Synthesis of Ninhydrin[1,2]

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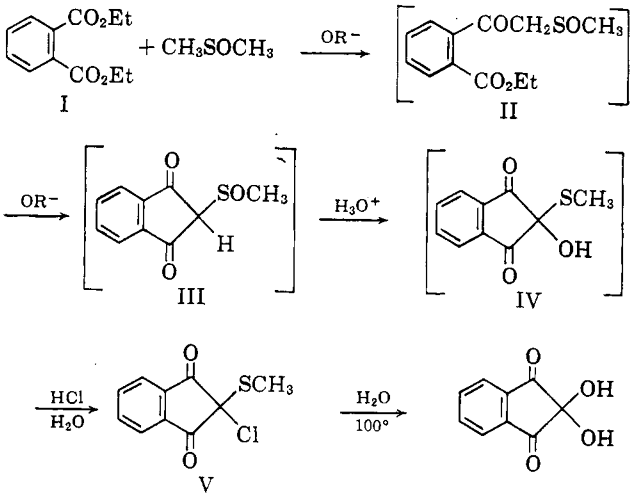
We have found that ninhydrin readily can be synthesized in two steps from ethyl phthalate. Ninhydrin is usually prepared by a six-step synthesis starting from esters of phthalic acid.[4] Other methods of preparation starting from 1,3-indandione or *p*-naphthoquinone give low yields of ninhydrin.[5]

We have reported recently that the condensation of esters with dimethyl sulfoxide in the presence of alkali metal alkoxides leads to *β*-keto sulfoxides which in the presence of mineral acids undergo the Pummerer rearrangement to give hemimercaptals of *α*-ketoaldehydes.[6]

$$RCO_2R' + CH_3SOCH_3 \xrightarrow{OR^-} RCOCH_2SOCH_3 \xrightarrow{H_3O^+} RCOCH(OH)SCH_3$$

When diethyl phthalate is used in this reaction, an intramolecular ester condensation leads to the formation of the 1,3-indandione system. The reaction product isolated upon acidification with hydrochloric acid proved to be the *α*-chloro thioether (V). The formation of V from I probably involves the as yet unisolated intermediates II–IV.



The condensation occurs upon the addition of diethyl phthalate to a solution (or suspension) of an alkali metal alkoxide in anhydrous dimethyl sulfoxide under an atmosphere of dry, oxygen-free nitrogen. Removal of the solvent by vacuum distillation leaves a salt (presumably the alkali metal salt of III) which is soluble in water. When the aqueous solution of this salt is added to 5 *M* hydrochloric acid V rapidly precipitates in a high state of purity.

When V is hydrolyzed in boiling water ninhydrin can be isolated in nearly quantitative yields. Because of the ease of hydrolysis V cannot be recrystallized from hydroxylic solvents. A color reaction typical of ninhydrin was obtained when V (absorbed on filter paper) was treated with a solution of glycine and heated to 80°.

Experimental[7]

Reagents.—Dimethyl sulfoxide (Crown Zellerbach Corp.) was distilled from calcium hydride at a pressure of about 1 mm. Sodium methoxide (Matheson Coleman and Bell) was used without purification. Diethyl phthalate was distilled under vacuum. In the condensation reaction described later it is important to use only anhydrous reagents since water has a deleterious effect due to the hydrolysis of the phthalate ester to phthalic acid.

2-Chloro-2-methylmercapto-1,3-indandione (V).—Sodium methoxide (5.4 g., 0.1 mole) was suspended in 75 ml. of anhydrous dimethyl sulfoxide in a 250-ml. round-bottomed flask under an atmosphere of nitrogen. The suspension was stirred by a stream of nitrogen introduced by a gas inlet tube extending to the bottom of the flask. Diethyl phthalate (5.5 g., 0.025 mole) was added dropwise to this suspension. The reaction mixture, which turned yellow after about 5 min., was kept under nitrogen for 4 hr. at room temperature after which it was subjected to vacuum distillation at 1-mm. pressure (bath temperature 65–70°) for 50 min. To the resulting sticky yellow residue 50 ml. of ether and 50 ml. of ice–water were added. The yellow aqueous layer was separated and added dropwise with stirring to a mixture of 60 ml. of water and 40 ml. of concentrated hydrochloric acid. The colorless precipitate which formed rapidly was removed by filtration and dried under vacuum to give V, 4.55 g. (80%), m.p. 63°. A sample recrystallized from ether containing a trace of ethanol had m.p. 63–64°.

Anal. Calcd. for $C_{10}H_7ClO_2$; C, 52.90; H, 3.25; Cl, 15.44; S, 14.38; mol. wt., 226.6. Found: C, 53.0; H, 3.10; Cl, 15.61; S, 14.13; mol. wt., 226 (dioxane).[8]

The infrared absorption of V gave the characteristic indandione absorption at 5.70 and 5.85 μ as well as absorption due to the carbon sulfur bond at 8.05 μ. Absorption characteristic of a sulfoxide at 9.8 μ was absent. The integrated n.m.r. (60 Mc./sec.) spectrum gave aromatic hydrogen (unresolved), intensity 4.0, at 481 cycles relative to tetramethylsilane and methyl hydrogens, (singlet) at $\tau = 7.52$, intensity 3.

Ninhydrin from V.—One gram of V was added slowly to 50 ml. of boiling water in a 100-ml. erlenmeyer flask. The slightly yellow solution was kept on a steam bath for 12 hr. during which most of the water evaporated. The concentrated aqueous solution was transferred to a 50-ml. beaker and evaporated on a steam bath for another hour to yield a crystalline residue which was dried under vacuum. The material thus prepared (775 mg., 99%) had m.p. 239–240° and an infrared spectrum identical with that of of commercial ninhydrin.

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[1] Reactions of Resonance Stabilized Anions, part VII. For part VI see H.-D. Becker and G. A. Russell, *J. Org. Chem.*, **28**, 1895 (1963).

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[3] Alfred P. Sloan Foundation Fellow, 1959–1963.

[4] L. F. Fieser and M. Fieser, "Advanced Organic Chemistry," Reinhold Publishing Corp., New York, N. Y., 1961, p. 472.

[5] See D. J. McCaldin, *Chem. Rev.*, **60**, 39 (1960).

[6] G. A. Russell and H.-D. Becker, Abstracts of Papers, 142nd National Meeting of the American Chemical Society, Atlantic City, N. J., September, 1962, p. 3Q.

[7] All melting points are uncorrected and were obtained using a Fisher-Johns melting point block.

[8] Determined by the thermoelectric osmometric method, Schwarzkopf Microanalytical Laboratories, Woodside, N. Y.

Preparation of β-Keto Sulfones by Condensation of Aromatic Esters with Dimethyl Sulfone[1,2]

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We have reported previously that in dimethyl sulfoxide (DMSO) solution aromatic esters undergo a con-

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