This mechanism is analogous to those previously proposed by Topchiev[7] and others[8] for the formation of acetopropanol from 2-methylfuran and by Swadesh and Dunlop[9] for the conversion of furfuryl alcohol to 2,5-bis-(trimethyleneoxy)-*p*-dioxane.

Since the structure of the hydroxyl-free product from furfuralacetone hydrogenation had not been satisfactorily established,[5,6] this material was treated with hydriodic acid and the resulting diiodoketone reduced to yield octanone-4. By analogy to the structure proof for 1,6-dioxaspiro[4.4]nonane[4] this evidence shows that the product in question is 2-methyl-1,6-dioxaspiro[4.4]nonane (III, R = CH_3).

Analytical data and physical properties of the hydroxyl-free compound obtained in admixture with 1,5-ditetrahydrofurylpentanol-3, from the hydrogenation of difurfuralacetone,[6] indicate that this product is 2-(β-2-tetrahydrofurylethyl)-1,6-dioxaspiro[4.4]nonane (III, R = $CH_2CH_2\underset{\underset{\text{O}}{\text{|}}}{\text{CH}}CH_2CH_2CH_2$)

Evidence of analogous products in the hydrogenation mixtures from other furfural–ketone condensation products[6] indicates that spirane formation is a general reaction of γ-(2-furyl)-alkanols on hydrogenation over copper chromite or nickel-on-kieselguhr catalysts.

Experimental

Catalysts and Apparatus.—The nickel-on-kieselguhr catalyst was prepared according to the procedure of Adkins.[10] All hydrogenations were conducted in a rocker-type, high-pressure hydrogenation bomb assembly.

1,6-Dioxaspiro[4.4]nonane.—1-Furylpropanol-3,[3] 126 g. (1.0 mole), dissolved in sufficient absolute alcohol to make a total volume of 370 ml., was hydrogenated over 6 g. of freshly reduced nickel-on-kieselguhr catalyst. The initial pressure was 2300 p.s.i. and 1.6 moles of hydrogen was absorbed in 90 minutes over a temperature range of 70–125°. Fractional distillation of the product yielded 48.6 g. (38%) of 1,6-dioxaspiro[4.4]nonane: b.p. 81–82° (60 mm.), $n^{25}D$ 1.4465, and 74 g. (57%) of 1-tetrahydrofuryl-propanol-3: b.p. 144° (60 mm.), $n^{25}D$ 1.4563.

2-Methyl-1,6-dioxaspiro[4.4]nonane.—One mole (140 g.) of 1-furylbutanol-3 was hydrogenated in dry cyclohexane (total volume 370 ml.) in the presence of 0.3 ml. of 90% formic acid over 6 g. of nickel-on-kieselguhr catalyst. The initial pressure was 2300 p.s.i. and 1.4 moles of hydrogen was absorbed in 90 minutes over the temperature range of 90–120°. Fractional distillation of the products gave 77 g. (54%) of a colorless liquid (A) having a terpene-like odor and b.p. 80° (46 mm.), $n^{25}D$ 1.4412, d^{25}_4 0.985.

Anal.[11] Calcd. for $C_8H_{14}O_2$: C, 67.60; H, 9.92; OH, 0.00. Found: C, 67.5; H, 9.82; OH, 0.55.

The higher boiling product, 58 g. (40%), b.p. 145° (58 mm.), $n^{25}D$ 1.4541, was 1-tetrahydrofurylbutanol-3.

Hydrogenation in absolute alcohol gave 40–50% yields of the spirane with corresponding increases in tetrahydrofurylbutanol formation. Elimination of the formic acid reduced the yield only slightly (to 51%). Addition of sodium methoxide apparently stopped spirane formation entirely.

Diiodoöctanone.—A mixture of 14.2 g. of the liquid (A), b.p. 80° (46 mm.), and 66 ml. of hydriodic acid, sp. gr. 1.7, was heated to boiling. The heavy oil which formed was separated, washed, taken up in ether, washed to neutrality, and the ether solution dried over magnesium sulfate. Removal of the ether left 34.9 g. of a dark oil which gave a positive test for carbonyl.

Anal. Calcd. for $C_8H_{14}OI_2$: C, 25.3; H, 3.71; I, 66.7. Found: C, 26.1; H, 3.84; I, 65.8.

Attempted distillation caused decomposition with evolution of hydrogen iodide.

Octanone-4.—Reduction of the above diiodo ketone with a zinc–copper couple in absolute alcohol yielded octanone-4; hydantoin, m.p. 173–174°.[12] A mixed melting point of this derivative with the hydantoin from an authentic sample of octanone-4 showed no depression.

Acknowledgments.—The authors wish to express their appreciation to Professor C. S. Marvel of the University of Illinois for the octanol-4 used for the preparation of the authentic sample of octanone-4.

(7) K. S. Topchiev, *Compt. rend. acad. sci. U. R. S. S.*, **19**, 497 (1938) [*C. A.*, **32**, 8411 (1938)].

(8) L. E. Schniepp, H. H. Geller and R. W. VonKorff, THIS JOURNAL, **69**, 672 (1947).

(9) S. Swadesh and A. P. Dunlop, *J. Org. Chem.*, **14**, 692 (1949).

(10) H. Adkins, "Reactions of Hydrogen," The University of Wisconsin Press, Madison, Wisconsin, 1937.

(11) All analyses are micro or semi-micro determinations by C. H. VanEtten and Mary B. Wiele of this Laboratory.

(12) H. R. Henze and R. J. Speer, THIS JOURNAL, **64**, 522 (1942).

PEORIA, ILLINOIS RECEIVED JANUARY 13, 1951

[CONTRIBUTION FROM THE GEORGE M. MOFFETT RESEARCH LABORATORIES, CORN PRODUCTS REFINING COMPANY]

Uronoside Formation Catalyzed by Cation Active Resin[1]

BY ELIZABETH M. OSMAN, KENNETH C. HOBBS AND WAYNE E. WALSTON

The reaction between methanol and glucuronolactone is catalyzed by cation exchange resin as well as by mineral acids. In addition to the γ-lactone of methyl β-glucofururonoside, a known product of the acid-catalyzed reaction, a second compound was isolated from the resin-catalyzed reaction; this was identified as the γ-lactone of methyl α-glucofuruonoside. Rotation data indicate that the latter compound undergoes mutarotation to the β-isomer as the reaction is prolonged.

Owen, Peat and Jones[2] have reported the preparation of the γ-lactone of methyl β-glucofururonoside by allowing methanol and glucuronolactone to react for several days at room temperature in the presence of hydrogen chloride. When the reaction product was boiled with methanolic hydrogen chloride, the lactone ring opened to yield an ester which was identified as the methyl ester of methyl glucopyruronoside, a shift of the acetal ring apparently having occurred during the course of the reaction.

Cation exchange resins have found increasing use as substitutes for mineral acid catalysts and offer the advantage that they can be removed by merely filtering the reaction mixture. In order to determine whether uronoside formation could be promoted by this type of catalyst, a methanolic solution of glucuronolactone was refluxed in the

(1) Presented before the Division of Sugar Chemistry, 118th Meeting of the American Chemical Society, Chicago, Illinois, September 3–8, 1950.

(2) L. N. Owen, S. Peat and W. J. G. Jones, *J. Chem. Soc.*, 339 (1941).

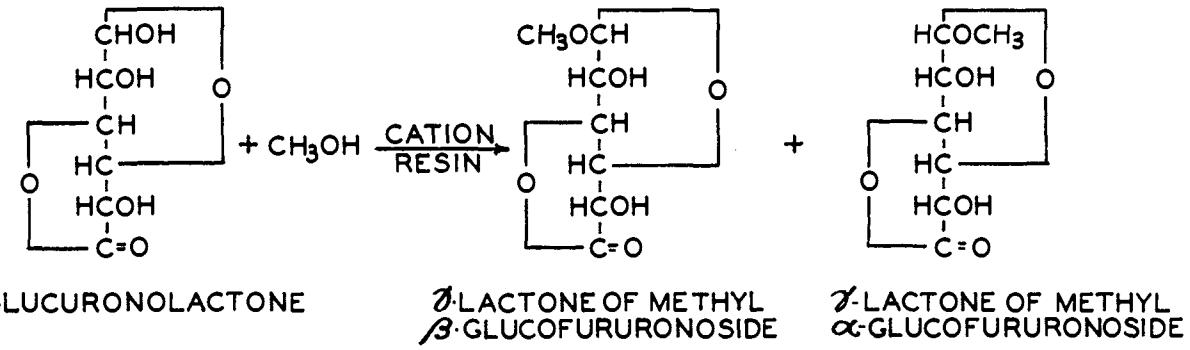

Fig. 1.

presence of Nalcite HCR[3] resin for six hours and the resin was removed by filtration. Upon evaporating the filtrate to a small volume, crystals separated spontaneously. Melting point and specific rotation of these crystals were in essential agreement with those reported for the γ-lactone of methyl β-glucofururonoside by Owen, Peat and Jones.

After several successive crops of crystals had been removed from the primary reaction mixture, a crop melting some 50° lower than the main product was obtained. Recrystallization of this material from absolute ethanol produced a mixture of two distinctly different types of crystals. Separating these by recrystallization proved difficult and the first actual separation to determine whether we were dealing with two compounds or merely two crystalline forms of the same compound was finally carried out mechanically. Both types of crystals had the same methoxyl content, the same neutral equivalent, and the same apparent uronic acid content; all of these values corresponded to those required by theory for the lactone of methyl glucuronoside. However, one form was levorotatory, having the rotation reported for the γ-lactone of methyl β-glucofururonoside, while the other was strongly dextrorotatory, having a rotation of +149° (H_2O). The melting point of this dextrorotatory compound, 147°, is not far removed from that of the levorotatory isomer. We now believe that this new compound is the γ-lactone of methyl α-glucofururonoside (Fig. 1).

Location of the methoxyl group at carbon 1 as the aglycon group of a uronoside rather than at carbon 6 in an ester linkage was indicated by the zero reducing value of the compound. The Weerman reaction was employed to determine whether the dextrorotatory compound had a pyranoid or a furanoid structure. The crystalline amide prepared from the dextrorotatory product yielded hydrazodicarbonamide when subjected to the Weerman reaction and must, therefore, have had an α-hydroxyl group. Thus, indications are that the original compound used in preparation of the amide had a fururonoside structure since a pyruronoside structure would have no free hydroxyl group in the α-position.

Titration data indicated that the dextrorotatory compound was a γ- rather than a δ-lactone, and that the neutral equivalent of the compound corresponded with the theoretical value for that of the lactone of methyl glucuronoside. When the dextrorotatory product was titrated with 0.1 *N* sodium hydroxide solution, at such a rate that *p*H 8.5 was maintained, consumption of alkali was considerably more rapid than was the case with the levorotatory compound but its behavior in this respect was still typical of a γ- rather than a δ-lactone. Figure 2 shows a comparison of the titration behaviors of these two compounds along with those of glucuronolactone (a γ-lactone) and δ-gluconolactone.

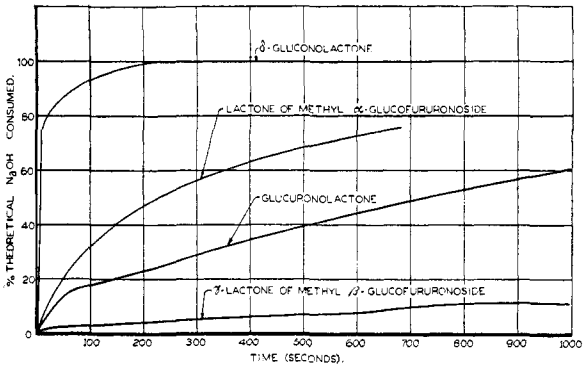

Fig. 2.—Titration of lactone.

Although the lactone ring of the dextrorotatory compound appeared to be hydrolyzed considerably more rapidly than that of the levorotatory compound, the latter was more subject to destruction by alkali than the former as judged by color formation during treatment with alkali. This behavior may explain the difference in the reaction of the two isomers when subjected to analysis for reducibles by the Schoorl method. Whereas the dextrorotatory compound had practically zero reducing value, that of the levorotatory isomer was found to be approximately 15% that of glucuronolactone. This finding probably can be attributed to the double ring structure of the compound, similar to that of D-mannosaccharo-1,4;3,6-dilactone, which was shown by Smith[4] to undergo isomerization and enolization in the presence of alkali, to give a substance analogous to L-ascorbic acid. The more rapid opening of the lactone ring of the dextrorotatory isomer by alkali apparently stabilizes the structure so that no reduction occurs.

Actual rate of uptake of alkali by the levorota-

(3) A product of the National Aluminate Corp., 6225 W. 66th Place, Chicago, Illinois.

(4) F. Smith, *Adv. in Carbohydrate Chemistry*, **2**, 101 (1946).

tory compound was surprisingly slow and no reliable value for its neutral equivalent could be obtained by direct titration. Owen, Peat and Jones[2] reported a value, apparently obtained by direct titration, of 130–160 depending upon the time allowed for titration. The dextrorotatory compound and glucuronolactone behave somewhat similarly when titrated directly but the tendency of the end-point to drift is not encountered until a greater portion of the theoretical requirement of alkali has been added. By employing a buffer technique, consisting of adding an excess of phosphate buffer (*p*H 7.3) of known titration value, boiling for 3–5 minutes and then titrating the amount of buffer consumed, we obtained a value of 189–195 for the levorotatory compound (theory 190). The value obtained by the same technique for the dextrorotatory compound was 191 (theory 190), for glucuronolactone 178–179 (theory 176), and for gluconolactone 176 (theory 178). As shown above, both the dextro and levo reaction products appear to contain furanoid and γ-lactone rings. Both have the same neutral equivalent, the same uronic acid value and the same methoxyl content. Since the nature of the reaction imposed is such that the configurations of the lower five carbon atoms in the two molecules should have remained unchanged, we conclude that the difference in the two compounds must lie in the configuration of carbon 1 and that the dextrorotatory product is the γ-lactone of methyl α-glucofururonoside.

A number of other observations made during the course of this work are of interest although their significance is, at present, only a matter for conjecture. For instance, when it became evident that more than one product was being formed, a prolonged reaction was carried out during which the optical rotation, reducing power, and methoxyl content were followed (Fig. 3). When a 2% solution of glucuronolactone in methanol was heated at reflux with regenerated cation exchange resin, the rotation, originally dextro, changed to levo, attaining a maximum levo-value in twelve hours. The rotation then gradually changed to dextro- and reached a final value representing a specific rotation of +41. Reducibles had reached a constant value at three to four hours. Complete disappearance of reducibles would not be expected, since the γ-lactone of methyl β-glucofururonoside (a known product of this reaction) reduces Fehling solution.

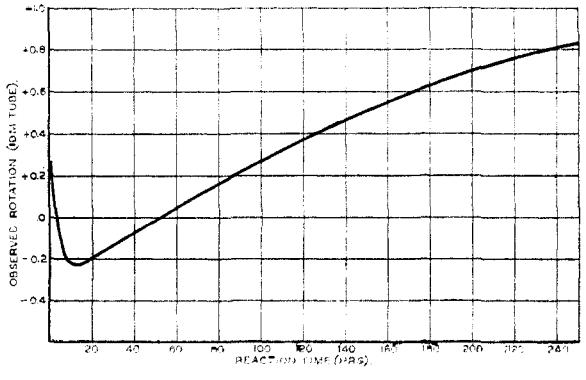

Fig. 3.—Glucuronolactone + methanol (resin catalyst).

Thus it appears that, following the initial glycoside formation, some product of the reaction changes temporarily to a more levorotatory form.

Isomerization of the γ-lactone of methyl α-glucofururonoside to the β-form may be largely responsible for this effect. Such an explanation is supported by the fact that when the α-isomer was heated with methanol at reflux in the presence of cation exchange resin, the rotation followed the same general pattern obtained during the reaction of unmodified glucuronolactone with methanol (Fig. 4). This behavior is similar to the mutarotation which Reeves[5] found to occur when the γ-lactone of 2,5-dimethyl methyl α-glucofururonoside was treated with methanolic hydrogen chloride. He isolated the β-isomer from the solution.

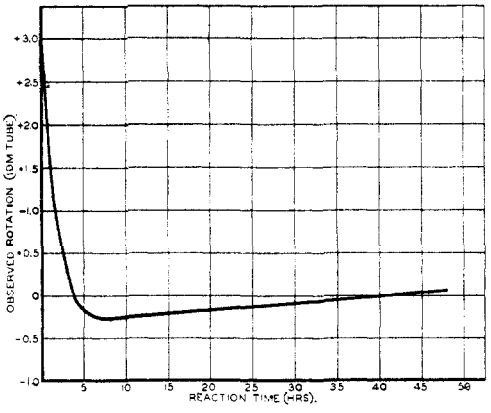

Fig. 4.—γ-Lactone of methyl α-glucofururonoside in methanol (resin catalyst).

The subsequent change in rotation from levo to dextro which we observed, however, is not explained by this reaction. Neither can it be explained by ester formation, since methoxyl determinations still showed the presence of only one methoxyl group per molecule after the rotation became dextrorotatory. That the γ-lactone of methyl β-glucofururonoside itself undergoes a similar shift was shown by the fact that heating the pure compound with methanol in the presence of cation exchange resin caused the rotation of the solution to change from levo to dextro (Fig. 5).

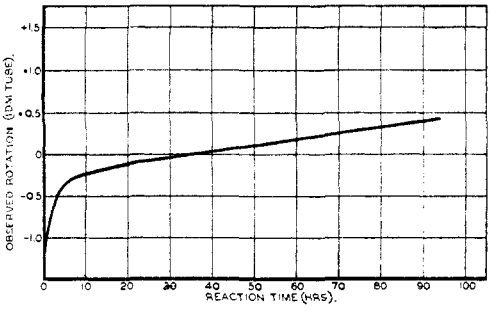

Fig. 5.—γ-Lactone of methyl β-glucofururonoside in methanol (resin catalyst).

This type of rotation behavior is not unique either for resin-catalyzed reactions or for reactions in which methanol is the alcohol used. When the

(5) R. E. Reeves, THIS JOURNAL, 62, 1616 (1940).

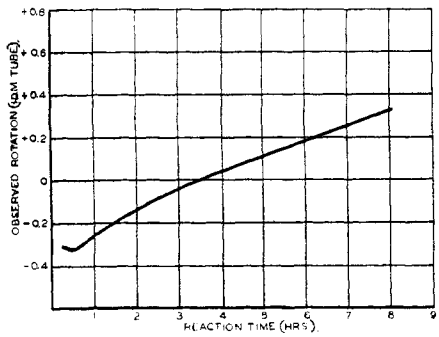

Fig. 6.—Glucuronolactone + methanol (HCl catalyst).

resin was replaced by hydrogen chloride, the same type of curve was obtained (Fig. 6). Formation of ester occurred in this case when the reaction was allowed to proceed for a sufficient length of time. When ethanol instead of methanol was allowed to react with glucuronolactone in the presence of cation exchange resin, similar rotation behavior was observed (Fig. 7).

Further study of these reaction systems may lead to a better understanding of the reactions involved.

Experimental

γ-Lactone of Methyl β-Glucofururonoside.—Three hundred grams of glucuronolactone, 150 g. of Nalcite HCR resin (regenerated, washed with methanol, and air-dried) and 3 l. of methanol were heated at reflux with stirring for six hours; solution was complete within the first hour. The resin was removed by filtration, and the filtrate was concentrated to about 300 ml. and allowed to stand overnight at room temperature. From the solution, 170 g. of nearly pure γ-lactone of methyl β-glucofururonoside separated. By further concentration an additional 62 g. of crystals was obtained, giving a total yield of 232 g. (72%). One recrystallization from absolute ethanol yielded the pure product, m.p. 139° (cor.); $[\alpha]^{23}D$ −59° (*c*, 1.0 in water); −61° (*c*, 1.0 in ethanol).

Anal. Calcd. for $C_7H_{10}O_6$: OCH_3, 16.3; reducing sugar, 0. Found: OCH_3, 16.2; reducing sugar (Schoorl method), 15% (see discussion); uronic acid (naphthoresorcinol method), 95%.

γ-Lactone of Methyl α-Glucofururonoside.—One hundred and fifty grams of glucuronolactone and 75 g. of Nalcite HCR resin were heated with stirring in 7.5 l. of methanol at reflux for three hours. The observed rotation at this time was −0.150°, the approximate value found to correspond to attainment of a constant reducing value. The resin was removed by filtration and the solution was evaporated under reduced pressure to dryness. The residue was dissolved in hot dioxane and allowed to cool. Two crops (86 g.) of strongly levorotatory crystals (lactone of methyl β-glucofururonoside) separated. After further concentration 3.7 g. of crude lactone of methyl α-glucofururonoside, $[\alpha]^{23}D$ +110.5° (*c*, 0.4 in ethanol) was obtained. The material was recrystallized from absolute ethanol until no further change in melting point or rotation was observed; final product, m.p. 148° (cor.); $[\alpha]^{23}D$ +149° (*c*, 1.0 in water), + 167° (*c*, 1.0 in ethanol).

Anal. Calcd. for $C_7H_{10}O_6$: OCH_3, 16.3; reducing sugar, 0. Found: OCH_3, 16.7; reducing sugar (Schoorl method), 0.61%; uronic acid (naphthoresorcinol method), 95%.

Amide of Methyl α-Glucofururonoside.—A solution of 0.7 g. of γ-lactone of methyl α-glucofururonoside in 40 ml. of liquid ammonia and 1 ml. of methanol was held in a Dry Ice-bath for 18 hours. The ammonia was allowed to evaporate and the residual sirup cooled to 0°. Crystallization occurred within a short time. The crystals were removed by filtration, washed well with cold methanol, and allowed to air dry. The 0.66 g. of product was recrystallized twice from 80% methanol, m.p. 263° (dec.), $[\alpha]^{25}D$ +147° (*c*, 0.5 in water).

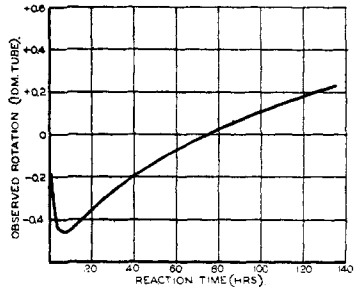

Fig. 7.—Glucuronolactone + ethanol (resin catalyst).

Anal. Calcd. for $C_7H_{13}O_6N$: OCH_3, 15.0; N, 6.76. Found: OCH_3, 15.1; N, 6.66.

The Weerman reaction was applied to the crystalline amide, using the method described by Haworth, Peat and Whetstone[6] and a positive test was obtained.

Prolonged Reaction of Glucuronolactone with Methanol in the Presence of Cation Exchange Resin.—A mixture of 50 g. of glucuronolactone, 25 g. of Nalcite HCR resin and 2.5 l. of anhydrous methanol was heated at reflux with stirring. Samples were taken at intervals. Changes in optical rotation of the solution are shown in Fig. 3. The reducing power of the solution, determined by the Schoorl method, reached a constant minimum value of 4.9 mg. per ml. (calculated as D-glucose) by the end of four hours.

Reaction of Lactone of Methyl α-Glucofururonoside in Methanol in the Presence of Cation Exchange Resin.—A mixture of 2.0 g. of γ-lactone of methyl α-glucofururonoside, 1.0 g. of Nalcite HCR resin and 100 ml. of methanol was heated at reflux with stirring. Samples were taken at intervals for observation of optical rotation. Results are shown in Fig. 4.

Reaction of Lactone of Methyl β-Glucofururonoside in Methanol in the Presence of Cation Exchange Resin.—A mixture of 6.0 g. of lactone of methyl β-glucofururonoside, 3.0 g. of Nalcite HCR resin and 300 ml. of methanol was heated at reflux with stirring. Samples were taken at intervals for observation of optical rotation. Results are shown in Fig. 5.

Prolonged Reaction of Glucuronolactone with Methanol in the Presence of Hydrogen Chloride.—A solution of 50 g. of glucuronolactone in 2.5 l. of 0.1 *N* methanolic hydrogen chloride was heated at reflux. Samples were taken at intervals. Changes in optical rotation of the solution are shown in Fig. 6. The reducing power of the solution reached a constant minimum value of 0.26 mg. per ml. (calculated as D-glucose) between 15 and 30 minutes.

A solution of 50 g. of glucuronolactone in 2.5 l. of 0.55 *N* methanolic hydrogen chloride was heated at reflux. Aliquots taken at 6 and 25 hours showed specific rotations of +63 and +65°, respectively. Methoxyl contents of the sirups resulting from removal of the methanol were 24.0 and 24.2%, respectively. Methoxyl content calculated for methyl ester of methyl glucuronoside is 27.9%.

Reaction of Glucuronolactone with Ethanol in the Presence of Cation Exchange Resin.—A mixture of 50 g. of glucuronolactone, 25 g. of Nalcite HCR resin and 2.5 l. of absolute ethanol was heated at reflux with stirring. Samples were taken at intervals. Changes in optical rotation of the solution are shown in Fig. 7. The reducing power of the solution reached a constant minimum value of 0.27 mg. per ml. (calculated as D-glucose) by the end of four hours.

ARGO, ILL. RECEIVED NOVEMBER 22, 1950

(6) W. N. Haworth, S. Peat and J. Whetstone, *J. Chem. Soc.*, 1975 (1938).