Synthesis of Ninhydrin[1,2]

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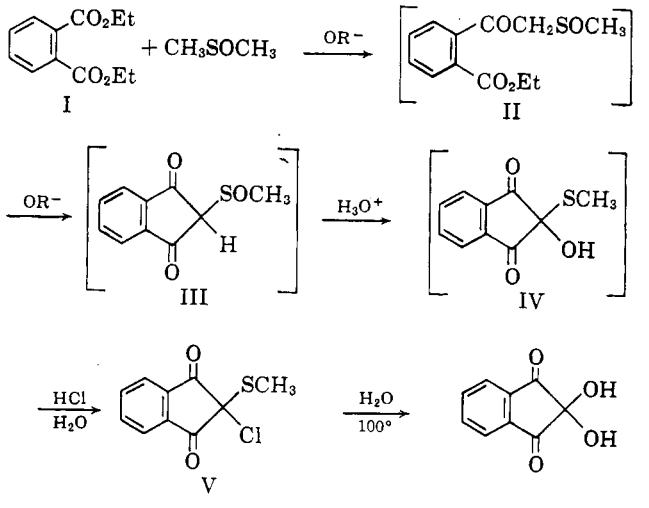
We have found that ninhydrin readily can be synthesized in two steps from ethyl phthalate. Ninhydrin is usually prepared by a six-step synthesis starting from esters of phthalic acid.[4] Other methods of preparation starting from 1,3-indandione or *p*-naphthoquinone give low yields of ninhydrin.[5]

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.

(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).

(2) This work was supported by a grant from the Alfred P. Sloan Foundation.

(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.

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 commercial ninhydrin.

(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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densation reaction with dimethyl sulfoxide in the presence of alkali metal alkoxides to form β-keto sulfoxides.[4] This suggested that other weak acids, such as dimethyl sulfone, should react with esters in dimethyl sulfoxide solution in the presence of alkoxide ions.

It is known that methyl ketones and esters readily undergo condensation in dimethyl sulfoxide containing sodium hydride to form β-diketones.[5] Moreover, reaction of dimethyl sulfone with ethyl benzoate in the presence of a sodium dispersion in benzene solution has been reported to give a 44% yield of the β-keto sulfone[6a] while numerous cyclizations of ω-methylsulfonyl esters (using sodium ethoxide in toluene) and ω-methylsulfonylnitriles (using sodium amide in refluxing benzene) are reported.[6]

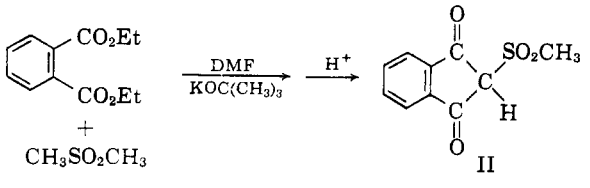
We have found that dimethyl sulfone in dimethyl sulfoxide solution containing potassium *t*-butoxide reacts with ethyl benzoate at 50–60° to form ω-(methylsulfonyl)acetophenone (Ia) in 90% yield. In a similar

$$RCOOR' + CH_3SO_2CH_3 \xrightarrow[KOC(CH_3)_3]{DMSO} RCOCH_2SO_2CH_3 \quad (I)$$

Ia, R = phenyl
Ib, R = *p*-methoxyphenyl

manner we have prepared ω-(methylsulfonyl)-*p*-methoxyacetophenone (Ib) in good yield. Thus, the condensation reaction using dimethyl sulfoxide as the solvent appears to be the preferred method of synthesis.

We have also studied the condensation reaction of dimethyl sulfone with diethyl phthalate. This reaction had been attempted earlier with negative results in hope of preparing a benzothiepin derivative.[7] In dimethyl sulfoxide solution the condensation also failed to yield identifiable products, although in the absence of dimethyl sulfone we have found that dimethyl sulfoxide condenses readily with diethyl phthalate to give an intermediate sulfoxide analogous to II.[1] When the condensation reaction was performed in dimethylformamide (DMF) solution, II was isolated in the form of a crystalline potassium salt which upon acidification with hydrochloric acid yielded colorless crystalline II in an over-all yield of 18%. The titration curve of II in aqueous solution resembles that of hydrochloric acid. In aqueous solution a 0.04 *M* solution of II gave a pH of 1.5 as measured by a calibrated glass electrode. This pH is approximately the same as found for 0.04 *M* solutions of hydrochloric acid. The pK_a value of II obviously is smaller than 2 but it can not be determined with any accuracy from the potentiometric titration curve.[8]



The structures of the β-keto sulfones prepared are supported by integrated n.m.r. spectra.[9] In addition to the absorption of the aromatic protons (intensity 5) the spectrum of Ia exhibits a singlet at $\tau = 5.37$ (intensity 2) for the methylene group and a singlet at $\tau = 6.89$ (intensity 3) for the methyl group. The spectrum of Ib has the following absorptions: protons (a_2b_2) at $\tau = 2.04$ and $\tau = 3.07$ ($J_{ab} = 9.05$ c.p.s.), total intensity 4; a singlet at $\tau = 5.47$ (intensity 2) for the methylene group; a singlet at $\tau = 6.12$ (intensity 3) for the methoxy group; and a singlet at $\tau = 6.89$ (intensity 3) for the methyl group. The n.m.r. spectrum of II shows four aromatic protons, a singlet at $\tau = 5.4$ (intensity 1) for the methine group, and a singlet at $\tau = 6.7$ (intensity 3) for the methyl group.

Experimental[10]

Reagents.—Dimethyl sulfoxide (Crown Zellerbach Corp.) was dried over calcium hydride and distilled under vacuum with a bath temperature of 60°. Dimethyl sulfone was recrystallized from chloroform. Potassium *t*-butoxide was sublimed under vacuum.

ω-(Methylsulfonyl)-acetophenone (Ia).—Potassium *t*-butoxide (2.44 g.) was suspended in a solution of 1.882 g. (20 mmoles) of dimethyl sulfone in 15 cc. of dimethyl sulfoxide under dry, oxygen-free nitrogen. To this solution 1.5 g. of ethyl benzoate (10 mmoles) was added dropwise. The mixture was maintained at 50–60° for 90 min. with agitation from a stream of nitrogen introduced at the bottom of the flask. Addition of 100 cc. of ice–water and 10 cc. of 5 *N* hydrochloric acid yielded 1.63 g. of a colorless crystalline precipitate, m.p. 105°. The filtrate was twice extracted with 100 cc. of ether to yield an additional 175 mg. of colorless product. The total crude yield of Ia was 1.8 g. (91%). Recrystallization from a chloroform–ethanol mixture raised the m.p. to 106–107° (lit.[6a] m.p. 107.5–108°).

Anal. Calcd. for $C_9H_{10}O_3S$ (198.17): C, 54.54; H, 5.09; S, 16.12. Found: C, 54.54; H, 5.32; S, 16.23.

ω-(Methylsulfonyl)-*p*-methoxyacetophenone (Ib).—Condensation of methyl *p*-anisate (1.66 g., 10 mmoles) with 1.882 g. (20 mmoles) of dimethyl sulfone in a manner similar to that employed in the preparation of Ia, yielded 1.92 g. (89%) of crude Ib, m.p. 135–136°. Recrystallization from chloroform, containing a little ethanol, gave colorless needles, m.p. 137–138°.

Anal. Calcd. for $C_{10}H_{12}O_4S$(228.20): C, 52.63; H, 5.30; S, 14.03. Found: C, 52.36; H, 5.25; S, 13.75.

2-(Methylsulfonyl)-1,3-indandione.—Dimethyl sulfone (471 mg., 5 mmoles) and 600 mg. of potassium *t*-butoxide were dissolved in 10 cc. of dimethylformamide with agitation from a stream of dry, oxygen-free nitrogen. Diethyl phthalate (1.1 g., 5 mmoles) was added dropwise to the solution at 50°. The mixture was agitated under nitrogen for an additional 30-min. period at 50°. After this time 10 cc. of water and 30 cc. of ether were added to the dark yellow reaction mixture. The yellow aqueous layer was separated and kept in an open Petri dish overnight. The resulting yellow oil was treated with 100 cc. of ethanol yielding a crystalline yellow potassium salt, which was separated by filtration, boiled briefly in 10 cc. of ethanol, filtered, and dried to give 250 mg. of product. This product when dissolved in 2 cc. of warm water followed by the addition of 0.5 cc. of 7.5 *N* hydrochloric acid yielded 210 mg. of colorless crystalline II (18.7%), m.p. 150–151°. Recrystallization from hot chloroform gave colorless prismatic needles, m.p. 150–151°. The substance turns yellow upon melting, forming colorless crystals on resolidification.

Anal. Calcd. for $C_{10}H_8O_4S$ (224.16): C, 53.58; H, 3.60; S, 14.28. Found: C, 53.71; H, 3.63; S, 14.46; neut. equiv., (potentiometrically), 226.

(4) 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.

(5) J. J. Bloomfield, *J. Org. Chem.*, **27**, 2742 (1962).

(6) (a) W. E. Truce and R. H. Knospe, *J. Am. Chem. Soc.*, **77**, 5063 (1955); (b) W. E. Truce, W. W. Bannister, and R. H. Knospe, *J. Org. Chem.*, **27**, 2821 (1962).

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(8) Preliminary results of a spectrophotometric determination of the pK_a of this unusually strong acid in perchloric acid solution by G. J. Mikol indicates a pK_a of −0.23.

(9) Determined at 60 Mc./sec. in chloroform-*d* solution.

(10) Melting points were determined on a Fisher-Johns apparatus and are uncorrected.

The infrared absorption of II in potassium bromide pellets did not indicate the presence of a hydroxyl group. The absence of an enolic structure was also consistent with the n.m.r. analysis.

Lithium Aluminum Hydride Reductions of Pyrazine Carboxylic Esters. Synthesis of Pyrazinealdehyde from Methyl Pyrazinoate

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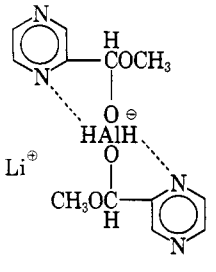
A search of the literature shows that only one pyrazinealdehyde, the 3-amino-2-pyrazinealdehyde,[1] has been described. It was obtained by the acid hydrolysis of the rather inaccessible pteridine. However, the existence of pyrazinealdehyde I, at least as a transitory species, was confirmed by the *in situ* preparations of the 2,4-dinitrophenylhydrazone and the thiosemicarbazone[2,3] *via* the McFadyen–Stevens reaction.

Kakemi, *et. al.*,[4] used the same reaction to prepare nicotinoyl- and isonicotinoylhydrazones of I. Behun and Levine synthesized[5] pyrazinealdehyde dimethyl acetal from sodium methoxide and dichloromethylpyrazine, but preliminary experiments to hydrolize the latter were unsuccessful. We have obtained I in 78% yield (as the 2,4-dinitrophenylhydrazone) by a novel, selective reduction of methyl pyrazinoate with lithium aluminum hydride. The reaction was carried out in tetrahydrofuran at −70° by "inverse" addition of 0.5 mole of lithium aluminum hydride per mole of ester. After standing at −70° for fifteen minutes, the reaction was stopped by adding glacial acetic acid.

A preliminary investigation of the reaction mechanism suggests the formation of a soluble hemiacetal complex. Aldehyde is then liberated upon the addition of acid.



In a series of experiments, increasing amounts of lithium aluminum hydride were used and the corresponding yields of aldehyde were determined. An optimum yield of pyrazinealdehyde was obtained when 0.5 mole of lithium aluminum hydride was allowed to react with one mole of methyl pyrazinoate while excess of the reductant had only a negligible effect. In a number of experiments, pyrazinealdehyde was substituted for methyl pyrazinoate and subjected to the stated lithium aluminum hydride reduction conditions. We were able to recover only small amounts of unchanged aldehyde, the remainder having undergone further reduction.

Pyrazinealdehyde is a light-sensitive, low melting solid (m.p. 31–33°, b.p. at 6 mm., 57–58°). It was characterized by conversion to the octahydroxanthene derivative as well as to the known 2,4-dinitrophenylhydrazone,[2] nicotinoylhydrazone, and isonicotinoylhydrazone.[4] I dissolves in a saturated sodium bisulfite solution with the formation of a soluble addition product. Like pyridine-2-aldehyde, which yields α-pyridyl-α-hydroxymethanesulfonic acid[6] when treated with aqueous sulfurous acid, I forms an analogous reaction product. The aldehyde undergoes a Cannizzaro reaction, yielding pyrazinoic acid and pyrazylmethanol. Since the latter compound is as yet unrecorded in the literature, it was characterized by ultraviolet and infrared spectra and the preparation of its α-naphthylcarbamate derivative.

Benzoin condensation of I affords pyrazoin in 85% yield. The absence of carbonyl absorption in its infrared spectrum as well as its behavior towards Tillmann's reagent[7] suggests an enediolic structure analogous to α-pyridoin.[8] Prior to the described reduction procedure we attempted to obtain pyrazinealdehyde by the reduction of pyrazinoyl chloride with lithium tri-*t*-butoxyaluminohydride.[9] The yield of I, however, never exceeded 20% (as the 2,4-dinitrophenylhydrazone). The major product of this reaction was pyrazylmethyl pyrazinoate, which was isolated in a 55% yield.

It was of interest to ascertain whether the low temperature reduction with lithium aluminum hydride could be extended to esters belonging to other series. Consequently, we initiated a series of experiments in which a number of esters were subjected to standardized reaction conditions. To simplify the experiments, only such esters were selected for which the corresponding aldehydes and their 2,4-dinitrophenylhydrazones were known, and the yields were determined by isolating the 2,4-dinitrophenylhydrazones. We found that while the reaction is not confined to methyl pyrazinoate it appears, however, to be limited to π-electron deficient systems. Aldehyde formation also is favored when the carbomethoxy group is in an electron deficient position. Thus, the three isomeric carbomethoxypyridines gave 75%, 12%, and 50% yields of the corresponding 2-, 3-, and 4-aldehydes. Quinoline-2-aldehyde was formed in 92% yield from methyl quinaldate. Ethyl acetate, methyl benzoate, diethyl phthalate, and benzonitrile failed to give carbonyl positive materials. Methyl *o*-nitrobenzoate produced only 5% of the expected aldehyde (probably because of steric hindrance), while the *p*-nitro ester reacted to the extent of 36% (a yield comparable to that of 4-carbomethoxypyridine).

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(9) H. C. Brown and B. C. Subba Rao, *J. Am. Chem. Soc.*, **80**, 5377 (1958).