solved, and then allowed to come gradually to room temperature. After 18 hours, the alcohol was removed in a current of air. The residue was dissolved in water and the solution passed through a column containing 5 ml. of cation exchange resin. The column was washed with water, and the combined effluent was evaporated under reduced pressure to a sirup. The boric acid was removed by the method previously described, and the glycitol crystallized from a suitable solvent.

In a preparation of D-mannitol-1-C^{14} from 238 μc. of D-mannono-γ-lactone-1-C^{14}, 192 μc. of D-mannitol-1-C^{14} was obtained without carrier, and an additional 10 μc. by use of 200 mg. of non-radioactive D-mannitol as carrier. The radiochemical yield was thus 85%.

In a similar reduction of one millimole of methyl D-galactonate, the unreduced ester was determined by saponifying with dilute alkali and titrating the excess. The result showed a reduction of 87.6%.

Reduction of D-glucono-γ-lactone in methanol was carried out similarly, except that granulated aluminum was added to the reaction mixture. The reduction, as determined by titration of residual acid or lactone, was 92.6%.

Two reductions in absolute ethanol were performed by adding one millimole of lactone to 10 ml. of absolute ethanol containing 3 millimoles of sodium borohydride and a small quantity of granulated aluminum. The mixture was stirred overnight at room temperature, and treated as previously described. By titrating the residual acid it was found that D-glucono-γ-lactone, D-arabono-γ-lactone and D-*glycero*-D-*gluo*-heptono-γ-lactone were reduced to the extent of 87.8, 89.2 and 95.4%, respectively.

Preparation of D-Mannitol-2-C^{14} by Reduction of D-Mannono-γ-lactone-2-C^{14} in the Presence of Sodium Acid Oxalate.—To two millimoles (356 mg.) of D-mannono-γ-lactone-2-C^{14} having an activity of 892 μc., and 4 millimoles of sodium acid oxalate (520 mg.), in an ice-bath, was added 10 ml. of ice-water. With continuous stirring of the lactone solution, 8 millimoles (320 mg.) of sodium borohydride in 20 ml. of water was added dropwise during a period of 1 hr. The ice-bath was removed, and the flask was allowed to stand at room temperature for 3 hr. The solution was then passed through a column containing 20 ml. of cation exchange resin, the effluent was mixed with 0.5 g. of calcium carbonate, and the precipitated calcium oxalate was removed by filtration. The filtrate was passed through a column containing 10 ml. of cation exchange resin, and the effluent and washings were concentrated under reduced pressure to a thick sirup. Boric acid was removed, and the mannitol-2-C^{14} brought to crystallization by the methods previously described. After recrystallization, 348 mg. (851 μc.) of D-mannitol-2-C^{14} was obtained, and an additional 26 μc. by use of 200 mg. of non-radioactive carrier. The total radiochemical yield, 877 μc., corresponds to 98.3% of the activity of the lactone originally used.

Radioactivity Measurements.—Known concentrations of the materials in formamide solution were counted with a windowless proportional counter.[16] The count was converted to microcuries by means of a factor based on the NBS carbon-14 standard. Samples were counted to a probable error of about 1% (10,000 counts).

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WASHINGTON 25, D. C.

[CONTRIBUTION NO. 1348 FROM THE STERLING CHEMISTRY LABORATORIES, YALE UNIVERSITY]

The Reaction of Some 5,6-Anhydro Derivatives of Glucose and Idose with Organo-lithium Compounds[1]

BY JAMES ENGLISH, JR., AND M. FRANK LEVY[2]

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The reaction of 1,2-*O*-isopropylidene-3-*O*-benzyl-5,6-anhydro-D-glucose and 1,2-*O*-isopropylidene-3-*O*-benzyl-5,6-anhydro-L-idose with methyllithium is described.

As a part of a program directed toward the synthesis of compounds containing carbon-to-carbon bonds between sugars and other molecules,[3] 1,2-*O*-isopropylidene-3-*O*-benzyl-5,6-anhydro-D-glucose[4] (I) was treated with excess methyllithium in ether solution. An exothermic reaction occurred and there was obtained by high vacuum distillation a colorless levorotatory sirup II having the analysis corresponding to the formula $C_{16}H_{20}O_4$. This was treated with hydrogen and Raney nickel (and palladium-on-charcoal) under conditions known to cleave benzyl ethers of this type.[5,6] A mixture was obtained containing crystalline material III that could be purified by crystallization and sublimation *in vacuo*. On the basis of the following evidence the structure 1,2-*O*-isopropylidene-5,6-dideoxy-D-glucose has been assigned to III. Fehling solution is not reduced by III until after hydrolysis in acid; a steam distillate from such an hydrolysate yields iodoform, indicating the presence of the 1,2-*O*-isopropylidene group. Although the free sugar has not yet been obtained in crystalline form, a periodate titration of a solution obtained from hydrolysis of a weighed pure sample of III showed an uptake of 3 moles of periodate per mole of III. This, together with the isolation of propionaldehyde (as its dimedon derivative) from the periodate reaction, establishes the presence of a 6-carbon chain with four adjacent hydroxyl groups and a terminal ethyl group. Carbon-hydrogen analysis, active hydrogen and molecular weight determinations are in good agreement with the proposed structure.

McSweeny and Wiggins[7] have reported the preparation of 1,2-*O*-isopropylidene-5,6-dideoxy-D-glucose by reaction of the corresponding 5,6-anhydro sugar with carbon disulfide followed by treatment with Raney nickel. Their product melted at 78°, $[\alpha]^{21}\mathrm{D}$ $-31.4°$; III melts at 79.0–79.6°, $[\alpha]^{21}\mathrm{D}$ $-21.9°$ and shows a depression in melting point on mixing with McSweeny and Wiggins com-

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[1] We are indebted to the Research Corporation for a grant in support of this work.

[2] Taken from the thesis submitted by M. Frank Levy to Yale University in partial fulfillment of the requirements for the Ph.D. degree.

[3] J. English, Jr., and P. Griswold, THIS JOURNAL, **67**, 2039 (1945); **70**, 1390 (1949).

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[5] C. E. Ballou and H. O. L. Fischer, THIS JOURNAL, **76**, 3191 (1954).

[6] A. S. Meyer and T. Reichstein, *Helv. Chim. Acta*, **29**, 192 (1946).

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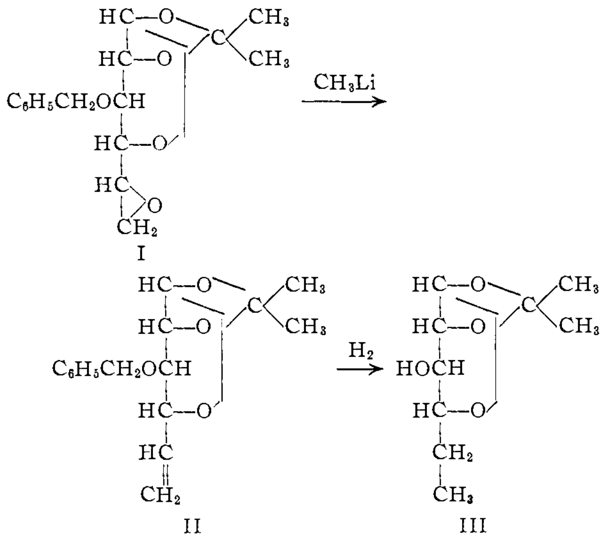

pound.[8] As the English investigators offer no evidence other than the method of synthesis for the structure of their compound, it is difficult to interpret the observed difference in properties; the possibility exists that the two are isomers and that some rearrangement occurred in the reaction of carbon disulfide and alkali with 5,6-anhydro-1,2-isopropylidene-D-glucose.

Acting on the hypothesis that the sirup II is 1,2-*O*-isopropylidene-3-*O*-benzyl-5-deoxy-5,6-D-glucoseen, $C_{16}H_{20}O_4$, a synthesis of this substance was carried out by standard methods.[9] The known 5,6-di-*O*-tosyl-3-*O*-benzyl-1,2-*O*-isopropylidene-D-glucose[6] was treated with sodium iodide and the product purified by distillation. The sirup IV so obtained showed an infrared spectrum identical in all respects to II and on paper chromatography in three different solvent systems exhibited the same R_F values. After mild acid hydrolysis both II and the synthetic glucoseen again exhibited identical chromatographic behavior. When IV was hydrogenated with a palladium-on-charcoal catalyst, there was obtained a mixture from which, as before, by sublimation and recrystallization 1,2-*O*-isopropylidene-5,6-dideoxy-D-glucose (III) was obtained. This had the same melting point as the sample obtained from the methyllithium reaction and showed no depression in a mixed melting point determination.

In an exactly parallel experiment the known[6] 1,2-*O*-isopropylidene-3-*O*-benzyl-5,6-anhydro-L-idose was treated with methyllithium and again crystalline III was obtained from the crude reaction mixture after hydrogenation.

This abnormal reaction product may be limited to the methyllithium reaction in this series; 6-deoxy-6-C-phenyl-D-glucose, as its crystalline acetate, was the only pure product isolated from the reaction of phenyllithium with 5,6-anhydro-3-*O*-benzyl-1,2-*O*-isopropylidene-D-glucose. Attempts to isolate III from the reaction of the same anhydro sugar with ethyllithium have failed. The sirupy product initially obtained (corresponding to II) showed no signs of unsaturation and no crystalline product could be isolated on hydrogenation. Attempted distillation (0.01 mm.) of the hydrogenated product of this reaction led to decomposition.

Present information does not seem to justify proposal of a mechanism for the observed loss of oxygen from the epoxides studied in this work. Two other examples of analogous reactions produced by the action of Grignard reagents on epoxides have been found in the literature.[10,11] Also, Bordwell, Anderson and Pitt[12] have described reactions of organolithium compounds with thio-epoxides in which the formation of olefins was observed; these reactions, and possibly the proposed mechanisms, closely resemble those described in the present work.

Experimental

1,2-*O*-Isopropylidene-3-*O*-benzyl-5,6-anhydro-D-glucose (I) was prepared according to Meyer and Reichstein[6] from the corresponding 6-*O*-tosyl derivative. It was obtained as a colorless sirup, b.p. 153–160° at 0.4 mm., $n^{25}\text{D}$ 1.5010, $[\alpha]^{26}\text{D}$ $-48.0°$ (*c* 4.84, in chloroform). In this and all other preparations involving 1,2-*O*-isopropylidene-3-*O*-benzylglucose, this starting material was always purified through its crystalline acetate, m.p. 120.0–120.8°, $[\alpha]^{26}\text{D}$ $-53.2°$ (*c* 2.48 in chloroform).[6,13]

1,2-*O*-Isopropylidene-3-*O*-benzyl-5,6-anhydro-L-idose was also prepared as described by Meyer and Reichstein.[6] The product was distilled in a short path apparatus at 160–165° bath temperature at 0.4 mm., to yield a colorless sirup, $[\alpha]^{31}\text{D}$ $-77.1°$ (*c* 6.50, in chloroform).

1,3-*O*-Isopropylidene-3-*O*-benzyl-5-deoxy-5,6-D-glucoseen (II).—A solution of methyllithium[14] in 45 ml. of ether was prepared from 11.8 g. of methyl iodide. To this was added gradually an ether solution (15 ml.) of 12.0 g. of the anhydroglucose derivative I and the mixture refluxed for 1.5 hr. Benzene, 100 ml., was then added and the mixture distilled until the vapor temperature reached 77° at which time another equal portion of methyllithium solution was added and the mixture refluxed an additional 1.5 hr. At the end of this time a test for methyllithium was still positive.[15] The mixture was decomposed with water and extracted with ether; the ether layer was washed with dilute acid and then with bicarbonate and evaporated. The residue was distilled with a small fractionating column to yield 5.19 g. of a fraction II, b.p. 124–129 at 0.2 mm., $[\alpha]^{28}\text{D}$ $-56.4°$ (*c* 3.22, in chloroform).

Anal. Calcd. for $C_{16}H_{20}O_4$: C, 69.54; H, 7.30. Found: C, 69.36; H, 7.63.

A similar reaction was carried out at ether reflux temperature without the addition of benzene or a second batch of methyllithium. From 6 g. of I there was obtained 3.66 g. of II in this way.

1,2-*O*-Isopropylidene-5,6-dideoxy-D-glucose (III).—The hydrogenolysis of the benzyl group of II was carried out in two ways: (a) Raney nickel catalyst and hydrogen under 1500 p.s.i. at 100° in methanol for 16 hr. These are the conditions used by Meyer and Reichstein[6] for similar debenzylations. (b) Palladium-on-charcoal in ethanol and hydrogen at atmospheric pressure as described by Ballou and Fischer.[5] Under these conditions about 2 hr. was required for the uptake of hydrogen to stop; about 1.5 moles of hydrogen was taken up.

In both cases solvent was removed *in vacuo* to leave a partially crystalline material; sublimation at 0.4 mm. pressure at a bath temperature of 50° yielded sticky crystals which were recrystallized from petroleum ether. The pure product

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[8] We are indebted to McSweeney and Wiggins for a small sample of their preparation.

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[10] R. C. Fuson, D. J. Byers, C. A. Sperati, R. E. Foster and R. F. Warfield, *J. Org. Chem.*, **10**, 69 (1945).

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[12] F. G. Bordwell, H. M. Anderson and B. M. Pitt, THIS JOURNAL, **76**, 1082 (1954).

[13] K. Freudenberg, H. H. Hochstetter and H. Engels, *Ber.*, **58**, 670 (1925).

[14] H. Gilman, E. A. Zoellner and W. M. Selby, THIS JOURNAL, **55**, 1272 (1933).

[15] A. B. Foster and W. G. Overend, *J. Chem. Soc.*, 680 (1951).

III melted at 79.0–79.6°, $[\alpha]^{26}\text{D}$ −21.96° (*c* 1.344, in chloroform). The yield of crude crystals was 65%.

Anal. Calcd. for $C_9H_{16}O_4$: C, 57.43; H, 8.57; active H, 1.0; mol. wt. (Rast), 188. Found: C, 57.45; H, 8.88; active H, 0.9; mol. wt. (Rast), 195.

The product III did not reduce Fehling solution although boiling with dilute hydrochloric acid and neutralization of the solution yielded a strongly reducing product.

Samples of about 25 mg. of III were dissolved in 2 ml. of 0.1 *N* hydrochloric acid and heated in the steam-bath for 2 hr. To the cooled hydrolysate was added 2 ml. of sodium metaperiodate (0.3 *M*) and the reaction allowed to proceed for 2 hr., by which time periodate uptake had stopped. The periodate consumed in three runs at varying times from 1 to 2 hr. was 2.94, 3.09, 2.99 moles per mole of $C_9H_{16}O_4$ (III). In one case about 3 ml. of the titrated solution was distilled into dimedon solution previously adjusted to *p*H 6; after acidification, the dimedon derivative[16] of propionaldehyde, m.p. 154–156°, was obtained in 66% yield. This showed no depression of melting point when mixed with authentic propionaldehyde dimedon derivative.

1,2-*O*-Isopropylidene-5,6-dideoxy-D-glucose (III) was also prepared by reaction in ether solution of 4.5 g. of 1,2-*O*-isopropylidene-3-*O*-benzyl-5,6-anhydro-L-idose with four equivalents of methyllithium. After refluxing for 3 hr. the mixture was decomposed by water and worked up as before. Distillation at 100–105° bath temperature and 0.2 mm. pressure gave 2.76 g. of sirup, $[\alpha]^{25}\text{D}$ −60.0° (*c* 5.16, in chloroform). From 2.30 g. of this sirup, by hydrogenation in methanol with a Raney nickel catalyst at 100° and 1500 p.s.i. as before, there was obtained 0.45 g. crude crystals of III. Further sublimation and recrystallization from petroleum ether gave 0.09 g. of pure 1,2-*O*-isopropylidene-5,6-dideoxy-D-glucose, m.p. 78.7–79.5°, $[\alpha]^{25}\text{D}$ −21.6 (*c* 1.730, in chloroform). This preparation showed no depression of melting point (78.6–79.6°) on mixing with III prepared from the gluco derivative as described above.

1,2-*O*-Isopropylidene-3-*O*-benzyl-5-deoxy-5,6-D-glucoseen was also prepared from 1,2-*O*-isopropylidene-3-*O*-benzyl-5,6-ditosyl-D-glucose. This starting material was prepared according to Meyer and Reichstein,[6] except that about twice as much *p*-toluenesulfonyl chloride, pyridine and chloroform were used. The colorless sirupy product, 3.50 g., evidently not quite pure (S, 9.61%, calcd. 10.36%), was mixed with 2.90 g. of sodium iodide in 23 ml. of acetone in a sealed tube. The tube was heated at 125° for 4 hr., cooled, opened and the contents diluted with 25 ml. of chloroform and filtered. There was obtained 2.6 g. of air-dried sodium *p*-toluenesulfonate (108%). The filtrate was diluted with a further 50 ml. of chloroform, washed with thiosulfate and dried and evaporated. By short path distillation at 0.14 mm. and a 75° bath temperature there was obtained 1.25 g. of 1,2-*O*-isopropylidene-3-*O*-benzyl-5-deoxy-5,6-D-glucoseen (IV) as an almost colorless sirup, $[\alpha]^{26}\text{D}$ −63.2 (*c* 3.33, in chloroform).

Identity of the two sirupy preparations of this glucoseen, II and IV, was established by comparison of infrared curves, which were superimposable, and by paper chromatography. Both II and IV were hydrolyzed by refluxing for 1 hr. with 10% acetic acid. Then both preparations, before and after the hydrolysis (presumed to have removed the isopropylidine group), were chromatographed on paper in butanol–water,[17] butanol–ethanol–water[18] and butanol–acetic acid–water.[19] The R_F values were nearly identical for the two preparations on all three systems 0.89, 0.80, 0.86, respectively, for the unhydrolyzed group and 0.84, 0.76, 0.93 for the hydrolysate.

Hydrogenation of 1,2-*O*-isopropylidene-3-*O*-benzyl-5-deoxy-5,6-D-glucoseen (IV) was carried out essentially according to Ballou and Fischer[5] with palladium-on-charcoal in methanol at atmospheric pressure. The reaction of 0.5 g. of IV consumed 88% of the theoretical 2 moles of hydrogen per mole of glucoseen in 67 minutes. Filtration of the catalyst and evaporation of the methanol yielded a partially crystalline product. This was purified by sublimation and recrystallization to yield 0.06 g. of 1,2-*O*-isopropylidene-5,6-dideoxy-D-glucose, m.p. 78.5–79.1, $[\alpha]^{26}\text{D}$ −21.2° (*c* 2.68, in chloroform).

6-Deoxy-6-C-phenyl-D-glucose Pentaacetate.—A solution of 0.035 mole of phenyllithium[20] in 30 ml. of ether was treated with a solution of 5.13 g. of 1,2-*O*-isopropylidene-3-*O*-benzyl-5,6-anhydro-D-glucose in 15 ml. of ether. After refluxing for 2 hr. the mixture was decomposed in water at 0.2 mm. at a bath temperature of 131–143° (3.0 g.).

This product was submitted to acetolysis rather than hydrogenation to avoid any possible reduction of the phenyl group. The procedure of Alberton and Fletcher[21] was followed except for an increase in the sulfuric acid concentration to 5%. Model experiments with 1,2-*O*-isopropylidene-3-benzyl-D-glucose-5,6-diacetate indicated that at 2% concentration, after constant rotation had been reached (93 hr.), there could still be isolated the phenylosazone of 3-*O*-benzylglucose. Using 5% acid only free glucosephenylosazone could be isolated at this point.

Accordingly, the acetolysis of 4 g. of the above sirup was carried out at room temperature for 12 days; the mixture was then poured into water and extracted with chloroform. The sirupy acetolysis product, 3.67 g., was treated with 200 ml. of water, 23 ml. of ethanol and 3.6 g. of Amberlite IR-112 under reflux. Evaporation gave an amorphous reducing compound, presumably 6-deoxy-6-phenylglucose, which we were unable to crystallize satisfactorily. Accordingly, it was acetylated with acetic anhydride and pyridine at room temperature. The crude tetraacetate, obtained on pouring the reaction mixture into water, was taken up in petroleum ether and decolorized with norite; on standing in the cold the solution deposited crystals which were filtered and recrystallized from carbon tetrachloride. 6-Deoxy-6-phenyl-D-glucose pentaacetate melts at 158.0–158.4°, $[\alpha]^{25}\text{D}$ +98.2° (*c* 1.936, in chloroform).

Anal. Calcd. for $C_{20}H_{20}O_9$: C, 58.82; H, 5.92. Found: C, 58.55; H, 5.55.

A weighed sample (0.04 g.) was allowed to stand in 2.5 ml. of 0.25% sodium methylate in methanol, neutralized to phenolphthalein and treated with 2 ml. of 0.3 *m* sodium metaperiodate for 1 hr. The excess periodate was then titrated by standard methods. Under these conditions control samples of glucose pentaacetate consumed 4.64 and 4.78 moles of periodate per mole (5.0 calcd.).

The periodate consumed by 6-deoxy-6-C-phenyl-D-glucose pentaacetate was 4.06 and 3.95 moles per mole of sugar derivative after 1 and 3 hr., respectively. After titration the reaction mixtures were combined and distilled into a solution of 2,4-dinitrophenylhydrazine; the 2,4-dinitrophenylhydrazone of phenyl acetaldehyde, m.p. 120–121.9°, identical with an authentic sample, was isolated.[22]

NEW HAVEN, CONNECTICUT

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