which on crystallization from ethanol melted at 132–133° and was identified by mixture melting point as IX[4] (it gave a mixture melting point depression with X).

Reduction of dimesitoylethane (X) as above gave an 80% yield of product which was recrystallized from ethanol; it melted at 128–132°. Fractional precipitation from chloroform by means of petroleum ether gave first fractions of m. p. 184–185°, which were identified as XI[4] by mixture melting point.

Summary

Lithium aluminum hydride reductions of *cis*- and *trans*-dibenzoylethylenes gave chiefly 1,4-diphenyl-4-hydroxybutanone and a small amount of the *trans* unsaturated 1,4-glycol. The structure of the hydroxyketone was shown by reactions and by ultraviolet absorption spectra. In reduction of dimesitoylethylene only the hydroxyketone was isolated.

These reductions are explained in terms of competing 1,2- and 1,4-reductions; 1,4-reduction is predominant and involves protection of the carbonyl involved, in the form of the monoenolate. These reductions are compared with additions of the Grignard reagent.

CHARLOTTESVILLE, VIRGINIA RECEIVED JULY 20, 1949

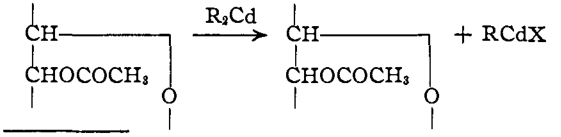
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

Reactions of Polyacylglycosyl Halides with Organocadmium Reagents

BY CHARLES D. HURD AND ROMAN P. HOLYSZ[1]

In recent years the use of organocadmium reagents has been recognized as a convenient means of preparing ketones from acyl halides.[2] As a result of the generally lower reactivity of organocadmium reagents as compared to that of Grignard reagents, the coupling reaction with acyl halides usually stops at the ketone stage. In contrast, Grignard reagents are capable of further reaction with the ketones to yield tertiary alcohols, except at very low temperatures. Furthermore, organocadmium reagents usually do not react readily with esters under ordinary conditions. For instance, cadmium alkyls react with carbethoxyacyl halides of the type EtOOC–$(CH_2)_n$–COX to give good yields of keto esters, EtOOC–$(CH_2)_n$–CO–R, with no appreciable attack on the ester function.[3] Reactions of organocadmium reagents with active halogen in compounds other than acyl halides have not been investigated extensively. Gilman and Nelson[4] reported that dialkylcadmium did not couple with *t*-butyl chloride, and that diphenylcadmium reacted with benzenesulfonyl chloride to yield diphenyl sulfone, benzenesulfinic acid and chlorobenzene. Summerbell and Bauer[5] obtained a 44% yield of 2,3-dibutyl-1,4-dioxane by the action of dibutylcadmium on 2,3-dichloro-1,4-dioxane, which is an *alpha* halogen ether.

With these facts in mind one might then expect a polyacylglycosyl halide, which may be visualized as an *alpha* halogen ether, to react with dialkyl- or diarylcadmium in the following manner.



The ester functions would remain intact, thereby making possible the use of only one mole (or a slight excess) of the organocadmium reagent per mole of polyacylglycosyl halide instead of the nine moles of Grignard reagent theoretically necessary in the Grignard glycosylation.[6] The attack of the ester functions by the Grignard reagent results in the major product being an unwanted carbinol, while the carbohydrate derivative is water soluble, necessitating lengthy isolation and acylation procedures.

The anticipated reactions were realized both in the glucose and mannose series with diphenylcadmium, although the yields were low. Tetraacetyl-α-D-glucopyranosyl bromide coupled with diphenylcadmium in refluxing benzene solution to give tetraacetyl-β-D-glucopyranosylbenzene in approximately 20% yield. The remaining sirupy product darkened considerably on standing and eventually became a black tar. The presence of bromine in the tarry product suggested that the reaction probably was not completed. There was no significant improvement of the yield of tetraacetyl-β-D-glucopyranosylbenzene when the reaction mixture was refluxed for a much longer period or the reaction carried out in refluxing toluene. Similarly, in the mannose series coupling to a limited extent without apparent attack of the ester functions was observed between diphenylcadmium and tetraacetyl-α-D-mannopyranosyl bromide in refluxing toluene solution. In this instance tetraacetyl-α-D-mannopyranosylbenzene was isolated in 29% yield in addition to sirupy products.

However, with dibutyl- and dibenzylcadmium entirely different and unexpected types of products were obtained. Dibenzylcadmium reacted with tetraacetyl-α-D-glucopyranosyl bromide in refluxing toluene solution to form in approximately 30% yield a crystalline substance which was not the anticipated α-(tetraacetylglucosyl)-toluene but an acetal-like compound (I).

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[1] Corn Products Refining Company Fellow, 1945–1947; du Pont Fellow, 1947–1948.

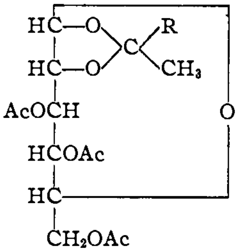
[2] Cason, *Chem. Rev.*, **40**, 15 (1947).

[3] Cason and Prout, THIS JOURNAL, **66**, 46 (1944).

[4] Gilman and Nelson, *Rec. trav. chim.*, **55**, 518 (1936).

[5] Summerbell and Bauer, THIS JOURNAL, **58**, 759 (1936).

[6] Hurd and Bonner, *ibid.*, **67**, 1972 (1945).

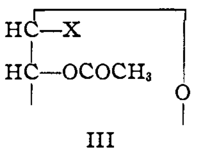


I, R = $C_6H_5CH_2$
II, R = C_4H_9

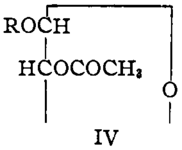
The assignment of such a structure was based on the following evidence. Three acetate groups were revealed by saponification with alkali. The deacetylated product did not reduce Benedict solution and it could be reacetylated to the original crystalline acetate. One equivalent of the deacetylated product consumed one equivalent of periodate ion, indicating one position of adjacent hydroxyl groups. Acid hydrolysis of the deacetylated non-reducing product yielded phenylacetone and D-glucose, the ketone being identified by means of its *p*-nitrophenylhydrazone, while the sugar moiety was acetylated to β-D-glucose pentaacetate. In keeping with the proposed rules of carbohydrate nomenclature (Rule 22)[7] compound I is named 1,2-(1-benzylethylidene)-3,4,6-triacetyl-D-glucose. Since the carbon atom bearing the benzyl and methyl groups is asymmetric, two stereoisomers are possible; however, only one crystalline product was isolated. The remaining sirupy product of the reaction between dibenzylcadmium and the glucosyl halide could not be recrystallized and it was not identified.

Dibutylcadmium reacted with tetraacetyl-α-D-glucopyranosyl bromide to yield the crystalline 1,2-(1-methylpentylidene)-3,4,6-triacetyl-D-glucose (II) to the extent of 57%. Saponification of the ester groups, periodate oxidation and acid hydrolysis of the unacetylated compound all supported structure II. The acid hydrolysis products, 2-hexanone and the reducing sugar, were identified by means of the 2,4-dinitrophenylhydrazone and the phenylosazone, respectively.

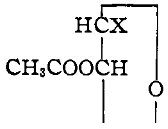
The formation of these alkylidenetriacetylhexoses in the glucose series was somewhat surprising. Polyacetylglycosyl halides in which the halide and the adjacent ester functions are in a *cis* relation to each other (III) react with alcohols or phenols in the presence of silver oxide or carbonate to yield the corresponding alkyl or aryl glycosides. For example, the polyacetylglycosyl halides of D-glucose, D-galactose or D-xylose (structure of type III) react with methanol in the presence of silver oxide to yield the corresponding methyl polyacetyl-β-D-glycosides (IV); while the polyacetylglycosyl halides having a mannose type structure (V) yield orthoacetates (VI) in a reaction of the Koenigs–Knorr type.[8]



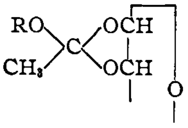
III



IV

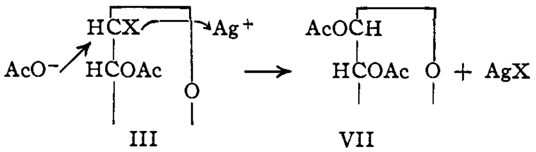


V

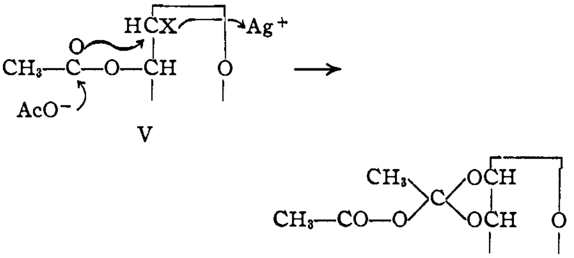


VI

Similarly, polyacetylglycosyl halides (III) react with silver acetate, apparently through inversion, giving rise to the normal acetate (VII) in an intermolecular reaction.[9] When the halogen and the neighboring acetoxy group were *trans* with respect to each other (V), the reaction with silver acetate was an intramolecular reaction leading to the formation of an orthoacetic ester (VIII).



III VII



V VIII

With these facts in mind one would not anticipate products of the type I and II, since the halogen and the neighboring acetate group in tetraacetyl-α-D-glucopyranosyl bromide are in a *cis* relation to each other. Furthermore, tetraacetyl-α-D-mannopyranosyl bromide should have given rise to such an acetal-like compound rather than a normal coupling product, tetraacetyl-α-D-mannopyranosylbenzene. Although the actual configuration about the carbon atom holding the halogen atom in the polyacetylglycosyl halides still remains controversial, such a mechanism as proposed by Isbell[9] apparently does not operate in the reactions between polyacetylglycosyl halides and organocadmium reagents.

Although the data presented here are insufficient to deduce a mechanism for the reactions between the polyacetylglycosyl halides and organocadmium reagents, it is interesting to speculate on one possible course. The organocadmium reagent may be considered to attack at the halide

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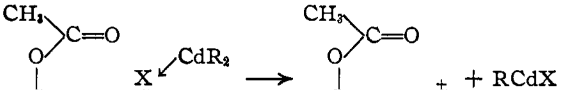
[7] *Chem. Eng. News*, **26**, 1626 (1948).

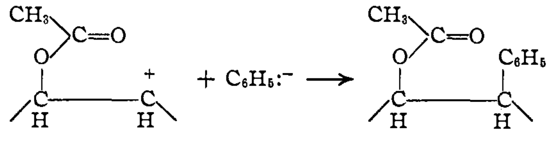
[8] Koenigs and Knorr, *Ber.*, **34**, 957, 978 (1901); Haworth, *et al.*, *J. Chem. Soc.*, 1395 (1950); 2864 (1931); Isbell, *et al.*, *J. Research Natl. Bur. Standards*, **7**, 1115 (1931); **19**, 189 (1937); **27**, 413 (1941).

[9] Isbell, *Ann. Rev. Biochem.*, **9**, 70 (1940).

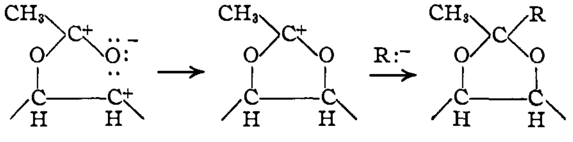
function, leaving a carbon deficient in electrons. This deficiency may be satisfied either by (1)



interaction with the carbonyl oxygen of the ester group or by (2) interaction with an R:$^-$ group.[10] If R is a highly electronegative group such as phenyl, then the normal coupling reaction apparently predominates. However, if R is a



relatively less electronegative group such as butyl or benzyl, then interaction of the deficient carbon and the electronegative carbonyl oxygen becomes significant.



On the basis of numerous considerations, Hurd and Bonner[5] argued that the stereochemical configurations in all the glycosylated hydrocarbons prepared by the action of Grignard reagents on polyacetylglycosyl halides parallelled the configurations of the parent sugars. These same considerations are applicable, at least to some extent, to the reactions of polyacetylglycosyl halides with organocadmium reagents, since tetraacetyl-β-D-glucopyranosylbenzene was isolated even under the relatively drastic conditions of reaction. Furthermore, tetraacetyl-α-D-mannopyranosylbenzene, which was isolated in fair yield, was identical to one of the products obtained from the Grignard glycosylation of mannose.[11] Deacetylation followed by acid hydrolysis of 1,2-(1-benzylethylidene)-3,4,6-triacetyl-D-glucose to D-glucose indicated that no inversions of configuration had occurred in the reaction of dibenzylcadmium with tetraacetyl-α-D-glucopyranosyl bromide at 110°.

Experimental

Reactions of Polyacetylglycosyl Halides and Organocadmium Reagents.—The general method for carrying out these reactions is illustrated in a specific example.

Phenylmagnesium bromide was prepared in the usual manner from 6.28 g. (0.04 mole) of bromobenzene and 0.96 g. (0.04 mole) of magnesium in 100 ml. of ethyl ether. Small portions of finely powdered anhydrous cadmium chloride were added with constant, rapid stirring to the Grignard solution over a period of about two hours. For this purpose reagent grade cadmium chloride was ground to a fine powder and dried *in vacuo* at 100° for several hours. After addition of 3.68 g. (0.02 mole) of the cadmium chloride, the reaction mixture was refluxed gently for two hours. The reflux condenser was then changed for downward distillation and a distilling head was attached to the flask. A solution of 8.22 g. (0.02 mole) of tetraacetyl-α-D-glucopyranosyl bromide in 150 ml. of toluene was added dropwise over a period of about one hour. At the same time the ether was distilled out of the reaction flask. When no more ether came over and all of the toluene solution had been added, the reflux condenser was reattached and the mixture was refluxed for ten to twelve hours in an atmosphere of dry nitrogen. After standing overnight at room temperature, the reaction mixture was hydrolyzed by pouring it into 100 ml. of ice water and acidifying with acetic acid until all the solid just dissolved. The layers were separated as quickly as possible, and the solvent layer was washed with saturated sodium bicarbonate solution, then with water. The toluene solution was dried over calcium chloride and evaporated *in vacuo*. There remained 7.70 g. of a brown colored sirup.

This sirup was dissolved in 10 ml. of benzene and the solution was chromatographed through activated alumina (80–200 mesh). Elution with benzene and later with chloroform resulted in a separation of the product into two major fractions, (1) 3.10 g. of a yellow sirup and (2) 2.34 g. of a dark sirup. The first fraction was taken up in boiling 2-propanol from which 1.80 g. of crystalline product was obtained after seeding with tetraacetyl-β-D-glucopyranosylbenzene and cooling slowly to ice temperatures. Concentration, cooling and seeding of the mother liquor yielded an additional 0.08 g. of product; yield, 1.88 g. or 23%.

After several recrystallizations from 2-propanol, the product melted sharply at 155.5–160°; a mixed melting point with an authentic sample of tetraacetyl-β-D-glucopyranosylbenzene was not depressed. The specific rotation in chloroform was −15.9°, *c*, 1.133 at 24°.

No crystalline material could be obtained from the second sirupy fraction; $[\alpha]^{24}D$ 6.1°, *c*, 3.756 in chloroform.

Other reactions were conducted analogously. The following proportions of reactants were used: alkyl or aryl halide, 0.050 mole; magnesium, 0.050 mole; cadmium chloride, 0.025 mole; tetraacetylglycosyl bromide, 0.020 mole. In most cases chromatographic purification was necessary before any crystalline products could be obtained.

Tetraacetyl-α-D-mannosyl Bromide.—Although this compound was described as a relatively low melting solid (53–54°) by Levene and Tipson,[12] it was obtained as a thick sirup. Nevertheless, the specific rotation, $[\alpha]^{26}D$ 116°, c. 5.333 in chloroform, indicated that the sirup was substantially the desired product. The reported rotation was 123° in chloroform at 26°.

Tetraacetyl-α-D-mannopyranosylbenzene.—This product was isolated in 29% yield (2.36 g.); m. p. 138–139°. A mixed melting point with a sample of the compound prepared by the Grignard reaction[10] showed no depression. The sirupy product remaining after separation of the crystalline fraction was not further investigated; $[\alpha]^{28}D$ 34.0°, *c*, 2.508 in chloroform.

1,2-(1-Methylpentylidene)-3,4,6-triacetyl-D-glucose.—The crude reaction product (6.98 g.) was dissolved in 15 ml. of benzene and the solution was chromatographed. Ultimately, 4.42 g. (57% yield) of crystalline product, m. p. 97–101°, was obtained. After several recrystallizations from hexane the melting point was constant at 103°; $[\alpha]^{22}D$ 24.7°, *c*, 2.226 in chloroform.

Anal. Calcd. for $C_{18}H_{28}O_9$: C, 55.66; H, 7.27; CH_3-CO-, 33.26. Found: C, 56.06; H, 7.15; CH_3CO-, 33.39.

The remaining product was a pale yellow sirup, $[\alpha]^{22}D$ 24.8°, *c*, 2.256 in chloroform.

1,2-(1-Methylpentylidene)-D-glucose.—The crystalline triacetate (2.00 g.) was dissolved in 25 ml. of methanol and a small chip of sodium was added. After standing at room

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[10] This intermediate is consistent with the observations reported by Cason, *J. Org. Chem.*, **13**, 231 (1948), for reaction of dibutylcadmium with 2-ethyl-2-butylglutaric anhydride.

[11] Hurd and Holysz, THIS JOURNAL, **72**, 1735 (1950).

[12] Levene and Tipson, *J. Biol. Chem.*, **90**, 89 (1931).

temperature overnight the solvent was evaporated in a stream of air, leaving a clear, colorless sirup (1.20 g.), $[\alpha]^{22}_{D}$ 37.7°, *c* 2.600 in methanol. Reacetylation of this sirup with 10 ml. of acetic anhydride and 5 ml. of pyridine at room temperature overnight yielded 1.96 g. (96% yield) of the triacetate, m. p. 102–103°.

Periodate Oxidation of 1,2-(1-Methylpentylidene)-D-glucose.—The details of this method have been described elsewhere.[10] The sample was weighed as the triacetate. Wt. of sample, 0.3141 g.; vol. of 0.0442 *N* KIO_4 soln., 50.00 ml.; vol. of 0.1000 *N* sodium arsenite soln., 50.00 ml.; vol. of 0.1152 *N* I_2 soln., 38.20 ml.; KIO_4 consumed, 0.8065 millimole; subst. oxidized, 0.808 millimole; subst.: KIO_4, 1.000: 0.997; acidity, negligible.

Acid Hydrolysis of 1,2-(1-Methylpentylidene)-D-glucose.—One gram of the crystalline triacetate was deacetylated with a trace of sodium methoxide in methanol. After evaporation of the methanol the residue was dissolved in 20 ml. of 1.0 *N* hydrochloric acid and the solution was heated on a steam-bath for two hours. At the end of this time the solution was cooled and neutralized. The neutral solution was extracted with three 10-ml. portions of ether. Distillation of the ether from the extract left about 0.5 ml. of colorless liquid. Treatment with a solution of 2,4-dinitrophenylhydrazine in concentrated hydrochloric acid and alcohol yielded 0.62 g. (88% yield) of 2-hexanone 2,4-dinitrophenylhydrazone, m. p. 108–110°. Melting points reported for this hydrazone ranged from 106–109°.

The neutral aqueous solution remaining after the ether extraction was heated with phenylhydrazine hydrochloride and sodium acetate. After two recrystallizations from alcohol, the resulting fine yellow crystals of D-glucose phenylosazone decomposed at 208°.

1,2-(1-Benzylethylidene)-3,4,6-triacetyl-D-glucose.—Following chromatographic fractionation of the crude reaction product (9.10 g.), the triacetate (2.52 g., 30% yield) was isolated in the form of white rectangular prisms, purified by recrystallization from mixtures of ethyl ether and pentane. The product melted at 78–79°; $[\alpha]^{22}_{D}$ 29.4°, *c*, 3.566 in chloroform.

Anal. Calcd. for $C_{21}H_{26}O_9$: C, 59.71; H, 6.21; CH_3CO—, 30.57. Found: C, 59.34; H, 6.20; CH_3CO—, 30.57.

The remaining sirupy fractions of the reaction products were not investigated further. All were optically active; $[\alpha]_{D}$ ranged from 18–25° in chloroform.

Periodate Oxidation of 1,2-(1-Benzylethylidene)-D-glucose.—The sample was weighed as the triacetate: Wt. of sample, 0.3459 g.; vol. of 0.0442 *N* KIO_4 soln., 50.00 ml.; vol. of 0.100 *N* sodium arsenite soln., 50.00 ml.; vol. of 0.1152 *N* I_2 soln., 38.40 ml.; KIO_4 consumed, 0.818 millimole; subst. oxidized, 0.819 millimole; subst.: KIO_4, 1.000:1.00; acidity, negligible.

Acid Hydrolysis of 1,2-(1-Benzylethylidene)-D-glucose.—Hydrolysis of the sirupy compound in 1.0 *N* hydrochloric acid yielded phenylacetone and D-glucose. The ketone was identified by means of its *p*-nitrophenylhydrazone, m. p. 145–145.5°. D-Glucose was isolated from the hydrolysis mixture and acetylated with acetic anhydride and sodium acetate at 100°. β-D-Glucose pentaacetate, m. p. 129–130°, did not depress the melting point of an authentic sample.

Tetraacetyl-α-D-mannosyl Bromide and Dibutylcadmium.—A yellow colored sirup (5.30 g.), $[\alpha]^{28}_{D}$ 6.2°, *c* 2.0 in chloroform, resulted from the reaction of the acetohalogenomannose and dibutylcadmium under the usual conditions. No crystalline products could be isolated.

Attempted Coupling of 2-Thiophenemercuric Chloride with Tetraacetyl-α-D-glucosyl Bromide.—2-Thiophenemercuric chloride was prepared in 55% yield.[13] A solution containing 4.00 g. of 2-thiophenemercuric chloride, 4.12 g. of tetraacetyl-α-D-glucopyranosyl bromide and 200 ml. of toluene was refluxed for twenty-four hours. Toluene was then distilled from the mixture until about 50 ml. of solution remained. On cooling to room temperature, 3.96 g. of 2-thiophenemercuric chloride, m. p. 180–183°, crystallized out of solution.

Analyses.—Microanalyses were performed by M. Hines. Analysis for acetyl was made by dissolving the acetate in alcohol, refluxing with alcoholic alkali, then titrating the excess alkali.

Summary

As a result of the generally lower reactivity of organocadmium reagents as compared to that of Grignard reagents, diphenylcadmium coupled with tetraacetyl-α-D-glucopyranosyl bromide and with tetraacetyl-α-D-mannopyranosyl bromide in refluxing toluene solution to yield the respective tetraacetyl-D-glycosylbenzenes in fair yields without attack of the ester functions.

Dibutyl- and dibenzylcadmium behaved differently and unanticipated products of an acetal-like structure resulted. On the basis of alkaline hydrolysis, periodate oxidation and acid hydrolysis data the products were 1,2-alkylidenetriacetylglucoses.

(13) Steinkopf and Killingtad, *Ann.*, **532**, 288 (1937).

EVANSTON, ILLINOIS RECEIVED NOVEMBER 4, 1949

[INVESTIGATION CONDUCTED IN THE DEPARTMENT OF BIOCHEMISTRY, UNIVERSITY OF SOUTH DAKOTA, MEDICAL SCHOOL, VERMILLION]

Carbohydrate Tests Using Sulfonated α-Naphthol

BY ARTHUR W. DEVOR[1]

It has been known for a long time that when furfural or hydroxymethylfurfural is treated with sulfuric acid and α-naphthol, a bluish-violet colored condensation product is formed[2–6] (Molisch reaction). Since furfural and hydroxymethylfurfural are formed, respectively, from pentoses and hexoses when these are treated with strong acids, similar color reactions occur when carbohydrate materials are acted upon directly by sulfuric acid in the presence of α-naphthol.

It is probable, moreover, that under the conditions employed normally for carrying out the Molisch reaction, there is also action of sulfuric acid upon α-naphthol so that colored condensation products are actually composed of various sulfonated naphthols in combination with furfural derivatives.

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(2) W. Alberda Van Ekenstein and Blanksma, *Ber.*, **43**, 2355-2361 (1910).

(3) Blanksma, *Chem. Weekblad*, **6**, 1047 (1910).

(4) F. Angelico and A. Cappola, *Gazz. chim. ital.*, **42**, II, 583 (1912).

(5) Bredereck, *Ber.*, **64B**, 2856 (1931).

(6) Bredereck, *ibid.*, **65B**, 1110 (1932).