension of 5.4 g. of sodium methoxide (0.1 mole) in 75 ml. of dimethyl sulfoxide placed under nitrogen in a 250-ml. round-bottom flask equipped with a magnetic stirring bar, distillation head, and receiver was slowly added 5 ml. of diethyl phthalate (0.025 mole). The stirred yellow reaction mixture was kept at room temperature at ~1-mm. pressure for 24 hr. The solvent was then removed completely by distillation for 1 hr. at a bath temperature of 65°. The yellow-colored semisolid residue was dissolved in 30 ml. of ice–water to which a mixture of 10 ml. of concentrated hydrochloric acid and 90 ml. of water was added slowly until the pH of the reaction mixture was about 5–6. Then 200 ml. of chloroform was added to the aqueous layer and the rest of the hydrochloric acid solution was added under quick shaking of the reaction mixture. The yellow chloroform solution was separated immediately, the extraction quickly was repeated three times, and the combined chloroform solutions were filtered and evaporated *in vacuo*. The yellow oily residue obtained crystallized quickly after addition of ether. The yield was 2.6 g. (50%) of 2-methylsulfinylindanedione-1,3, m.p. 105°. Purification by precipitation from chloroform by adding ether raised the melting point to 110–111°.

Anal. Calcd. for $C_{10}H_8O_3S$ (mol. wt., 208.16): C, 57.69; H, 3.87; S, 15.4. Found: C, 57.70; H, 3.90; S, 15.7.

2-Hydroxy-2-methylmercaptoindanedione-1,3 (VIII). A. From Ninhydrin.—Ninhydrin (2 g., 11 mmoles) was suspended in 15 ml. of absolute ethanol in a 25-ml. erlenmeyer flask and a stream of methanethiol was bubbled through for 45 min. The ninhydrin went completely into solution with evolution of heat. Evaporation of the solvent at room temperature gave 2 g. of VIII

(15) Boiling of 2-methylsulfinylindanedione-1,3 (VII) in inert solvents (chloroform) leads to high-melting materials not further investigated. Since rearrangement of VII in the presence of its own anion results in the formation of water, it is possible that 2-hydroxy-2-methylmercaptoindanedione (VIII) is formed (see below). Also, simple heating of VII yields a product which exhibits an OH peak in its infrared spectrum. The infrared spectrum, however, is not identical with that of VIII.

(16) F. G. Bordwell and B. M. Pitt, *J. Am. Chem. Soc.*, **77**, 572 (1955).

(17) According to these considerations, catalytic amounts of water should be sufficient to convert β-keto sulfoxides into α-hydroxy thioethers, and this indeed has been found. Crude or impure samples of keto sulfoxides rearrange in the solid state,[5,13] making the reaction *appear intramolecular*.

(18) R. B. Morin, B. G. Jackson, R. A. Mueller, E. R. Lavagnino, W. B. Scanlon, and S. L. Andrews, *J. Am. Chem. Soc.*, **85**, 1896 (1963).

(19) All melting points are taken on a Fisher-Johns apparatus and are not corrected. Analyses were carried out by Schwarzkopf Microanalytical Laboratory, Woodside 77, N. Y.

as light yellow crystals of m.p. 120° (85%). Recrystallization from a mixture of hot ethanol and petroleum ether raised the melting point to 121–123°.

Anal. Calcd. for $C_{10}H_8O_3S$ (mol. wt., 208.16): C, 57.69; H, 3.87; S, 15.4. Found: C, 57.66; H, 3.86; S, 15.4.

B. From 2-Methylsulfinylindanedione-1,3 (VII).—VII (100 mg., 0.48 mmole) was dissolved in 40 ml. of water. Then 60 ml. of 0.5 *N* hydrochloric acid was added and the colorless (slightly cloudy) solution was extracted twice after 15 min. with 75 ml. of chloroform. The yellowish-colored chloroform solution was evaporated *in vacuo* yielding a yellow oil which rapidly crystallized. The yield was 90 mg. (90%), m.p. 121°; mixture melting point with the substance obtained under A showed no depression.

2-Chloro-2-methylmercaptoindanedione-1,3 (IX). A.—The direct preparation from diethyl phthalate and dimethyl sulfoxide has been described previously.[7a]

B. From 2-Methylsulfinylindanedione-1,3 (VII).—VII (70 mg.) was dissolved in 2 ml. of 10% sodium carbonate solution. The yellow colored solution was then added to a mixture of 2 ml. of concentrated hydrochloric acid and 3 ml. of water, giving a colorless precipitate. The yield was 50 mg. (66%) of IX, m.p. 64–65°; mixture melting point with authentic[7a] IX showed no depression.

2-Acetoxy-2-methylmercaptoindanedione-1,3. A. From 2-Chloro-2-methylmercaptoindanedione-1,3.—2-Chloro-2-methylmercaptoindanedione-1,3 (300 mg., 1.3 mmoles) was dissolved in 5 ml. of glacial acetic acid and refluxed for 3 hr. The reaction mixture was then poured into a Petri dish. Evaporation of the solvent at room temperature gave 275 mg. of 2-acetoxy-2-methylmercaptoindanedione-1,3 (83%), m.p. 138°.

Anal. Calcd. for $C_{12}H_{10}O_4S$ (mol. wt., 250.20): C, 57.60; H, 4.03; S, 12.79. Found: C, 57.59; H, 4.15; S, 12.84.

B. From 2-Methylsulfinylindanedione-1,3 (VII) and Acetic Acid.—VII (100 mg., 0.48 mmole) was dissolved in 25 ml. of acetic acid and kept at 50° for 20 hr. The originally yellow-colored solution had turned almost colorless. Evaporation of the solvent under vacuum gave a slightly yellow-colored oil which gave colorless crystals upon addition of little methanol. The yield was 85 mg. (71%), m.p. 136–137°; mixture melting point with 2-acetoxy-2-methylmercaptoindanedione-1,3 obtained under A showed no depression. In concentrated solutions of VII in acetic acid, a higher melting product not further investigated was formed.

C. From 2-Methylsulfinylindanedione-1,3 (VII) and Acetic Anhydride.—VII (100 mg., 0.48 mmole) was dissolved in 3 ml. of acetic anhydride. The reaction mixture was kept at 50° for 15 hr. Evaporation of the solvent at room temperature gave 90 mg. of colorless 2-acetoxy-2-methylmercaptoindanedione-1,3 (75%), m.p. 136–138°; mixture melting point with authentic sample from procedure A gave no depression.

D. From 2-Hydroxy-2-methylmercaptoindanedione-1,3 (VIII) and Acetic Anhydride.—VIII (500 mg., 2.4 mmoles) was dissolved in 5 ml. of pyridine and 5 ml. of acetic anhydride. The reaction mixture was refluxed for 5 min. The dark solution yielded 450 mg. (75%) of 2-acetoxy-2-methylmercaptoindanedione-1,3 as colorless crystals, m.p. 138°, after evaporation of the solvents at room temperature and washing of the residue with cold methanol; mixture melting point with authentic sample obtained under A showed no depression.

2-Ethoxy-2-methylmercaptoindanedione-1,3. A. From 2-Chloro-2-methylmercaptoindanedione-1,3 (IX).—One gram of 2-chloro-2-methylmercaptoindanedione-1,3 (IX) was dissolved in 5 ml. of absolute ethanol and refluxed for 3 hr. Evaporation of the solvent at room temperature gave a yellow oil which crystallized after 5 days. The substance was recrystallized from hot ethanol, yielding 950 mg. (91%) of 2-ethoxy-2-methylmercaptoindanedione-1,3, m.p. 65–66° (yellowish prismatic needles).

Anal. Calcd. for $C_{12}H_{12}O_3S$ (mol. wt., 236.22): C, 61.01; H, 5.12; S, 13.55. Found: C, 60.83; H, 5.16; S, 13.77.

B. From 2-Methylsulfinylindanedione-1,3.—VII (100 mg., 0.48 mmole) was dissolved in 10 ml. of absolute ethanol and kept at 55° for 12 hr. Evaporation of the solvent at room temperature gave 60 mg. (52%) of crystalline 2-ethoxy-2-methylmercaptoindanedione-1,3, m.p. 63–64°; mixture melting point with authentic sample obtained under A showed no depression.

Reaction of 2-Chloro-2-methylmercaptoindanedione-1,3 (IX) with Ammonia.—IX (200 mg., 0.9 mmole) was dissolved in 3 ml. of ether. Addition of 6 ml. of 15% aqueous ammonia solution and shaking for a few minutes caused precipitation of colorless crystals (aqueous layer was brown colored). The reaction mixture was kept in an open beaker for 1 hr. and then filtered. The yield was 100 mg. (63%) of 3-methylmercaptophthalimidine, m.p. 156°. Recrystallization from hot methanol raised the melting point to 158°.

Anal. Calcd. for C_9H_9NOS: C, 60.33; H, 5.06; N, 7.82; S, 17.82; mol. wt., 179.16. Found: C, 60.55; H, 5.03; N, 7.88; S, 17.89; mol. wt.,[20] 166.

Ultraviolet Spectra.—The ultraviolet spectra were taken on a Perkin-Elmer recording instrument (Model 202). The solutions were prepared by diluting a 10^{-4} *M* aqueous solution of 2-methylsulfinylindanedione-1,3 to a molarity of 2.5×10^{-5} with 10^{-2} and 5×10^{-2} *N* hydrochloric acid, respectively.

Acknowledgment.—The initial experiments on the condensation of dimethyl sulfoxide and dimethyl sulfone with phthalic esters were carried out in collaboration with Dr. G. A. Russell at Iowa State University, Ames, Iowa, under support provided by the Air Force Office of Scientific Research.

(20) Thermoelectric measurement was made in dioxane.