

Anal. Calcd. for C₁₉H₁₅ClS: C, 73.41; H, 4.86. Found: C, 73.32; H, 4.89.

p-Chlorobenzhydryl Methyl Sulfide. *p*-Chlorobenzhydryl mercaptan¹³ was treated with methyl iodide in the same way as described⁹ for the synthesis of benzhydryl methyl sulfide. The initial product was an oil, which after some difficulty could be induced to crystallize from hexane, m.p. 31–32°.

Anal. Calcd. for C₁₄H₁₃ClS: C, 67.60; H, 5.27. Found: C, 67.71; H, 5.41.

Kinetic Studies of Thiocarbonate Decomposition.

Infrared Method. The apparatus used was of the same basic design as that employed by Kice and Bowers¹⁴ for kinetic studies of sulfinic acid disproportionation. Its principal feature is that it permits a sample to be removed without exposing the reaction solution to the external atmosphere.

A solution of the thiocarbonate was placed in the reaction flask, and a slow stream of nitrogen was passed through the solution for 1 hr. at room temperature to deaerate it. The reaction flask was then immersed in a constant temperature bath held at the desired temperature. A very slow stream of nitrogen was bubbled through the solution during the entire decomposition. Small samples were removed at convenient time intervals, including one infinity time sample removed after decomposition was complete.

The infrared absorption spectrum of these samples was then determined over the region 1800–1600 cm.⁻¹. Earlier experiments with standard solutions of the various thiocarbonates in the reaction solvents employed had shown that the intensity of the thiocarbonate ester carbonyl band, which, depending on

the ester, occurs at frequencies from 1720 to 1705 cm.⁻¹, followed Beer's law and that a plot of optical density vs. milligrams of thiocarbonate per milliliter of solution was satisfactorily linear.

Carbon Dioxide Evolution Method. An apparatus, similar to that employed for kinetic study of the thermal decomposition of thiosulfonates,¹¹ was used as the reaction flask. This permitted one to pass a stream of nitrogen through the solution throughout the decomposition. This nitrogen stream served to sweep the carbon dioxide evolved in the decomposition out of the reaction flask and into an apparatus for determination of carbon dioxide of the type described by Patchornik and Shalitin.¹⁵ In this apparatus the evolved carbon dioxide was trapped in an ethanol-dioxane-benzylamine solution (3:3:1) and determined by direct titration with a 0.08 *N* solution of sodium methoxide in methanol-benzene. Thymol blue (0.2% in dioxane) was used as indicator. Provided one avoids decompositions having very rapid rates, there is no difficulty in passing nitrogen through the reaction solution at a rate which keeps the time between the evolution of a molecule of CO₂ and its absorption in the ethanol-dioxane-benzylamine solution small enough so as not to interfere with accurate determination of the rate of decomposition of the thiocarbonate.

Purification of Solvents. Bromobenzene was purified as outlined in an earlier paper.¹¹ Benzonitrile was subjected to one additional purification step besides those previously described.¹¹ A slow stream of nitrogen was passed through the purified solvent while it was heated to 165° for 6 hr. This treatment served to remove a small amount of a slowly volatile carbonyl impurity which otherwise interfered seriously with the infrared procedure for following the kinetics.

(13) H. Fukada, *J. Pharm. Soc. Japan*, **72**, 1472 (1952); *Chem. Abstr.*, **47**, 8706 (1953).

(14) J. L. Kice and K. W. Bowers, *J. Am. Chem. Soc.*, **84**, 605 (1962).

(15) A. Patchornik and Y. Shalitin, *Anal. Chem.*, **33**, 1887 (1961).

The Mechanism of the Hinsberg Thiophene Ring Synthesis^{1,2}

Hans Wynberg and H. J. Kooreman

Contribution from the Department of Organic Chemistry, The University, Groningen, Holland. Received January 11, 1965

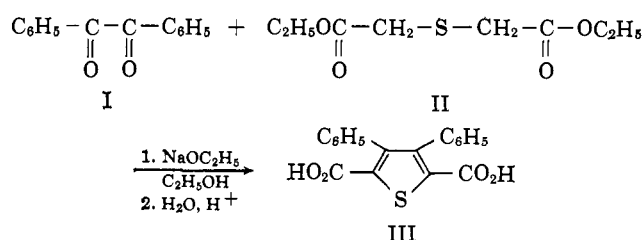
Using conventional as well as O¹⁸ isotope techniques it has been shown that the reaction between α -diketones and thiodiacetates to yield thiophenes (Hinsberg condensation) is a Stobbe-type condensation proceeding via a δ -lactone intermediate.

More than 50 years ago Hinsberg³ first described the reaction between benzil (I) and diethyl thiodiacetate (II) to produce the thiophene ring system. The reaction, run essentially under Claisen-type conditions, was always worked up by diluting the alcoholic alkaline mixture with water, boiling for some time, and isolating the free dicarboxylic acid (III) thus formed.

(1) Presented in part at the 145th National Meeting of the American Chemical Society, New York, N. Y., Sept. 1963.

(2) Abstracted in part from the Doctoral Thesis of H. J. K.

(3) O. Hinsberg, *Ber.*, **43**, 901 (1910).



The reaction proved to be quite general and Hinsberg,^{3,4} Backer and Stevens,^{5,6} Dimroth,^{7,8} and others⁹ have used the reaction to prepare thiophenes,

(4) O. Hinsberg, *ibid.*, **45**, 2413 (1912).

(5) W. Stevens, Thesis, Groningen, 1940.

(6) H. J. Backer and W. Stevens, *Rec. trav. chim.*, **59**, 423, 899 (1940).

(7) K. Dimroth and H. Freyschlag, *Ber.*, **89**, 2602 (1956).

(8) K. Dimroth and U. Pintschovius, *Ann.*, **639**, 102 (1961).

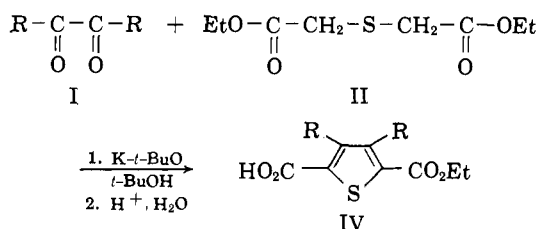
(9) D. E. Wolf and K. Folkers, *Org. Reactions*, **6**, 410 (1951).

furans, selenophenes, and pyrroles by varying the ester component from the sulfur to the oxygen, selenium, and nitrogen analogs.

The review by Wolf and Folkers⁹ is especially noteworthy since the reaction products are described as *diesters*, an incorrect generalization which has found its way into the literature to date. There is however no authentic report in the literature^{3-6,9} which could be interpreted as indicating that a *diester* has been isolated as the primary condensation product from the reaction between α -diketones and thiodiacetates.^{9,10}

This discrepancy made us suspect that the α -diketone reaction was fundamentally a Stobbe-type condensation furnishing the half-acid, half-ester as shown so elegantly by Johnson¹¹ and co-workers for the reaction between monocarbonyl compounds and succinic esters.

We have now shown this supposition to be correct. The condensation between α -diketones and thiodiacetates furnishes the half-acid, half-ester thiophene derivative IV in high yield.



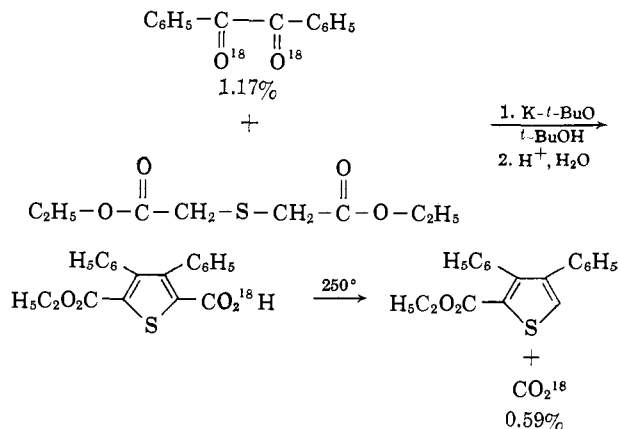
When benzil (I, R = C₆H₅) and diethyl thiodiacetate (II) were allowed to react for 15 min. at room temperature in *t*-butyl alcohol containing potassium *t*-butoxide, and the reaction mixture was worked up under Stobbe-Johnson¹¹ conditions, the monoethyl ester of 3,4-diphenylthiophene-2,5-dicarboxylic acid (IV, R = C₆H₅) could be isolated in 93% yield. It showed no depression in melting point (224–225°) on admixture with an authentic sample of half-ester, prepared by partial hydrolysis of the diester.⁵ Conversion of the crude half-ester to 2-carbomethoxy-5-carbomethoxy-3,4-diphenylthiophene in 80% confirmed the structure. Diacetyl (I, R = CH₃) and diethyl thiodiacetate similarly yielded the corresponding half-ester (IV, R = CH₃) in 85–90% yield.¹²

For a normal Stobbe condensation,¹¹ the half-ester product cannot be obtained by partial hydrolysis of the diester during the reaction.

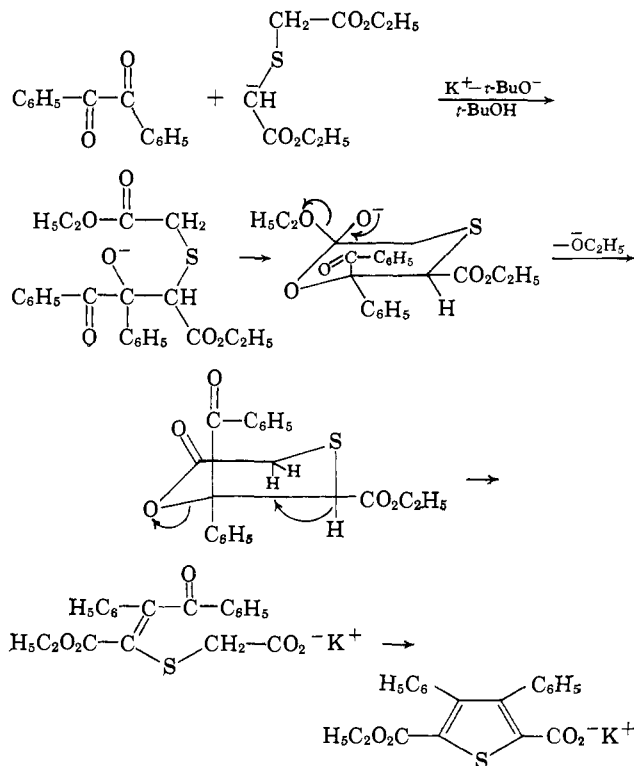
Similarly when some dimethyl 3,4-diphenylthiophene-2,5-dicarboxylate was added to the reaction mixture containing benzil, diethyl thiodiacetate, *t*-butyl alcohol, and potassium *t*-butoxide, the dimethyl ester was recovered in 75% yield while the monoethyl ester was again isolated in high yield as before.

The condensation was then performed using O¹⁸-enriched benzil. If a Stobbe-type condensation^{11,13} was operable, the δ -lactone intermediate would cause the transfer of 50% of the isotope in the benzil to the oxygen of the carboxylic acid group in the product. When the half-ester, resulting from the condensation

using O¹⁸-enriched benzil, was decarboxylated the carbon dioxide was found to contain exactly 50% (within the experimental error) of the O¹⁸ originally present in the benzil. In a separate nonisotopically enriched experiment the decarboxylated ethyl ester of 3,4-diphenylthiophene-2-carboxylic acid was isolated (and identified) in 53% yield.



It is clear from these experiments that the half-ester acid must be formed by a nonhydrolytic route, and a δ -lactone intermediate suggested itself at once. The ring synthesis may then follow the course:



Initial condensation of the thiodiacetate with benzil is followed by δ -lactone formation. Opening of the lactone ring furnished the unsaturated half-acid ester. The Knoevenagel-type condensation to form the thiophene ring may have as driving force the production of the stable aromatic system in an essentially irreversible step.¹⁴ Acyclic analogs are known in the Stobbe reaction of 2 moles of ketone with succinic esters and diethyl thiodiacetate.¹¹

It seems reasonable to propose that the analogous syntheses of furans,^{5,6} pyrroles,^{7,8} and selenophenes^{5,6}

(10) Related condensations, namely between oxalic esters and thiodiacetates, do furnish diesters.

(11) W. S. Johnson and G. H. Daub, *Org. Reactions*, **6**, 1 (1951).

(12) H. Wynberg and D. J. Zwanenburg, *J. Org. Chem.*, **29**, 1919 (1964).

(13) D. Jeffery and A. Fry, *ibid.*, **22**, 735 (1957), performed a similar experiment confirming the mechanism of the Stobbe reaction.

follow a similar reaction sequence. In fact, the mechanism outlined above would furnish a reasonable explanation for the formation of 3,4-diphenylfuran-2-carboxylic acid (and its methyl ester) and 3,4-diphenylselenophene-2-carboxylic acid^{6,6} as well as most of the reaction products found by Dimroth.⁸

Experimental

All melting points and boiling points are uncorrected. The ultraviolet spectra were determined in 96% ethanol solution with a Zeiss spectrophotometer, Model PMQ II. The infrared spectra were measured with a Perkin-Elmer Model 137 spectrophotometer. The microanalyses were carried out in the analytical section of our department under the direction of W. M. Hazenberg. Mass spectral data were obtained with a AEI-MS2-H and a Metropolitan-Vickers MS3 mass spectrometer, respectively, of the Universities of Amsterdam and Leiden.

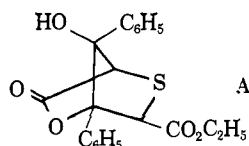
2-Carboethoxy-3,4-diphenylthiophene-5-carboxylic Acid (IV). Using the apparatus described in detail by Johnson and Daub,¹¹ 4.2 g. (0.11 g.-atom) of potassium was dissolved in 100 ml. of anhydrous *t*-butyl alcohol. To the solution kept at 30° a mixture of 8.0 g. (0.038 mole) of benzil (m.p. 95°) and 14.0 g. (0.068 mole) of diethyl thiodiacetate (b.p. 100–102° at 1.5 mm.) was added. The reaction mixture was stirred for 15 min. and acidified with 20 ml. of hydrochloric acid (1:1). After removal of most of the alcohol by distillation (aspirator) the residue was extracted with ether. The organic layer was then extracted with 50-ml. portions of 2 *N* ammonia until a sample of the aqueous layer gave no precipitate upon acidification.

The combined ammonia layers were briefly warmed on a steam bath to remove the dissolved ether, and then acidified furnishing 12.4 g. (93%) of 2-carboethoxy-3,4-diphenylthiophene-5-carboxylic acid, m.p. 205–210°, as a slightly tan solid. A pure sample, obtained by recrystallization from acetic acid, melted at 224–225° and gave no depression on admixture with a sample prepared by hydrolysis of the diester,⁵ $\lambda_{\text{max}}^{\text{alcohol}}$ 226 m μ (ϵ 21,000) and 282 m μ (ϵ 11,600).

3,4-Diphenyl-2-carboethoxy-5-carboethoxythiophene. An ethereal solution of diazomethane prepared from 2.14 g. (0.01 mole) of *p*-tolylsulfonylethyl nitrosamide¹⁵ was distilled in an erlenmeyer containing 1.0 g. (0.0028 mole) of the crude monoethyl ester and 100 ml. of anhydrous ether. During the reaction the monoester dissolved. The solution was allowed to stand overnight.

After removing most of the ether the methyl ethyl ester was deposited in white crystals. The yield was 0.40 g., m.p. 146–147°. *Anal.* Calcd. for C₂₁H₁₈O₄S (mol. wt., 366.4): C, 68.85; H, 4.95; S, 8.75. Found:

(14) A bridged intermediate (A) is sterically and mechanistically feasible.



(15) Th. J. de Boer and H. J. Backer, *Org. Syn.*, **36**, 16 (1956).

C, 69.0; H, 5.2; S, 8.6. Further concentration of the mother liquor yielded another 0.43 g., m.p. 142–144° (total yield 80%).

Condensation in the Presence of Dimethyl 3,4-Diphenylthiophene-2,5-dicarboxylate. The condensation of 1.3 g. (0.0062 mole) of benzil and 2.3 g. (0.012 mole) of diethyl thiodiacetate using 0.70 g. (0.018 g.-atom) of potassium in 25 ml. of *t*-butyl alcohol was repeated in the presence of 1.0 g. of dimethyl 3,4-diphenylthiophene-2,5-dicarboxylate (m.p. 187–188°). Working up the reaction mixture as described above yielded 1.6 g. of 3,4-diphenyl-2-carboethoxythiophene-5-carboxylic acid (73%). From the neutral ethereal solution 0.75 g. of dimethyl 3,4-diphenylthiophene-2,5-dicarboxylate, m.p. 180–182°, was recovered.

This dimethyl ester did not contain any diethyl ester as shown clearly by infrared spectroscopy. The latter compound showed a splitting of the ester peak at 1740 and 1710 cm.⁻¹ with a shoulder at 1690 cm.⁻¹. The dimethyl ester gives a sharp peak at 1730 cm.⁻¹. The remainder of the spectrum was also identical with that of authentic starting dimethyl ester. The infrared spectrum of the crude condensation product was completely in agreement with that of pure monoethyl ester.

Ethyl 3,4-Diphenylthiophenecarboxylate. 3,4-Diphenyl-2-carboethoxythiophene-5-carboxylic acid (IV) (10.0 g., 0.014 mole) was placed in a flask and heated at 300° at aspirator vacuum. A vigorous reaction took place and 7.1 g. of an oil distilled and solidified in the condenser. Crystallization from ethanol furnished 4.6 g. (53%) of ethyl 3,4-diphenylthiophene-2-carboxylate, m.p. 64–66°. From the mother liquor 1.4 g. (14%) of starting material was recovered (identified by its infrared spectrum). Analytically pure monoester melted at 74–75°. *Anal.* Calcd. for C₁₉H₁₆O₂S (mol. wt., 308.1): C, 74.01; H, 5.19; S, 10.41. Found: C, 73.8; H, 5.3; S, 10.5.

Preparation of O¹⁸-Labeled 3,4-Diphenyl-2-carboethoxythiophene-5-carboxylic Acid. Benzil-O¹⁸, m.p. 95.5–96°, containing 1.17% O¹⁸ was prepared according to the procedure of Roberts and Urey.¹⁶ A solution of 2.1 g. (0.054 g.-atom) of potassium in 50 ml. of anhydrous *t*-butyl alcohol was treated with 4.0 g. (0.019 mole) of benzil-O¹⁸ and 7.0 g. (0.034 mole) of the ethyl ester of thiodiacetic acid as described above. The crude half-ester was extensively washed with water (to get rid of traces of *t*-butyl alcohol) and dried *in vacuo*.

Analysis for O¹⁸. The O¹⁸ content of the benzil was determined following the method of Dahn, Moll, and Menassé.¹⁷ The apparatus used was that described by Talman.¹⁸ This procedure involves the heating of a sample of benzil with an excess of *o*-phenylenediamine and an exactly known quantity of carbon dioxide in a sealed Pyrex tube. Thus, the reaction between the α -diketone and the *o*-phenylenediamine and the exchange reaction between the liberated water and the carbon dioxide take place in one operation. The O¹⁸ content of benzil is calculated from the mass spectrometrically measured data of this carbon dioxide.

(16) I. Roberts and H. C. Urey, *J. Am. Chem. Soc.*, **60**, 880 (1938).

(17) H. Dahn, H. Moll, and R. Menassé, *Helv. Chim. Acta*, **42**, 1225 (1959).

(18) E. Talman, Thesis, Leiden, 1961.

Decarboxylation of the half-ester IV and measuring the O¹⁸ content of the liberated carbon dioxide seem the most direct route to determine the isotopic composition of the carboxylic acid group of the half-ester. To this end a sample (± 200 mg.) of the half-ester was heated at 240–250° during 15 min. in a sealed, evacuated, small Pyrex tube, which had an extended point on one side. The Pyrex tube was cooled and connected with this pointed end to a high-vacuum apparatus by a rubber vacuum tube. The apparatus was evacuated, the Pyrex tube was cooled in a mixture of Dry Ice and acetone, the pointed end of the Pyrex tube was broken in the rubber tube, and finally the carbon dioxide was collected in a sample trap immersed in liquid nitrogen.

This sample of carbon dioxide proved to be contaminated by some gaseous impurities. It was purified by the elegant method of Ehrensvärd.¹⁹ A 0.75% solution of octadecylamine in dry petroleum

(19) G. Ehrensvärd, *Z. Naturforsch.*, **14b**, 607 (1959).

ether (b.p. 80–100°) was leaked into the sample trap and the carbon dioxide precipitated as the carbamate. The latter was isolated by centrifugation and drying *in vacuo* over silica gel. As the carbamate decomposed within several minutes by heating at 100°, the carbon dioxide was recovered by essentially the same procedure as described above for the decarboxylation of the half-ester. The carbon dioxide thus obtained proved to be mass spectrometrically pure.

Three samples of benzil as well as three samples of carbon dioxide, obtained by decarboxylation of the half-ester IV, were analyzed for their O¹⁸ content. Mass spectrometric analyses gave the following results. *Anal.* Found for benzil: 1.16, 1.15, 1.19 (average, 1.17% O¹⁸). Found for CO₂: 0.61, 0.59, 0.56; (average, 0.59% O¹⁸).

Acknowledgment. We are indebted to Drs. H. J. Hofman and K. J. Klebe, respectively, of the Universities of Amsterdam and Leiden for cooperation with the mass spectrometric determinations. The assistance of Miss J. Meijer is gratefully acknowledged.

The Action of Acids on Nitronic Esters and Nitroparaffin Salts. Concerning the Mechanisms of the Nef and the Hydroxamic Acid Forming Reactions of Nitroparaffins^{1,2}

Nathan Kornblum and R. Alan Brown

Contribution from the Department of Chemistry, Purdue University, Lafayette, Indiana. Received November 20, 1964

Nitronic esters are rapidly decomposed by acids; the course which the reaction follows is strongly dependent on the acid concentration. Thus, the ethyl nitronic ester of p-nitrophenylnitromethane gives p-nitrobenzaldehyde in 80% yield on treatment with 4 N sulfuric acid while, in contrast, 31 N sulfuric acid converts it into p-nitrobenzhydroxamic acid in 98% yield. The reaction of nitroparaffin salts with sulfuric acid also exhibits this dependence on acid concentration. The mechanisms of these new nitronic ester reactions, and of the Nef and the hydroxamic acid forming reactions of nitroparaffins, are discussed in the light of these facts.

The salts of primary nitroparaffins when treated with aqueous mineral acid are smoothly converted to aldehydes. This reaction, known as the Nef Reaction, is of considerable synthetic value³ (eq. 1).



(1) This work was supported by the Air Force Office of Scientific Research, Office of Aerospace Research, United States Air Force, under AFOSR Grant No. 122-65.

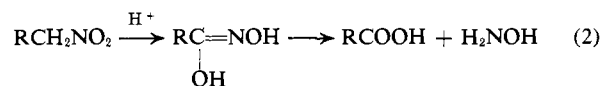
(2) Paper XXII in the series, "The Chemistry of Aliphatic and Alicyclic Nitro Compounds." For the preceding paper see N. Kornblum and R. A. Brown, *J. Am. Chem. Soc.*, **85**, 2681 (1963).

(3) (a) J. U. Nef, *Ann.*, **280**, 264 (1894); (b) J. C. Sowden, "Advances

in Carbohydrate Chemistry," Vol. 6, Academic Press Inc., New York, N. Y., 1951, pp. 291–318; (c) W. E. Noland, *Chem. Rev.*, **55**, 136 (1955).

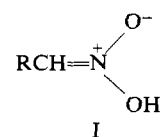
(4) V. Meyer and C. Wurster, *Ber.*, **6**, 1168 (1873); E. Bamberger and E. Rüst, *ibid.*, **35**, 45 (1902); S. B. Lippincott and H. B. Hass, *Ind. Eng. Chem.*, **31**, 118 (1939); M. J. Kamlet, L. A. Kaplan, and J. C. Dacons, *J. Org. Chem.*, **26**, 4371 (1961).

(5) W. E. Noland, ref. 3c; E. E. van Tamelen and R. J. Thiede, *J.*



since the reaction was first observed by Victor Meyer his name is sometimes attached to it.⁴

Protonation of a nitroparaffin salt occurs preferentially at oxygen to give the *aci* structure I. Not surprisingly, it is generally agreed that the Nef reaction proceeds by way of the *aci* form of the nitroparaffin I.⁵ But, as Noland has pointed out,^{3c} there is reason



in Carbohydrate Chemistry," Vol. 6, Academic Press Inc., New York, N. Y., 1951, pp. 291–318; (c) W. E. Noland, *Chem. Rev.*, **55**, 136 (1955).

(4) V. Meyer and C. Wurster, *Ber.*, **6**, 1168 (1873); E. Bamberger and E. Rüst, *ibid.*, **35**, 45 (1902); S. B. Lippincott and H. B. Hass, *Ind. Eng. Chem.*, **31**, 118 (1939); M. J. Kamlet, L. A. Kaplan, and J. C. Dacons, *J. Org. Chem.*, **26**, 4371 (1961).

(5) W. E. Noland, ref. 3c; E. E. van Tamelen and R. J. Thiede, *J.*