Anal. Calcd. for $C_7H_{10}O_7Sr \cdot 2H_2O$: H_2O, 10.93. Found: loss in wt. at 105°, *in vacuo*, 10.18, 11.0. Calcd. for $C_7H_{10}O_7Sr$: Sr, 29.84. Found: 29.40, 29.25. Calcd. for $C_6H_8O_8Sr$: Sr, 33.23.[18]

Summary

1. The rates of oxidation of a number of glycosides by lead tetraacetate in glacial acetic acid have been measured.

2. All the glycosides which contain a *cis* glycol structure consumed the first mole of lead tetraacetate much more rapidly than those which contain only *trans* glycol structures, suggesting that the initial attack is at the *cis* position when such is present.

3. In two cases, substitution of benzyl for methyl on the first carbon has no effect upon the oxidation rates.

4. In several cases, α- and β-isomers have been found to show a general similarity in the oxidation experiments.

5. The glycosides containing glycol structures have been separated by experimental study into two groups: (A) those which consume a second mole of oxidant with a speed comparable to that at which the first is consumed, and those (B) which consume the second mole at a distinctly lower rate, and a hypothesis has been proposed to explain this difference.

6. The substitution of a trityl radical at carbon six of α-methyl-*d*-mannopyranoside is shown to shift this glycoside from group (A) to group (B) in accord with the prediction of the hypothesis.

7. α-Methyl-*l*-fucoside (−197°) has been oxidized by one mole of lead tetraacetate in chloroform solution and by strontium hypobromite to a dibasic acid containing all the carbon of the original substance.

(18) The physical properties of our salt also differ markedly from those of the strontium salt obtained by Maclay and Hudson (ref. 11) which contains one carbinol group less.

CAMBRIDGE, MASS. RECEIVED APRIL 5, 1939

[CONTRIBUTION FROM THE FRICK CHEMICAL LABORATORY OF PRINCETON UNIVERSITY]

Glycofuranosides and Thioglycofuranosides. VI. Preparation of Dimethyl Acetal and Methylfuranosides from *d*-Fructosediethylmercaptal

BY EUGENE PACSU

In a preliminary communication[1] it was reported that the application of the furanoside synthesis developed[2] in this Laboratory to *d*-fructosediethylmercaptal had resulted in the unexpected formation of *d*-fructosedimethylacetal. This was the second observed case where a sugar acetal had been formed from a starting material that contained all of its hydroxyl groups unprotected, the first case being that of the *l*-rhamnosedimethylacetal.[2e] The starting material, fructosediethylmercaptal, could not be obtained directly from fructose and mercaptan. Since Emil Fischer showed[3] that his general method for the preparation of sugar mercaptals had failed in the case of fructose and sorbose, it appeared as though the ketose mercaptals could not exist at all. However, Brigl and Schinle found[4] that the benzoyl analog of pentaacetyl-*keto*-fructose, for which the open-chain structure with a free carbonyl group was previously established[5] by Pacsu and Rich, gave readily a mercaptal derivative on treatment of the substance with ethyl mercaptan and dry hydrogen chloride. Subsequently, Wolfrom and Thompson reported[6] the formation of pentaacetyl fructosediethylmercaptal from pentaacetyl-*keto*-fructose and ethyl mercaptan in the presence of zinc chloride. From the acetylated mercaptal, on deacetylation with ammonia in methy alcoholic solution, the authors obtained fructosediethylmercaptal in about 78% yield. It has now been found that the yield of the latter compound can be increased almost to that required by the theory, if the deacetylation be carried out at room temperature in methyl alcoholic solution in the presence of a small quantity of barium methylate.

The reaction between sugar mercaptals and mercuric chloride in neutral alcoholic solution was hitherto believed[2b] only to proceed through the following two stages

(1) Pacsu, THIS JOURNAL, **60**, 2277 (1938).

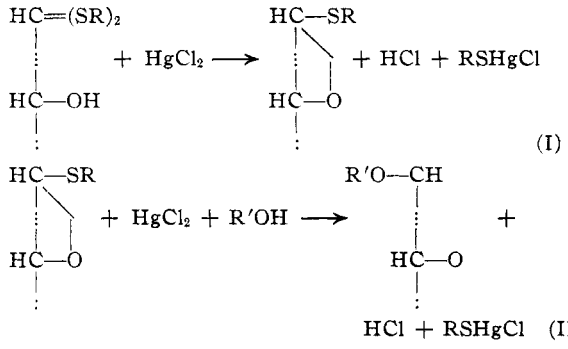
(2) (a) Pacsu and Green, *ibid.*, **58**, 1823 (1936); (b) Green and Pacsu, *ibid.*, **59**, 1205 (1937); (c) Green and Pacsu, *ibid.*, **59**, 2569 (1937); (d) Green and Pacsu, *ibid.*, **60**, 2056 (1938); (e) Green and Pacsu, *ibid.*, **60**, 2288 (1938); (f) Pacsu and Scattergood, *ibid.*, **61**, 534 (1939).

(3) Fischer, *Ber.*, **27**, 673 (1894).

(4) Brigl and Schinle, *ibid.*, **66**, 325 (1933).

(5) Pacsu and Rich, THIS JOURNAL, **54**, 1697 (1932); **55**, 3018 (1933).

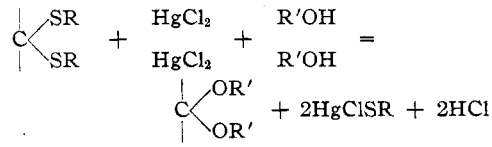
(6) Wolfrom and Thompson, *ibid.*, **56**, 880 (1934).



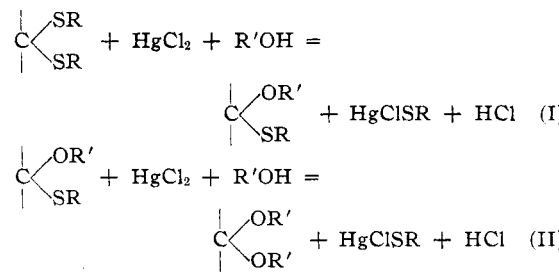
(I)

HCl + RSHgCl (II)

Usually, the final products of the reaction were found to be the more negative rotating forms of the furanosides admixed to a much smaller quantity of the diastereomers. Only in the case of glucose mercaptals was it possible to isolate the intermediate thiofuranosides, because the latter type of compounds, with the exception of the thioglucofuranosides, evidently reacted faster with mercuric chloride than the sugar mercaptals themselves. However, the reaction between *l*-rhamnose ethylmercaptal and methyl alcoholic mercuric chloride was shown recently[2e] to give rise to rhamnosedimethylacetal beside a large quantity of a sirupy product which undoubtedly was a mixture of the methyl rhamnofuranosides. Now it has been found that fructose ethylmercaptal reacts with mercuric chloride in methyl alcohol to yield almost exclusively the dimethylacetal, provided that the reaction is carried out at a very low temperature (−80°). In the formation of dimethylacetals the reaction must have proceeded either directly, according to the following general equation

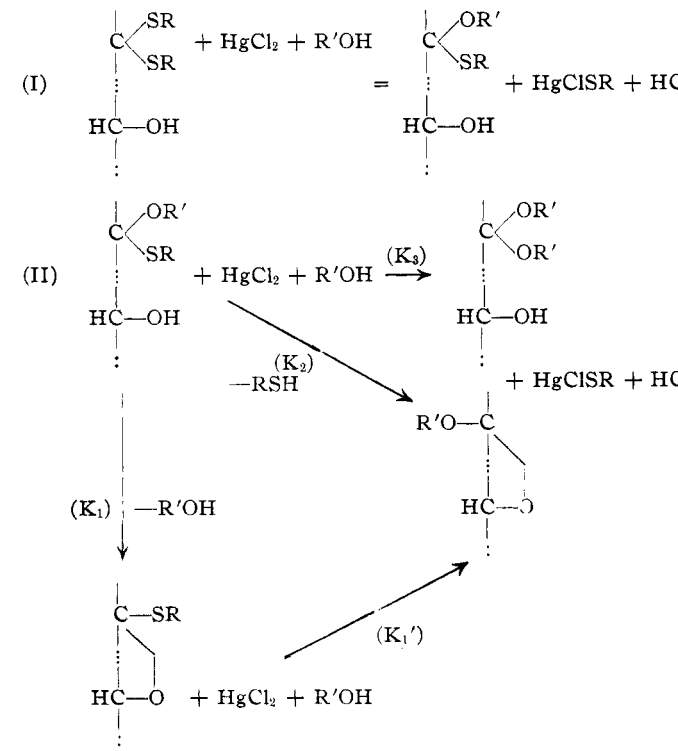


or in two stages, through the mixed acetal, as follows



Since it has not been possible to isolate the postulated intermediate product, the mixed acetal, it is to be concluded that if the dimethylacetal formation took place indirectly, according to the latter equations, then the velocity of the second stage of the reaction must have been very much faster than that of the first phase of the process. In the light of this interpretation the acetal formation in either direct or indirect way from a mercaptal appears to be a distinct reaction, which, depending upon unknown factors, may or may not occur as a side-reaction accompanying the usual conversion of the sugar mercaptals into furanosides and thiofuranosides.

However, it should be pointed out that it is entirely possible to consider all the observed products of the reaction, namely, thioglycofuranosides, glycofuranosides and acetals as being derived from one common intermediate, the mixed acetal. This view is best illustrated by the following diagram



According to this conception, the mixed acetal may undergo three distinct transformations: (1) loss of one mole of alcohol results in the formation of thioglycosides (K_1) which usually react further (K_1') to give rise to furanosides; (2) intramolecular loss (K_2) of one mole of mercaptan

yields furanosides; (3) intermolecular loss (K_3) of one mole of mercaptan produces acetals. Of course, the yields of the final product or products will depend upon the relative rates of the single stages. Until the mixed acetal can be isolated and the rates of its different transformations studied, this interpretation appears to be the most plausible for the mechanism of the complex reaction of sugar mercaptals with alcoholic mercuric chloride.

By the preparation of fructosedimethylacetal, it became quite definite that Purves and Hudson's[7] "gamma-methylfructoside (a)" is not identical with this acetal. From the results of analysis of gamma-methylfructoside mixtures by means of invertase the authors concluded that the constituent hydrolyzed by invertase and fermented by yeast must have a specific rotation of $-52 \pm 2°$, calculated for a true methylfructoside of molecular weight 194. Since this "gamma-methylfructoside (a)" has never been isolated and analyzed in substance, it could have represented the acetal, the hemiacetal or the β-methylfructofuranoside. In fact, its specific rotation ($-54°$) if calculated for a dimethyl acetal of molecular weight 226, becomes $-46.3°$, whereas the crystalline fructosedimethylacetal was found to have $[\alpha]^{20}D$ $-46.5°$. It was, therefore, of great interest to investigate the behavior of the crystalline acetal toward invertase and yeast.

On the addition of a powerful invertase solution the rotation of the crystalline acetal was found to remain unchanged for several hours in an unbuffered solution and dropped very slowly in a solution buffered to *p*H 4.5. Under identical conditions the same invertase solution hydrolyzed 75.7% of a 1.28% sucrose solution at *p*H 4.5 in thirty minutes. Furthermore, it partially hydrolyzed in thirty-five minutes the gamma-methylfructoside mixture prepared according to Purves and Hudson,[7a] the time of hydrolysis and final rotation being practically the same as those reported by the authors. The negative action of the invertase solution on the acetal was not due to inactivation, since the mixture rapidly inverted sucrose or hydrolyzed the gamma-methylfructoside mixture. The very slow change of rotation observed in the acetal-enzyme solution at *p*H 4.5 subsequently was found to be caused by the slow hydrolysis of the acetal due to the hydrogen ions, since it also occurred in the absence of invertase.

(7) Purves and Hudson, (a) THIS JOURNAL, **56**, 702 (1934); (b) **56**, 708 (1934).

Experiments carried out in fermentation saccharimeters showed that the acetal was fermented by yeast in distilled water, as measured by the volume of the carbon dioxide generated, about four times slower (twenty-three hours) than sucrose under identical conditions (six hours). However, yeast was without any effect on the acetal in a citric acid–disodium phosphate buffer solution of *p*H 7, while sucrose reacted in about twenty hours under similar conditions. When the hydrogen-ion concentration of the former solution was afterward adjusted to *p*H 5.6, a very slow fermentation began, the carbon dioxide generation reaching the end in about one week. These results clearly indicated that the action of yeast on the acetal in an unbuffered solution was due to the fermentation of fructose liberated from the acetal by the acid content of the yeast and that it was not a genuine enzymotic effect. They also suggested that the acetal must be extremely sensitive toward acid, a fact which subsequently was found to be the case, since the substance was hydrolyzed at room temperature in a 0.08 *N* hydrochloric acid within two minutes, and in a 0.00089 *N* acid in about six hours.

In a preliminary experiment carried out in anhydrous methyl alcoholic solution containing 0.84% hydrogen chloride, the specific rotation of the acetal was found to change in one hour from the initial rotation of $-63°$ to a dextrorotatory maximum of 14° calculated for methylfructoside. This transformation followed a unimolecular course with the velocity constant of $10^4 K = 347 \pm 20$. After the point of maximum rotation had been reached the rotation diminished very slowly, but the solution was still non-reducing. A detailed study is being made of the behavior of the acetal in acid media to discover the nature of substances present in the equilibrium mixture.

The reaction between fructose diethylmercaptal and methyl alcoholic chloride does not always give rise to the acetal exclusively. The acetal was found to be the single product only when the temperature had been kept very low during the reaction. At 0° or at higher temperature the reaction also proceeded in other directions and, beside the acetal, it gave rise to a considerable amount of a non-reducing, sirupy mixture. On systematic extractions with acetone and ethyl acetate, this mixture was finally separated into a crystalline product and a liquid fraction. The former was identified as the "crystalline gamma-

methylfructoside" of Purves and Hudson,[7b] showing the correct m. p. 69° and $[\alpha]^{20}D$ 93.0° in water solution. The liquid fraction has not yet been obtained in sufficient purity, but its specific rotation and especially the fact that invertase hydrolyzes it rapidly, lend support to the view that it represents the assumed "gamma-methylfructoside (a)" of Purves and Hudson. Attempts are being made to obtain this interesting substance in pure form.

Experimental

Preparation of *d*-Fructosediethylmercaptal.—Pentaacetyl-*keto*-fructose prepared according to Cramer and Pacsu[8] was converted into its ethyl mercaptal by the procedure of Wolfrom and Thompson.[6] The deacetylation was best carried out in small portions and the crude products obtained were united and recrystallized from methyl alcohol and ether. In a typical experiment 0.5 cc. 0.33 *N* barium methylate solution, prepared by refluxing barium oxide in anhydrous methyl alcohol for thirty minutes, was added to 5 g. of the acetylated mercaptal dissolved in 15 cc. of anhydrous methyl alcohol. After sixteen to twenty hours of standing at room temperature, one drop of the solution remained clear on addition of water, indicating that the reaction was completed. The residue obtained from the solution was crystallized from a small amount of methyl alcohol containing twice the volume of ether; yield, almost quantitative; m. p. and specific rotation in methyl alcohol agreed with the values given by Wolfrom and Thompson. The specific rotation of the mercaptal in water solution was found to be $[\alpha]^{20}D$ 16.5°; $[\alpha]^{20}_{6563}$ 12.9°; $[\alpha]^{20}_{5463}$ 20.2°; $[\alpha]^{20}_{61}$ 27.4° (*c*, 2.174).

Preparation of *d*-Fructosedimethylacetal.—To 11.4 g. of the mercaptal in 100 cc. of anhydrous methyl alcohol 17 g. of yellow mercuric oxide was added in a three-necked flask equipped with a mercury-sealed mechanical stirrer, a separatory funnel and a reflux condenser. The apparatus was placed in a Dewar flask containing an acetone–carbon dioxide mixture and the flask was immersed in an ice–salt bath. Under vigorous stirring a solution of 21.8 g. of mercuric chloride (2 moles) in 60 cc. of anhydrous methyl alcohol was added in about fifteen minutes to the mercaptal through the separatory funnel. After seventeen hours of continuous stirring at the freezing mixture's temperature, a filtered sample failed to produce $HgCl\text{-}SC_2H_5$ precipitate on heating, an indication that the reaction was completed. Then the reaction mixture was filtered and 5 cc. of pyridine was added to the filtrate for the removal of the excess of mercuric chloride. After two hours' standing at 0° the solution was filtered from the mercuric chloride–pyridine precipitate and evaporated *in vacuo* to a sirup. In order to remove the last traces of the pyridine salt the sirup was dissolved in ice cold water and the solution filtered with carbon. The filtrate was then made alkaline to phenolphthalein with a few drops of dilute alkali and evaporated *in vacuo* to a sirup. This was dissolved in methyl alcohol, filtered with carbon, if necessary, and the solution evaporated under diminished pressure to a colorless, non-reducing sirup, which gradually changed into a mass of diamond-shaped crystals. The substance crystallized from hot *n*-propyl alcohol in beautifully developed prisms. After a final recrystallization from absolute ethyl alcohol it had m. p. 107–108°; $[\alpha]^{20}D$ −45.6°; $[\alpha]^{20}_{6563}$ −35.6° and $[\alpha]^{20}_{5463}$ −53.6° in water solution (0.2977 g of substance, 10 cc. of solution; 2-dm. tube; rotations, 2.71, 2.12 and 3.19° to the left, respectively); yield, 7 g. In methyl alcohol solution the acetal had $[\alpha]^{20}D$ −63.0°, $[\alpha]^{20}_{6563}$ −50.0° and $[\alpha]^{20}_{5463}$ −76.1° (*c*, 1.15).

Anal. Calcd. for $C_8H_{18}O_7$: OCH_3, 27.4. Found: OCH_3, 27.1.

Preparation of Pentaacetyl *d*-Fructosedimethylacetal.—One gram of the acetal was acetylated at 100° with acetic anhydride containing 5% of anhydrous sodium acetate. After the solution was evaporated *in vacuo*, a sirupy residue was obtained which, on addition of water, changed at once into crystals. On recrystallization from absolute alcohol, the substance was obtained in well-developed prisms with m. p. 109° and $[\alpha]^{20}D$ 0° in chloroform solution. In an acetyl estimation 0.1453 g. of the compound required 16.4 cc. of 0.1 *N* sodium hydroxide solution. The value calculated for the hydrolysis of five acetyl groups is 16.6.

Action of Methyl Alcoholic Mercuric Chloride on *d*-Fructosediethylmercaptal at 0° and Higher Temperature.—The experiment described for the preparation of fructosedimethylacetal was repeated with the modification that the apparatus was kept in ice cold water and the mercuric chloride solution was added to the mercaptal in about two hours. After eighteen hours of continuous stirring at 0° the reaction mixture was worked up in the usual manner. There was obtained 6.3 g. of a sirupy material which, on seeding with acetal crystals, gradually changed into a crystalline mass. Crystallization from *n*-propyl alcohol yielded 1.8 g. of pure acetal.

In another experiment the mercuric oxide was added to the methyl alcoholic mercuric chloride solution which was kept boiling gently. Then the mercaptal solution was added drop by drop in one hour to the mixture which was refluxed for an additional hour. After standing at room temperature for several days, the sirupy product obtained from this experiment changed into a partly crystalline mass, from which about 2 g. of pure acetal was isolated by crystallization from *n*-propyl alcohol.

From the residue of the united mother liquors of the crystalline acetal obtained in these two experiments a non-reducing, sirupy product with $[\alpha]^{20}D$ 6.4 was isolated by extraction with hot ethyl acetate and evaporation of the solution. This product was separated by treatment with hot acetone into an acetone-soluble (sp. rot. +14°) and an acetone-insoluble (−15.7°) fraction. From the +14° fraction hot ethyl acetate dissolved a portion which had +35°, while the part insoluble in ethyl acetate deposited from its acetone solution a small quantity of the crystalline acetal. Then the +35° and the −15.7° fractions were united and extracted with hot ethyl acetate giving a solution (A) and an insoluble sirup (B). Solution (A) was cooled to 0° and, after it had cleared up, it was decanted from an insoluble sirup. On prolonged standing at room temperature the solution deposited a small amount of crystalline acetal, which was removed by filtration. In

(8) Cramer and Pacsu, THIS JOURNAL, **59**, 1148 (1937).

the filtrate, on standing at room temperature, well-shaped, pointed prisms commenced to form which, after recrystallization from methyl alcohol containing a little amyl alcohol, had m. p. 69° and $[\alpha]^{20}D$ 92.8° in water solution. The substance was, therefore, identical with Purves and Hudson's "crystalline gamma-methylfructoside." The ethyl acetate-insoluble substance (B) was again extracted with hot ethyl acetate and the aqueous solution of the insoluble portion was tested with invertase solution. The initial rotation (−35.2°) of the nonreducing solution then dropped rapidly to −64.4° and the solution became strongly reducing. The substance, therefore, must represent the "gamma-methylfructoside (a)" postulated by Purves and Hudson.

Acknowledgment is made to Dr. C. S. Hudson for the invertase samples used in this investigation. The author also wishes to thank Messrs. Walter J. Kauzmann and E. Justin Wilson, Jr., for their helpful assistance in the experimental work.

Summary

1. *d*-Fructosediethylmercaptal reacted at −80° with methyl alcoholic mercuric chloride to give crystalline *d*-fructosedimethylacetal in excellent yield.

2. The same reaction when carried out at 0° or higher temperature gave rise to a partly crystalline material, from which, beside the acetal, the "crystalline gamma-methylfructoside" of Purves and Hudson was isolated. Another constituent obtained from the mixture represented the "gamma-methylfructoside (a)," whose presence in the liquid gamma-methylfructoside mixtures was postulated by the same authors. This substance was hydrolyzed rapidly by invertase.

3. The apparent reaction of the acetal with invertase and yeast was found to be due to the hydrolyzing effect of the acidic media rather than to a genuine enzymotic effect. In solutions buffered to *p*H 7 the action of both invertase and yeast was found to be completely negative.

4. A new mechanism for the reaction of sugar mercaptals with alcoholic mercuric chloride was suggested.

5. Crystalline pentaacetyl *d*-fructosedimethylacetal was prepared.

PRINCETON, NEW JERSEY RECEIVED APRIL 6, 1939

[A COMMUNICATION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

Hydrogenation of Hydroxyamides

BY JAMES D. D'IANNI[1] AND HOMER ADKINS

The multiplicity of reactions that may occur when a hydroxyamide reacts with hydrogen under the influence of copper chromite[2] made it seem desirable to investigate rather carefully the nature of the products in the hydrogenation of representative compounds of this type.[3] Oeda failed to obtain amino alcohols by the hydrogenation of α-hydroxyamides.[4]

Monohydroxy Amides.—Five hydroxyamides, in which hydroxyl was in the α, β, γ, δ or ε position with respect to the N-pentamethylenecarbonamido or —C(O)NC_5H_{10} group, were submitted to hydrogenation over copper chromite. The detailed results are given in Table I. A typical reaction was

$$CH_3CHOH(CH_2)_2C(O)NC_5H_{10} \longrightarrow CH_3CHOH(CH_2)_2CH_2NC_5H_{10} + H_2O$$

The yields of the corresponding hydroxyamines were as follows: α, 51%, β, 0%, γ, 79%, δ, 76%, ε, 60%.

In the case of the β-hydroxybutyramide the chief product was N-*n*-butylpiperidine in 78% yield, formed according to the reaction

$$CH_3CHOHCH_2C(O)NC_5H_{10} \longrightarrow CH_3(CH_2)_2CH_2NC_5H_{10} + 2H_2O$$

This reaction is in accord with the well-established labilizing effect toward hydrogenolysis of nitrogen or oxygen substituents in the β-position with respect to each other.[5] A 4% yield of propylpiperidine from a lactamide was also isolated and presumably was formed by the same type of reaction.

Evidence for another type of hydrogenolysis

(1) This investigation was carried out in part while Dr. D'Ianni was a teaching assistant of the University and in part while he was a Procter and Gamble Fellow in 1937–1938.

(2) Groger first prepared the compound $CuCr_2O_4$ which he called copper chromite [Groger, *Z. anorg. Chem.*, **58**, 412 (1908); **76**, 30 (1912). When this compound was first reported by Connor, Folkers and Adkins as a catalyst for hydrogenation (for references on its early use see Adkins, *Ind. Eng. Chem., News Ed.*, **15**, 548 (1937)], it was referred to by the same name. In later papers from this Laboratory the catalyst has been called "copper–chromium oxide," since in some cases, a change in composition occurred during the course of a hydrogenation. However, W. A. Lazier and others prefer the use of the more convenient term, copper chromite (Lazier, U. S. Patents 1,746,782, 1,746,783 (1930), 1,964,000 (1934)).

(3) For references to earlier work by Wojcik, Paden, Sauer and Adkins see THIS JOURNAL, **60**, 402 (1938).

(4) Oeda, *Bull. Chem. Soc. Japan*, **12**, 121–127, 377–381 (1937).

(5) Adkins, "Reactions of Hydrogen, etc.," University of Wisconsin Press, Madison, 1937, p. 88.