tion of 0.12 mole of octanes plus part of the 0.17 mole of pentane plus some lower layer material.

A second experiment was carried out at a higher temperature. A glass liner containing 21 g. (0.17 mole) of 1-chloro-3,3-dimethylbutane, 77 g. (1.3 moles) of isobutane and 5 g. of aluminum chloride was placed in the autoclave, nitrogen was added to a pressure of 50 atm., and the autoclave was rotated at room temperature for one hour and then at 40° for three hours. The products consisted of 52 g. of isobutane, 20 g. of liquid product, 9 g. of a viscous red-brown catalyst layer and 4.5 g. of hydrogen chloride (73% of the theoretical yield) which was measured as the increase in weight of the soda lime tower in the exit line. The liquid product was completely paraffinic. No *t*-butyl chloride or unreacted 1-chloro-3,3-dimethylbutane was obtained. The reaction temperature was high enough to cause complete reaction of even the primary chloride. At least 90% of the liquid product boiled below 120°. Isopentane, 2,3-dimethylbutane and octanes were again the principal products of the reaction.

Summary

A chain mechanism which involves the following reactions is proposed for the alkylation of isoparaffins with olefins: 1. Conversion of the isoparaffin to a *t*-alkyl ester. 2. Addition of the *t*-alkyl ester to the olefin to yield an ester of higher molecular weight. 3. Reaction of the ester of higher molecular weight with the isoparaffin to yield the observed paraffin product and a new molecule of the *t*-alkyl ester.

The *t*-alkyl ester formed in the third step reacts with olefin as in the second step and the cycle is repeated.

Evidence in support of the mechanism is presented.

CHICAGO, ILL. RECEIVED MARCH 8, 1945

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING OF THE UNIVERSITY OF PENNSYLVANIA]

The Willgerodt Reaction. I. The Use of Aliphatic Carbonyl Compounds[1]

BY LIEBE CAVALIERI, DEXTER B. PATTISON[2] AND MARVIN CARMACK

Numerous examples of the use of the Willgerodt reaction with aryl alkyl ketones have appeared in the literature.[3,4] Practically all of the successful reactions can be represented by the generalized equation

$$\text{Aryl—CO(CH}_2)_n\text{CH}_3 \xrightarrow{(\text{NH}_4)_2\text{S}_x} \text{Aryl—CH}_2(\text{CH}_2)_n\text{CONH}_2$$

in which the aryl group may be any of a wide variety of aromatic nuclei not affected by the reagent, and *n* may vary from 0 to at least 4. The reaction is caused by the action of aqueous ammonium polysulfide on the ketone in a closed system at temperatures up to 200° or higher. The use of dioxane in addition to the ammonium polysulfide, introduced by Fieser and Kilmer,[4] permits the Willgerodt reaction to be carried out at temperatures in the neighborhood of 160° and usually with better yields than in aqueous solution alone.

It appears to have been generally assumed that the presence of an aromatic group on the carbonyl unit is essential for the occurrence of the Willgerodt reaction, since there is no record of an attempt to apply the method to a completely aliphatic ketone. In an early paper, Willgerodt reported[3] that acetone reacts with ammonium polysulfide at room temperature to form a complex sulfur-containing compound of unknown structure, but he apparently did not study the reaction of acetone at the higher temperatures required for the formation of amides.

We have found that aliphatic carbonyl compounds of the type $\text{RCO(CH}_2)_n\text{H}$, in which R represents an aliphatic hydrocarbon radical, may undergo reactions with ammonium polysulfide reagent to yield products analogous to those from aryl alkyl ketones. The products have the structures represented by $\text{R(CH}_2)_n\text{CONH}_2$. This paper describes experiments with compounds in which *n* has values from 0 to 3. The carbon skeleton present in the starting compound remains unchanged in the final amide, a fact which is of considerable interest in connection with the formulation of a general mechanism for the Willgerodt reaction and the related Kindler reaction.[5,6] Since, in the R group, the carbon atom directly attached to the carbonyl group may be primary, secondary, or tertiary, it can be seen that this extension of the Willgerodt reaction affords a new approach to the synthesis of branched chain as well as straight chain fatty acids and amides. Particular interest attaches to certain branched chain aliphatic acids because of their relationship to phthioic acid and the evidence that some, *e. g.*, β,β-dioctylbutyric acid, are bactericidal to tubercle bacilli.[7]

The equations shown below represent the reactions of a number of typical carbonyl compounds which we have studied. Yields of amides are indicated in parentheses.

---

[1] Material from this paper was presented before the Organic Division at the Spring Meeting held by the Philadelphia Section of the American Chemical Society in Philadelphia on June 13, 1945.

[2] A portion of a thesis submitted by Dexter B. Pattison to the Graduate School of the University of Pennsylvania in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Chemistry.

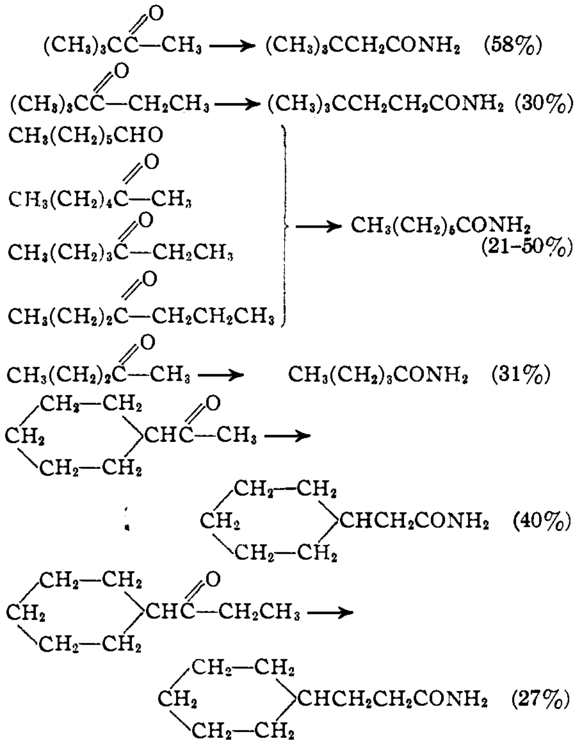
[3] Willgerodt, *Ber.*, **20**, 2467 (1887); **21**, 534 (1888).

[4] Fieser and Kilmer, THIS JOURNAL, **62**, 1354 (1940). A bibliography of earlier articles on the Willgerodt reaction appears as a footnote in this publication.

[5] Kindler and Li, *Ber.*, **74B**, 321 (1941).

[6] Schwenk and Bloch, THIS JOURNAL, **64**, 3051 (1942).

[7] Robinson, *J. Chem. Soc.*, 505 (1940).



In most of the experiments with aliphatic carbonyl compounds, the ammonium polysulfide reagent was prepared immediately before use by adding flowers of sulfur to a stock solution of aqueous ammonium sulfide. The latter solution was prepared by passing hydrogen sulfide into concentrated (15 *M*) aqueous ammonia. The best results were obtained with aliphatic compounds when the concentration of sulfide, determined by iodimetric titration, was approximately 7 *M*; in such a solution the concentration of ammonia determined by titration with standard acid was of the order of 12 *M*. A considerable excess of sulfur (up to twenty gram atomic weights for each mole of ketone) was used. Dioxane[4] or pyridine[7a] was added to increase the solubility of the organic reactant in the reagent. Dioxane appeared to be superior to pyridine in some cases, *e. g.*, pinacolone, while pyridine gave better results with some other compounds, *e. g.*, 4-heptanone.

Numerous experiments were made with each compound to determine the best proportions of reagents to carbonyl compound and the optimum conditions of time and temperature. The experiments described are typical of the best results with each compound. The use of a smaller proportion of sulfur to carbonyl compound usually resulted in a decrease in the yield of amide, while the use of larger excesses of sulfur did not increase the yield. Attempts to increase the weight of carbonyl compound used in a run without proportional increases in all other reactants gave less satisfactory results.

The reaction temperature was chosen in each case on the basis of preliminary experiments so that unreacted ketone could not be detected after a heating period of four to six hours. When the aliphatic group, R, had a primary or secondary carbon atom attached to the carbonyl group, temperatures in the range 140–170° were found to be most satisfactory, but when a tertiary carbon atom was attached directly to the carbonyl group, as in pinacolone, a much higher temperature of approximately 210° was found necessary to produce complete reaction within six hours. The lower order of reactivity of pinacolone and its homolog in the Willgerodt reaction is analogous to their relatively low reactivity in many other reactions, an effect usually attributed to steric influences. It is to be noted, however, that when the proper adjustment in reaction temperature is made, better yields of amides are obtained from pinacolone and ethyl *t*-butyl ketone than from the less branched compounds.

In every case the identity of the final amide obtained in the Willgerodt reaction was proved by direct comparison of the crystalline product with an authentic synthetic specimen of the amide for crystal form, solubility behavior, melting point, and mixed melting point. In most cases, the amide was converted to the anilide, and a direct comparison was made of the anilides with synthetic specimens having the assigned structures. In no case was there evidence of the formation of isomeric amides in which a rearrangement of the carbon skeleton had occurred during the Willgerodt reaction.

Experimental

Ammonium Sulfide Solution.—Except where otherwise specified, a stock solution of ammonium sulfide was made up and used to prepare the ammonium polysulfide for the reactions with aliphatic ketones and aldehydes. Hydrogen sulfide was bubbled into concentrated ammonium hydroxide (15 *M*) until the resulting solution contained approximately 7 *M* sulfide as determined by iodimetric titration. The solution so prepared usually was found to contain the equivalent of approximately 12 *M* ammonia. Sulfur was added to this solution just before use.

Willgerodt Reaction with Pinacolone.—Four grams of pinacolone, 16 cc. of ammonium sulfide solution, 12.8 g. of sulfur, and 8 cc. of dioxane were sealed in a hard glass tube and heated in a bomb furnace at 210 ± 5° for six hours. The tube was allowed to cool to room temperature and was opened.[8] The reaction mixture was filtered at approximately 0° and the solid was leached with 30 cc. of boiling hot water, from which, upon cooling, 1.52 g. of β,β-dimethylbutyramide separated as glistening colorless plates, m. p. 134.0–134.3° cor. (reported m. p. 132°[9]). The filtrate yieded an additional 0.59 g. of crystals, m. p. 133–134°. The filtrate from the original reaction mixture was evaporated to dryness on a water-bath to eliminate ammonium polysulfide; extraction of the dry residue with hot water dissolved an additional 0.57 g. of amide, m. p.

[7a] Pyridine was first used with aryl alkyl ketones in This Laboratory, DeTar and Carmack, Unpublished Thesis, 1944.

[8] In most successful experiments little or no residual pressure was noted in the cooled tubes. It is advisable, however, in all cases to use caution in opening the sealed tubes.

[9] Hommelen, *Bull. soc. chim. Belg.*, **42**, 243 (1933); *C. A.*, **27**, 5306 (1933).

129–130°. The total yield of β,β-dimethylbutyramide was 2.68 g. (58% of the theoretical). There was no depression of the melting point when the product of the Willgerodt reaction was mixed with a sample of authentic β,β-dimethylbutyramide prepared as described in the following paragraph. A portion of the amide from the Willgerodt reaction was hydrolyzed to the acid and this in turn was converted into the anilide, m. p. 129.4–130.4° cor. (reported m. p. 131.0°[10]).

β,β-Dimethylbutyramide.—Pivalyl chloride (4.6 g.) in 50 cc. of absolute ether was added dropwise with stirring to a solution of diazomethane prepared from 25 g. of nitrosomethylurea.[11,12] The mixture was allowed to stand in an ice-bath for one and one-half hours, after which the ether and excess diazomethane were removed by distillation. The residual brown oil was refluxed with 35 cc. of concentrated ammonium hydroxide, 8 cc. of 10% aqueous silver nitrate solution, and 20 cc. of dioxane for three hours. The solvent was removed from the clarified solution and the crude β,β-dimethylbutyramide (2.5 g.) was recrystallized from ethyl acetate–ligroin, m. p. 132–132.6° cor.

Ethyl *t*-Butyl Ketone.—Ethyl-*t*-butylcarbinol, b. p. 135–138°, was prepared in 62% yield by means of the reaction of 1.2 moles of propionaldehyde in dry ether with the Grignard reagent made from 2 moles of *t*-butyl chloride. The solution of propionaldehyde was added to the solution of Grignard reagent at temperatures of 0–5°.

The ethyl-*t*-butylcarbinol was oxidized to ethyl *t*-butyl ketone with an aqueous solution of sodium dichromate and sulfuric acid.[13] The fraction of product boiling at 124–126° was used in the Willgerodt reaction.

Willgerodt Reaction with Ethyl *t*-Butyl Ketone.—A mixture of 4.0 g. of ethyl *t*-butyl ketone, 20 cc. of ammonium sulfide solution, 10 g. of sulfur, and 8 cc. of dioxane was heated in a sealed glass tube at 210 ± 5° for six hours. The reaction mixture yielded a total of 1.36 g. (30%) of γ,γ-dimethylvaleramide, isolated by a procedure similar to that described above for pinacolone. The first crop (1.26 g.) consisted of fine, colorless needles, m. p. 141.0–141.5° cor. (reported m. p. 140–141°[14]). The small second crop melted at 134–135°. The identity of the product with an authentic sample of γ,γ-dimethylvaleramide was proved by mixed melting point determination. The amide was converted to the anilide by the usual methods and the anilide was found to melt at 136–137°; the melting point was not depressed by admixture with an authentic specimen of γ,γ-dimethylvaleranilide.

The sample of γ,γ-dimethylvaleramide used for the proof of structure was synthesized from β,β-dimethylbutyramide. The latter was hydrolyzed to the acid and converted to the acid chloride, which in turn was submitted to the Arndt–Eistert reaction in aqueous ammonia.[12] The final amide melted at 140–141°. The anilide prepared from the amide melted at 136–137°.

Willgerodt Reaction with *n*-Heptanal.—A mixture of 4.0 g. of freshly distilled *n*-heptanal, 8 cc. of ammonium sulfide solution, 11.2 g. of sulfur, and 8 cc. of pyridine was heated in a sealed glass tube at 140 ± 5° for five hours. The reaction mixture was worked up as described for pinacolone, yielding 2.06 g. (46%) of colorless plates of *n*-heptanamide, m. p. 97.0–97.6° cor. (reported m. p. 96.5°[15]). A second crop of somewhat brown *n*-heptanamide was isolated, making a total yield of 50%. The identity of the product was proved by direct comparison of the melting points and mixed melting point with authentic *n*-heptanamide, m. p. 97–97.5° cor., prepared from *n*-heptanoyl chloride (Eastman Kodak Co.).

Willgerodt Reaction with 2-Heptanone.—The reaction of 4.0 g. of 2-heptanone (Eastman Kodak Co.) was carried out at 150 ± 5° for four hours, using the same quantities of reagents as with *n*-heptanal. The first crop of *n*-heptanamide consisted of 1.43 g. of very pale tan plates, m. p. 97–97.5° cor.; the melting point was not depressed by admixture with an authentic sample. The second crop weighed 0.27 g.; m. p. 95–97°; total yield 38%. The amide was converted to the anilide, m. p. 65° (reported m. p. 65°[16]), which was identical in melting point and mixed melting point with a sample prepared from *n*-heptanoyl chloride and aniline.

Willgerodt Reaction with 3-Heptanone.—3-Heptanol was prepared by the reaction of *n*-butylmagnesium bromide and propionaldehyde. The carbinol was oxidized to 3-heptanone with aqueous sodium dichromate–sulfuric acid solution[17]; a fraction of ketone boiling at 147–150° was used.

The Willgerodt reaction was carried out with 4.0 g. of 3-heptanone at 145 ± 5° for four hours, and the proportions of reactants were the same as for *n*-heptanal. The first crop of *n*-heptanamide amounted to 0.86 g., m. p. 97°. The second crop of 0.15 g., m. p. 93–95°, brought the total yield to 23%. The melting points were not depressed by admixture with authentic *n*-heptanamide.

Willgerodt Reaction with 4-Heptanone.—4-Heptanol was prepared by the reaction of *n*-propylmagnesium bromide with *n*-butyraldehyde, and the carbinol was oxidized with sodium dichromate–sulfuric acid solution to 4-heptanone[17]; the portion of product boiling at 144–145° was used.

The reaction of 4.0 g. of 4-heptanone was carried out at 145 ± 5° for four hours, and the proportions of reactants were the same as for *n*-heptanal. One crop of *n*-heptanamide was obtained as 0.95 g. (21%) of light brown plates, m. p. 95–96°.

Willgerodt Reaction with 2-Pentanone.—A mixture of 4.0 g. of 2-pentanone, 16 cc. of ammonium sulfide solution, 9.2 g. of sulfur, and 8 cc. of dioxane was heated in a sealed glass tube at 170 ± 5° for six hours. The contents of the tube were transferred to a beaker and evaporated to dryness. The amide was dissolved from the dry residue with hot water and, after removal of the water, was purified by sublimation under reduced pressure. The *n*-valeramide so obtained consisted of 1.44 g. (31%) of pale yellow solid, m. p. 90–93°. Several recrystallizations from chloroform raised the melting point to 102–103° (reported m. p., 106°[16]). There was no depression of the melting point when this material was mixed with an authentic sample of *n*-valeramide (Eastman Kodak Co.), m. p. 102–103°.

Willgerodt Reaction with Methyl Cyclohexyl Ketone.—Methylcyclohexylcarbinol was prepared from cyclohexylmagnesium bromide and acetaldehyde by the method of Bouveault.[18] The carbinol was oxidized to the ketone by the following method: 29 g. of the carbinol was added dropwise to a solution of 41 g. of chromium trioxide in 41 cc. of water and 41 cc. of glacial acetic acid at temperatures of 40–50°. The mixture then stood for three hours before being made alkaline and steam distilled. The ketone was extracted from the distillate with ether; the ether extracts were dried and distilled; b. p. 181–185°, yield 60%.

Ammonium polysulfide reagent for the Willgerodt reaction with this ketone and its homolog was prepared in a different manner from reagents in experiments described above. Sulfur (20 g.) was suspended in 40 cc. of concentrated ammonium hydroxide, and hydrogen sulfide was passed into the mixture with agitation until the sulfur dissolved completely. A mixture of 4.0 g. of methyl cyclohexyl ketone, 40 cc. of ammonium polysulfide reagent, and 20 cc. of dioxane was heated in a sealed glass tube at 165 ± 5° for six hours. The cooled reaction mixture yielded 1.1 g. of crystalline product directly. Evaporation of the filtrate to dryness on a water-bath and extraction of the dry residue with hot water afforded an additional 0.90 g.

---

[10] Homeyer, Whitmore and Wallingford, THIS JOURNAL, **55**, 4211 (1933).

[11] Arndt, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, New York, 1943, p. 165.

[12] Bachmann and Struve, "Organic Reactions," Vol. I, John Wiley and Sons, New York, 1942, p. 51.

[13] Faworsky and Aschmarin, *J. prakt. Chem.*, [2] **88**, 675 (1913).

[14] Moureu and Delange, *Bull. soc. chim.*, [3] **29**, 665 (1903).

[15] Mitchell and Reid, THIS JOURNAL, **53**, 1881 (1931).

[16] Robertson, *J. Chem. Soc.*, **115**, 1220 (1919).

[17] Sherrill, THIS JOURNAL, **52**, 1990 (1930).

[18] Bouveault, *Bull. soc. chim.*, [3] **29**, 1050 (1903).

The whole product was purified by sublimation under reduced pressure, giving 1.8 g. (40%) of cyclohexylacetamide, m. p. 163–165°. Recrystallization from methanol raised the melting point to 169.5–170.3°, cor. (reported m. p. 171–172°[19]). An authentic sample of cyclohexylacetamide for comparison was prepared from cyclohexyl bromide by the malonic ester synthesis[20]; it melted at 169.6–170.1° cor., and the melting point of a mixture of the synthetic sample with the product of the Willgerodt reaction showed no depression. The amide was converted to the anilide, m. p. 130.7–131.5°. The mixed melting point of the anilides derived from the product of the Willgerodt reaction and the synthetic sample showed no depression.

Willgerodt Reaction with Ethyl Cyclohexyl Ketone.—Ethylcyclohexylcarbinol was prepared by the reaction of cyclohexylmagnesium bromide with propionaldehyde. The carbinol was oxidized to the corresponding ketone by means of chromium trioxide in water and acetic acid.

The Willgerodt reaction was carried out with 4.0 g. of ketone at 165 ± 5° for six hours; the quantities of the reagents and the composition of the ammonium polysulfide were the same as for the reaction with methyl cyclohexyl ketone. The crude amide was sublimed under reduced pressure; the sublimate weighed 1.20 g. (27%), m. p. 113–115°. One recrystallization from methanol gave colorless plates of β-cyclohexylpropionamide, m. p. 119–120° cor. (reported m. p., 120°[21]). An authentic sample of this amide, prepared from cyclohexylacetic acid by the Arndt-Eistert reaction, melted at 118–119° cor.,[22] and a mixture of the latter sample with the product from the Willgerodt reaction showed no depression of melting point. Both specimens of amide were converted into the corresponding anilides, m. p. 97–97.5°, and mixtures of the two anilides showed no depression of melting point.

Summary

The Willgerodt reaction has been found to occur with completely aliphatic compounds of the type $RCO(CH_2)_nH$ to yield amides of the type $R(CH_2)_nCONH_2$ without rearrangement of the carbon skeleton, in analogy with known reactions of aryl alkyl ketones. The reactions of nine aliphatic carbonyl compounds with ammonium polysulfide are described.

---

[19] Gutt, *Ber.*, **40**, 2068 (1907).

[20] Hope and Perkin, *J. Chem. Soc.*, **95**, 1364 (1905).

[21] Zelinsky, *Ber.*, **41**, 2677 (1908).

[22] We are indebted to Miss Doris C. Koch for this preparation.

PHILADELPHIA, PA. RECEIVED JULY 5, 1945

[CONTRIBUTION FROM THE EASTERN REGIONAL RESEARCH LABORATORY,[1] PHILADELPHIA 18, PA.]

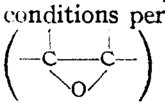
Hydroxylation of Monounsaturated Fatty Materials with Hydrogen Peroxide

BY DANIEL SWERN, GERALDINE N. BILLEN, THOMAS W. FINDLEY AND JOHN T. SCANLAN

The reaction of hydrogen peroxide with the lower fatty acids to form per-acids is reversible[2] and therefore it goes to completion if the per-acid is allowed to react as formed with an unsaturated compound. If the conditions favor rapid formation of the per-acid without causing decomposition, quantitative utilization of the active oxygen for such an oxidation is feasible, since the per-acid usually reacts very rapidly with unsaturated compounds. With most aliphatic acids, formation of the per-acid is a very slow reaction at moderate temperatures (40° or below) unless catalyzed.[3] For example, hydroxylation of oleic acid with a large excess of hydrogen peroxide in acetic acid solution requires a week at room temperature,[4] and during that extended period decomposition, probably of the hydrogen peroxide, results in considerable loss of active oxygen. Raising the temperature increases the rate of reaction considerably but aggravates the loss of active oxygen by increasing the rate of decomposition.[5]

Unlike the other aliphatic acids, however, formic acid reacts rapidly with hydrogen peroxide at moderate temperatures to give performic acid.[6] We have found that when oleic acid is mixed with hydrogen peroxide (25 to 30% aqueous solution) and formic acid at room temperature, an exothermic reaction begins almost immediately and is complete within two to four hours at 40°. Because of the short reaction time and the low temperature, little active oxygen is lost by decomposition, and the hydrogen peroxide is utilized in almost stoichiometric proportions.

The outstandingly rapid rate of formation of performic acid is not due entirely to the high acidity of formic acid. Its rate of formation is three times that at which peracetic acid is produced from hydrogen peroxide and glacial acetic acid with sulfuric acid as catalyst.

Reasoning from the successful epoxidation of fatty materials with perbenzoic[7] and peracetic acids,[8] we expected that under the same mild conditions performic acid also would yield epoxy  $\left(\begin{array}{c}-\overset{|}{C}-\overset{|}{C}-\\ \diagdown O \diagup\end{array}\right)$ compounds. Such was not the case, however; no epoxy compounds were present in the oxidation products even when the reaction was carried out at 25°. The products consisted almost exclusively of hydroxy-formoxy derivatives. There is little doubt that epoxy compounds are the initial products of the reaction and that further action of the strongly acidic formic acid results in the opening of the oxirane ring with addition of formic acid to yield the hydroxy-

---

[1] One of the laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, United States Department of Agriculture.

[2] d'Ans and Frey, *Ber.*, **45**, 1845 (1912); d'Ans and Kneip, *ibid.*, **48**, 1136 (1915).

[3] Smit, *Rec. trav. chim.*, **49**, 675 (1930).

[4] (a) Hilditch, *J. Chem. Soc.*, 1828 (1926); (b) Hilditch and Lea, *ibid.*, 1576 (1928).

[5] Scanlan and Swern, THIS JOURNAL, **62**, 2305 (1940).

[6] Toennies and Homiller, *ibid.*, **64**, 3054 (1942).

[7] Swern, Findley and Scanlan, *ibid.*, **66**, 1925 (1944).

[8] Findley, Swern and Scanlan, *ibid.*, **67**, 412 (1945).