TABLE III

PINACOLONYLBARBITURIC ACIDS,

$(\mathrm{CH_3})_3\mathrm{COCH_2}\underline{\mathrm{C(R)CONHCONHCO}}$

R is	Formula	M. p., °C.[a]	Yield, %	N Analyses, % Calcd.	N Analyses, % Found
Ethyl	$C_{12}H_{18}O_4N_2$	204–205	42	11.0	11.1
Allyl	$C_{13}H_{18}O_4N_2$	190–191	40	10.5	10.5
Isoamyl	$C_{15}H_{24}O_4N_2$	209–210	73	9.5	9.4

[a] These melting points were determined on material that had been dried at 100° and under 15 mm. pressure.

Summary

The preparation of three pinacolonylbarbituric acids, $(\mathrm{CH_3})_3\mathrm{CCOCH_2}\underline{\mathrm{CRCONHCONHCO}}$, in which R is ethyl, allyl and isoamyl, is described. These acids are prepared from the corresponding malonic esters which are obtained from a series of reactions that start with pinacolone and oxomalonic ester.

Each of these new barbituric acids has a higher minimum anesthetic dose, a much longer duration of action and a higher minimum lethal dose than does amytal, the 5-ethyl-5-isoamylbarbituric acid.

MADISON, WISCONSIN RECEIVED JUNE 24, 1941

[CONTRIBUTION FROM THE RESEARCH LABORATORY OF ORGANIC CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY, No. 249]

The Rates of Reaction of Diacetone Glucose, Diacetone Galactose and Diacetone Sorbose with Triphenylchloromethane in Pyridine Solution[1]

BY R. C. HOCKETT, H. G. FLETCHER, JR., AND J. B. AMES

Triphenylchloromethane has found many uses in the investigation of carbohydrates because its property of only partially etherifying most polyalcohols, when restricted quantities of agent are applied in pyridine solution, has added a number of compounds to the list of partially substituted sugars which are necessary for synthesis of saccharides and correlation of properties with structure.[2]

A widespread erroneous impression that the etherification is confined entirely to primary hydroxyl groups has been shown groundless by the preparation of trityl ethers from such compounds as α-methyl-L-fucopyranoside which contains only secondary groups[3] as well as by preparation of ditrityl ethers from several glycosides[4] which contain only one primary group. Despite these reports, the use of trityl chloride[5a] as an agent for detecting primary alcohol structures continues to be reported.[5b]

The frequency with which partially tritylated sugar derivatives are encountered is probably due to two factors: the relatively low activity of trityl chloride as compared with many acylating agents and the relatively great crystallizing tendencies of trityl ethers. Even if acetyl chloride shows the same degree of "preference" for the primary hydroxyl group that is shown by trityl chloride (and it may), the fact has remained obscured by the poor crystallizing properties of monoacetates in the sugar group.

This "preference" of trityl chloride for the primary hydroxyl group is most simply interpreted by the hypothesis that such groups generally react to break the hydrogen–oxygen bond more rapidly than do most secondary or tertiary alcohols. The hypothesis is merely extended here to the reaction with triphenylchloromethane from the well-known cases of hydrogen displacement by sodium and rates of esterification by oxygen acids. If "selectivity" is regarded as the ratio between two reaction velocities, it will be recognized that only under favorable conditions can a reaction be depended upon to show which type of group is present. Either the reaction velocities must be very widely separated so that the mere presence or absence of reaction under given conditions may be depended upon to give the correct answer, or else definite knowledge must be had concerning the actual reaction rates of various types of hy-

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(1) A preliminary study with diacetone glucose and diacetone galactose was carried out by Mr. J. B. Ames as a thesis for the degree of *Bachelor of Science*. The measurements were refined and extended to the sorbose derivative by Mr. H. G. Fletcher, Jr., as a thesis for the same degree. A paper covering this work was read at the Boston Meeting of the American Chemical Society in September, 1939.

(2) Helferich, *Z. angew. Chem.*, **41**, 871 (1928).

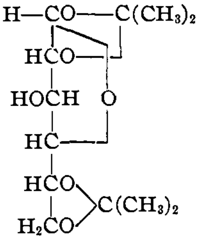
(3) Hockett and Hudson, THIS JOURNAL, **56**, 945 (1934); *cf.* Verkade, *Rec. trav. chim.*, **57**, 824 (1938).

(4) Jackson, Hockett and Hudson, THIS JOURNAL, **56**, 947 (1934).

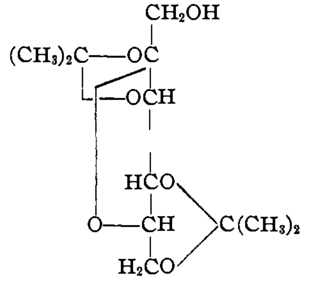
(5) (a) This convenient abbreviation for triphenylchloromethane has become widely accepted; (b) von Vargha, *Ber.*, **68**, 18 (1935); Zemplén, Gerecs and Illés, *ibid.*, **71B**, 590 (1938).

droxyl groups under various conditions. Such knowledge has so far been lacking.

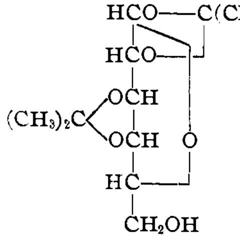
The method of assay which has often been used consists of warming the sample with pyridine and triphenylchloromethane at steam-bath temperature or at least for many hours at room temperature. The isolation of a trityl ether has been deemed indicative that a primary hydroxyl group was present. Our experience with α-methyl-L-fucoside and β-methyl-D-xyloside shows that the degree of selectivity (ratio of reaction velocities) is far too small to make this method reliable. The isolation of a certain amount of product from interaction of any polyalcohol with triphenylchloromethane in pyridine is to be expected even under mild conditions and whether or not primary hydroxyl groups are present.[6] To distinguish between a "large" yield which would tend to indicate the presence of primary groups and a "small" yield indicating only secondary or tertiary groups appears an impractical hope owing to the vaguely qualitative nature of this distinction.



Diacetone-D-glucose



Diacetone-L-sorbose



Diacetone-D-galactose

The purpose of the present investigation was to attempt making a direct comparison of the speed of etherification of sugar derivatives containing only one free primary hydroxyl group with an isomeric derivative containing one free secondary hydroxyl group. The diisopropylidene derivatives of D-glucose, D-galactose and L-sorbose were selected for this purpose because they can be obtained in a very pure state, their structures have been determined with a high degree of certainty, they are isomers, and they are optically active. The last property made possible following the reactions polarimetrically.

The measurements were carried out in specially made, all-glass polarimeter tubes which could be kept filled for long periods without the seepage characteristic of standard tubes. A large excess of triphenylchloromethane was used in order to make the reactions approximate the unimolecular law and in the hope of pushing the reaction rate close to the maximum for the temperature and concentration of substance employed. Determinations made with four-fold and eight-fold excesses of the chloride show some indication of how close we approached the maximum rate. Limitations in solubility and magnitude of polarimeter reading made attainment of truly maximum reaction rate impractical.

The results are shown both by the accompanying graphs and by the table. It should be noted that the rotations at "infinite" time were obtained in the case of the diacetone glucose by warming the solutions until the rotation became constant. To await an approach to the limiting rotation at 20° appeared impractical.

TABLE I

Substance	Excess of trityl chloride	K	Time of "half-change," hr.
Diacetone galactose	4-fold	0.014	21.6
Diacetone galactose	8-fold	.036	8.3
Diacetone sorbose	4-fold	.0052	57.9
Diacetone sorbose	8-fold	.0055	54.7
Diacetone glucose	4-fold	.00012	2500.0
Diacetone glucose	8-fold	.00016	1880.0

The samples consisted of 1.000 g. of substance in a 50.0-cc. volume of pyridine solution.

$$K = 1/t \log_{10} \frac{\alpha_0 - \alpha}{\alpha_t - \alpha},\ t = \text{hours}$$

Several conclusions may be drawn: First, all three compounds react under the conditions used.[7] Second, both substances containing a primary hydroxyl group react much faster than that containing only a secondary hydroxyl free. Third, there is a rather wide difference between the reaction rates of the two compounds containing primary groups.

It is recognized that steric and activation factors are not eliminated. The hydroxyl groups are not equally accessible to reagents. Until a large number of substances have been measured it will

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(6) *Cf.* Arnold and Evans, THIS JOURNAL, **58**, 1950 (1936).

(7) *Cf.* Josephson, *Ann.*, **493**, 175 (1932).

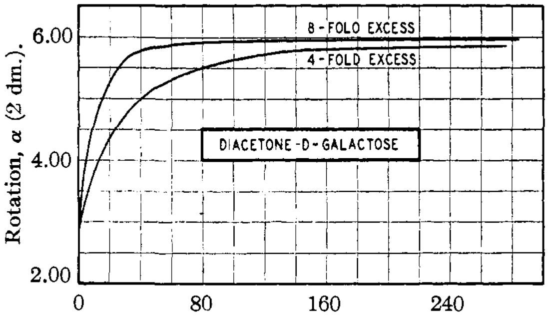

Fig. 1.—Diacetone-D-galactose.

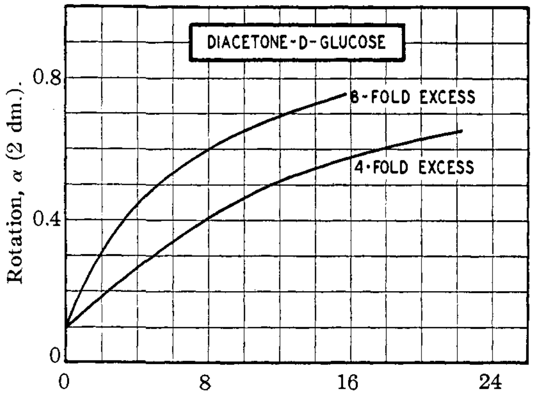

Fig. 2.—Diacetone-D-glucose.

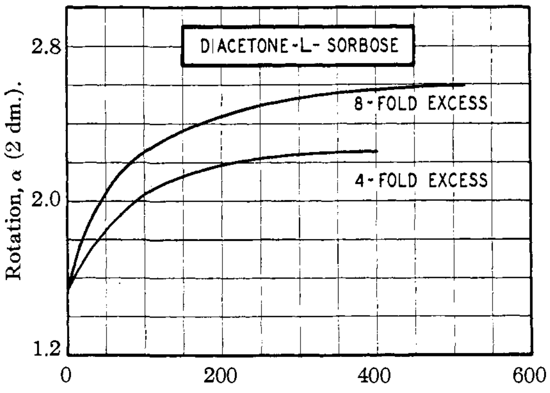

Fig. 3.—Diacetone-L-sorbose.

be impossible to set the limits between which the primary hydroxyls will vary in reactivity or to state whether this range may ever overlap the range characteristic of secondary alcohols.

The measurements are being extended to certain acylating agents in order to obtain a rough comparison between the "degree of specificity" of these reagents and triphenylchloromethane.[8] Measurements at another temperature are also in progress.

The ethers formed in all these reactions were isolated in crystalline condition and their constants were determined.

We express our thanks to Mr. Julius Kovitz of this Laboratory for combustion analyses and to Hoffman-La Roche, Inc., of Nutley, N. J., for the gift of a quantity of diacetone sorbose.

Experimental

1,2;5,6-Diisopropylidene-D-glucofuranose.—Twenty-five grams of finely powdered anhydrous D-glucose was shaken with 500 cc. of dried commercial acetone (Drierite) and 20 cc. of concentrated sulfuric acid (sp. gr. 1.84) for twenty-four hours. With cooling by ice, ammonia gas was passed in to complete neutralization, the ammonium sulfate was filtered, the filtrate was concentrated under reduced pressure to a sirup, and the residue was extracted with hot, high-boiling ligroin. On refrigeration, the extracts deposited crystals of the product which were recrystallized from ligroin until they melted at 110–111° (uncor.) and showed a specific rotation of −16.9°[10] (*C*, 2.428; H_2O; 21°).

1,2;3,4-Diisopropylidene-6-acetyl-D-galactopyranose.—Thirty grams of zinc chloride was transferred immediately after fusing to 500 cc. of dry acetone. To this was added 8 cc. of a homogeneous mixture made by mixing 30 cc. of 85% phosphoric acid with 26 g. of phosphorus pentoxide and 25 g. of dried, powdered D-galactose.[9]

After overnight shaking, the mixture was neutralized with a thick, aqueous suspension of sodium carbonate (litmus), filtered and concentrated under reduced pressure at 70° to a sirup which was extracted with warm ethanol. The extracts, after decolorizing with carbon, were concentrated free of alcohol under reduced pressure, and the residue was acetylated by treatment with one-half its weight of acetic anhydride mixed with pyridine in a ratio of 1–2 by volume. After four days at 35° and six hours at 50–60°, the reaction mixture was treated with four volumes of ice water, shaken vigorously and seeded. The brown, impure precipitate was recrystallized from hot alcohol with the addition of water until the product melted at 109–110° (uncor.) and rotated at −47.2° in chloroform[10] (*C*, 2.916).

1,2;3,4-Diisopropylidene-D-galactopyranose.—In a typical experiment, 10 g. of diacetone galactose monoacetate was dissolved in 130 cc. of dry methanol and treated with 3 cc. of approximately 0.2 *N* sodium methylate in methanol at room temperature for about twenty-four hours. The mixture was neutralized exactly with 0.1 *N* sulfuric acid and then concentrated solvent-free under reduced pressure. After heating for several hours at 100° at around 15 mm. pressure to remove solvents completely, the temperature was raised to 125° and the diacetone galactose itself distilled at a pressure of 1–3 mm. The distillation was

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[8] *Cf.* Compton, This Journal, **60**, 395 (1938); Brigl and Grüner, *Ber.*, **65**, 641 (1932).

[9] Grunenberg, Bredt and Freudenberg, This Journal, **60**, 1507 (1938).

[10] All rotations reported in this paper refer to specific rotations of the D line of sodium at 20° unless otherwise specified. Concentration is stated in grams per one hundred cc. of solution.

interrupted at 140–145°. The product showed a rotation of -68.64° (C, 1.0008; pyridine, 21°).

2,3;4,6-Diisopropylidene-L-sorbofuranose.—This compound was given us by Hoffman–La Roche, Inc., of Nutley, N. J. It melted at 77° (uncor.) and showed a rotation of -16.7[10] (C, 4.332; acetone, 21°).

Triphenylchloromethane.—This substance was prepared from the carbinol by the action of acetyl chloride in hot, anhydrous benzene. A sample heated under reflux for one hour with excess 0.1 N sodium hydroxide and then titrated back with standard acid showed chlorine, 12.75%; calculated for $C_{19}H_{15}Cl$, 12.74%.

The Determination of Reaction Rates.—Exactly 1.0000 g. of sugar derivative was weighed into a 50.0-cc. volumetric flask. The desired quantity of triphenylchloromethane was weighed into a similar flask and made up to the mark with good quality pyridine which had been distilled from potassium hydroxide after long standing with the latter. After attainment of temperature in a constant-temperature room, the sample was made up to the mark with pyridine–triphenylchloromethane solution. The error due to the volumes of the solid substances was well within the limits of accuracy in reading the polarimeter, and its effect minimized also by the fact that trityl chloride was in large excess.

When solution was complete, the mixture was poured into an all-glass polarimeter tube. Observations on the polarimeter were made at intervals measured from the time of mixing until the rotation became constant, in the case of the sorbose and galactose derivatives, and until the diacetone glucose mixture was removed for warming.

A crystalline precipitate sometimes separated at the bottom of the tube but did not interfere with readings because of the large diameter of the special tubes used. The precipitated substance was optically inactive.

1,2;3,4-Diisopropylidene-6-trityl-D-galactopyranose.—A mixture from the rate determination was diluted with ice water until a definite precipitate was formed. After several hours of refrigeration, a precipitate of triphenylcarbinol was removed. Addition of fresh water precipitated an oil which, after repeated washings with water, was crystallized from alcohol by gradual addition of water. The fine white crystals were finally recrystallized from redistilled ligroin until they melted at 80–82° (uncor.) and rotated -58.4°[10] (C, 1.027, $CHCl_3$).

Anal. Calcd. for $C_{31}H_{34}O_6$: C, 74.1; H, 6.81. Found: C, 74.00; H, 6.80, 6.86.

1-Trityl-2,3;4,6-diisopropylidene-L-sorbofuranose.—To a solution of 2.58 g. of diacetone L-sorbose in 15 cc. of anhydrous pyridine was added 3.06 g. of trityl chloride. After a week at room temperature and one and a half hours on the steam-bath, the separated crystals were filtered and the filtrate was treated with 250 cc. of cold water. The fine crystals which separated during overnight refrigeration were removed and recrystallized first from alcohol by the gradual addition of water, and then from hot high-boiling ligroin, until the melting point of well-pulverized samples dried *in vacuo* over calcium chloride rose to 182° (cor.) and a rotation[10] of -27.5° (C, 0.519; 21.5°) was found in $CHCl_3$, -29.4° (C, 1.060; 21.5°) in pyridine.

Anal. Calcd. for $C_{31}H_{34}O_6$· C, 74.1; H, 6.81. Found: C, 74.30, 74.31; H, 7.03, 7.32.

Khouvine and Valentin[11] found m. p. 182° and a rotation of -29.6° in chloroform.

1,2;5,6-Diisopropylidene-3-trityl-D-glucofuranose.—When a sample of 2.37 g. of diacetone glucose was treated as described in the last paragraph (except that heating was for two and a half hours) a brown sirup was obtained. After rubbing well with fresh water, this was dissolved in warm alcohol and brought to crystallization by careful addition of water. The substance then separated as large colorless tablets from alcohol or from ligroin. They showed m. p. 115° (cor.) and when dried as described rotated -24.1° (C, 1.520; 21.5°) in chloroform or in pyridine (C, 1.140; 21.5°).

Anal. Calcd. for $C_{31}H_{34}O_6$: C, 74.1; H, 6.81. Found: C, 74.30, 74.40; H, 6.62, 6.87.

Summary

1. The diisopropylidene derivatives, respectively, of D-glucose, L-sorbose and D-galactose have been treated with large excesses of triphenylchloromethane in dry pyridine solution under such conditions that the rates of reaction could be followed polarimetrically.

2. All three substances reacted with triphenylchloromethane when four- and eight-fold excesses were employed at room temperature.

3. The reactions conformed closely to the unimolecular law, with times of half change in the ratio 226:6.6:1 in the order named above when the eight-fold excess was used.

4. The glucose derivative containing only one secondary hydroxyl free reacted much more slowly than the galactose and sorbose derivatives which contain one free primary hydroxyl each.

5. The galactose and sorbose derivatives showed a rather wide difference in speed.

6. The products of reaction were isolated crystalline and described.

CAMBRIDGE, MASSACHUSETTS RECEIVED JUNE 20, 1941

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(11) Khouvine and Valentin, *Compt. rend.*, **207**, 636 (1938).