Experimental

Methoxyacetonitrile.—The method used by Gauthier[7] was found satisfactory for this preparation. One hundred and forty-one grams of monochloromethyl ether was added slowly with stirring to 141 g. of cuprous cyanide over a period of one hour. The mixture was warmed on a steam-bath for four hours longer and distilled, the yield being 74% of the theoretical; b. p. 120–121° (759 mm.)(corr.); d_4^{20} 0.9492; n_D^{20} 1.3831; M_R calcd., 17.34; M_R found, 17.46.

Preparation of Methoxymethyl Alkyl Ketones.—The ketones were obtained from methoxyacetonitrile by means of the Grignard reaction. The Grignard reagents were prepared in the usual manner, the cyano ether being added slowly with cooling and the reaction product allowed to stand for about eighteen hours before being hydrolyzed by hydrochloric acid. The ether layer was separated, washed with sodium carbonate solution and dried over anhydrous calcium chloride. The keto ethers were carefully fractionated at atmospheric pressure in all cases except that of the tertiary butyl derivative. Boiling points were taken with short, calibrated Anschütz thermometers and the properly corrected values are reported.

The ten alkoxy ketones synthesized are limpid, colorless liquids with slightly rancid, ester-like odors. Although miscible with the usual organic solvents, the solubility in water decreases rapidly with increasing molecular weight. The carbonyl group is fairly reactive as the ketones reduce Fehling's and Tollens' solutions when boiled with these reagents; addition products are formed with saturated sodium bisulfite solution and the magenta color is restored to Schiff's reagent after standing for several hours in the cold, the primary alkyl derivatives bringing about this change most rapidly and the tertiary least readily. All the ketones reacted to give liquid phenylhydrazones which were unstable and showed no tendency to crystallize. When the keto ethers were treated with aqueous solutions of sodium nitroprusside and sodium hydroxide, a dark red coloration resulted which rapidly faded to a light yellow color. The physical data concerning the ten ketones synthesized are collected in Table I.

Summary

1. The Grignard reaction has been utilized to prepare the ten simplest members of the methoxymethyl alkyl ketone series. The condensation, involving an alkoxynitrile and Grignard reagents derived from secondary and tertiary alkyl halides, has for the first time been accomplished.

AUSTIN, TEXAS RECEIVED FEBRUARY 9, 1934

---

[7] Gauthier, *Compt. rend.*, **143**, 831 (1906), reported b. p. 118–9° (731 mm.); d_4^{28} 0.9373; n_D^{28} 1.380; [M_R calcd., 17.34; M_R found, 17.56].

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF INDIANA UNIVERSITY]

Studies Concerning the Relationships of the Isomeric *d*-Glucoses and *d*-Glucose Phenylhydrazones[1]

BY GUIDO H. STEMPEL, JR.[2]

This investigation was undertaken to determine if any structural relationships could be shown to exist between the hydrazones of α- and β-*d*-glucose and the isomeric *d*-glucoses. Isbell and Pigman[3] have demonstrated that β-glucose is oxidized by bromine about thirty-five times as fast as α-glucose, a result which they explain as being due to the configuration of an intermediate molecular compound formed by bromine with glucose, rather than to any inherent difference between the *d*-glucose isomers themselves,

M. Frèrejacque,[4] in attempting to correlate the isomers of *d*-glucose phenylhydrazone with α- and β-*d*-glucose, reported that the hydrolysis of the α- and β-*d*-glucose phenylhydrazones described by Behrend and Lohr[5] leads in both cases to the formation of α-*d*-glucose. He drew this conclusion from the observation that upon completion of the hydrolysis the rotatory power of the solution decreased, which he explained by assuming that the α-*d*-glucose formed mutarotated. This would indicate a very close relationship to exist between α-*d*-glucose and *d*-glucose phenylhydrazones. Frèrejacque carried out the hydrolysis, which is catalyzed by acids, in the presence of oxalic and of picric acid, both of which form insoluble salts with phenylhydrazine, thus removing it from solution and causing the reaction to go practically to completion. Since Frèrejacque's paper is devoid of any quantitative data, the first part of this study was undertaken in an attempt to follow the reaction quantitatively with the hope of proving the presence of α-*d*-glucose in the hydrolysis products by its mutarotation rate, and thus show definitely that the hydrolysis results primarily in the formation of the α-isomer of *d*-glucose.

---

[1] Extracted from a thesis for the Degree of Doctor of Philosophy at Indiana University.

[2] Present address: Carnegie Institute of Technology, Pittsburgh, Pa.

[3] H. S. Isbell and W. Pigman, *Bur. Standards J. Research*, **10**, 337–356 (1933).

[4] M. Frèrejacque, *Compt. rend.*, **180**, 1210 (1925).

[5] R. Behrend and Lohr, *Ann.*, **362**, 78 (1908).

It has been shown by Butler and Cretcher[6] that the method described by Behrend and Lohr[5] for the preparation of a phenylhydrazone of *d*-glucose, m. p. 160°, which Behrend and Lohr have designated as the α-phenylhydrazone, yields only *d*-glucosazone. Butler and Cretcher were, of course, unable to seed the mixture of phenylhydrazine, glucose and acetic acid as recommended by Behrend and Lohr. By altering the procedure somewhat they obtained a gelatinous variety of *d*-glucose phenylhydrazone, m. p. 112°, first described by Skraup[7] and obtained by him in a crystalline form melting at 116°. A reliable method for the preparation of α-*d*-glucose phenylhydrazone is described below as well as its mutarotation in water.

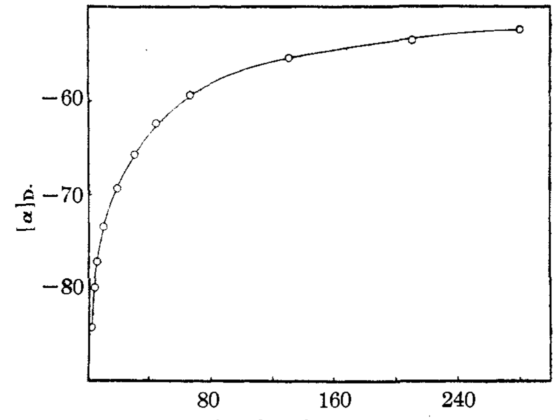

Fig. 1.—The mutarotation of *d*-glucose α-phenylhydrazone in water at 25°.

Materials Used

1. **α-*d*-Glucose Phenylhydrazone.**—To a solution of 40 g. of *d*-glucose in 30 g. of acetic acid and 10 g. of water, prepared by heating the glucose–acid–water mixture and then cooling to room temperature, was added a solution of 28 g. of phenylhydrazine in 320 cc. of absolute alcohol. The resulting solution was then stirred vigorously. By examining a sample of the reaction solution in a polarimeter it was found that within one hour the rotation had become constant at −5°. However, precipitation of the hydrazone was about 45% complete in eight hours and 65% complete in twelve hours. The crude hydrazone usually melted at about 145°.

Two methods of purification were tried: (a) After three recrystallizations from hot absolute alcohol shining white platelets, m. p. 160°, $[\alpha]_D$ −87° (initial), −52.5° (final), were obtained. These crystals decomposed slowly, becoming quite colored after standing for four weeks. Cooling the alcoholic solutions below 20° resulted in the precipitation usually of the Skraup hydrazone, but sometimes of mixtures melting between 140 and 150° in which two distinct crystalline forms were visible, one of which melted at 116°, the other at 140°.

(b) After six thorough washings by decantation with acetone at room temperature a product melting at 157°, $[\alpha]_D$ −87° (initial), −52.5° (final), was obtained. Further washings failed to raise the melting point.

2. **Oxalic acid,** reagent grade, manufactured by Mallinckrodt.

3. **α-*d*-Glucose,** $[\alpha]_D$ 112.3° (initial), and **β-*d*-glucose,** $[\alpha]_D$ 18.2° (initial), were prepared by the method described by Hudson and Dale.[8] The α-*d*-glucose was washed thoroughly with ammonia in alcohol to remove the last traces of acetic acid, from which the glucose was crystallized. The purity of the glucoses was checked by determining the mutarotation constant, $k_1 + k_2$, at 30°, the value obtained, 0.0169, agreeing well with the accepted value of 0.0167.

4. **Phenylhydrazine,** m. p. 18–19°, manufactured by Eastman Kodak Company.

5. **Ethanol,** ordinary 95% c. p.

The Mutarotation of α-*d*-Glucose Phenylhydrazone in Water at 25°.—Table I shows the course of the mutarotation of a 0.208-g. sample of α-*d*-glucose phenylhydrazone dissolved in enough distilled water to make 10 cc. of solution. Figure 1 shows a plot of $[\alpha]_D$ against time.

TABLE I

Time, minutes	$[\alpha]_D$	$k_1 + k_2$
2	−84.2	
4	−80.0	0.0309
6	−77.2	.0271
10	−73.5	.0244
19	−69.4	.0161
30	−65.8	.0133
44	−62.5	.0119
66	−59.6	.0101
130	−55.6	.0079
210	−53.9	.0065
280	−52.5	

Discussion

In Table I the "constant," $k_1 + k_2$, was calculated in the usual way for a reversible unimolecular reaction. The steady drift of the "constant," as shown in the table, proves that the reaction is not unimolecular and that, therefore, at least three substances are involved in the equilibrium, a result which is also in accord with the more recent examinations of the mutarotation of *d*-glucose[9] and of *d*-galactose.[10]

---

(6) C. L. Butler and L. H. Cretcher, THIS JOURNAL, **51**, 3161 (1929).

(7) H. Skraup, *Monatsh.*, **10**, 406 (1889).

(8) C. S. Hudson and J. K. Dale, THIS JOURNAL, **39**, 324 (1917).

(9) F. P. Worley and J. C. Andrews, *J. Phys. Chem.*, **32**, 307–315 (1928).

(10) T. M. Lowry, *J. Chem. Soc.*, 666–685 (1928); C. N. Riiber, *ibid.*, 2173–2185 (1929).

The Hydrolysis of α-*d*-Glucose Phenylhydrazone in the Presence of Oxalic Acid

1. In Table II are shown the results of a typical experiment. A 0.544-g. sample of the α-hydrazone was diluted to 10 cc. with 0.53 molar aqueous oxalic acid solution. The course of the reaction was followed polarimetrically at 30°. The constant, "*K*," was calculated for a unimolecular reaction in the usual way. The rotations (α) were taken for the mercury line at 5461 Å.

TABLE II

Time, minutes	$\alpha \cdot 100$ degrees	K
0.8	−249	
2.9	−177	0.0383
5.8	−101	.0374
8.3	− 46	.0375
10.6	− 7	.0377
13.2	+ 30	.0376
15.1	57	.0389[a]
32.3	165	.0517
37.3	174	

[a] Precipitation of phenylhydrazine oxalate first noticed.

Similar readings were taken with various concentrations of oxalic acid at different temperatures, the value of "*K*" for any given run always remaining constant.

2. The precipitate from experiment 1 was washed twice with alcohol and then shaken with 20 cc. of water. The resulting water extract showed a rotatory power of +0.1°. This procedure could be repeated several times with any given precipitate, an optically active water solution resulting each time.

3. The half-life period of α-*d*-glucose in 0.53 molar aqueous oxalic acid solution at 30° was found to be 3.1 minutes.

Discussion

The velocity constants given in Table II show that the hydrolysis of the α-hydrazone follows the unimolecular law quite closely, and is therefore pseudo-unimolecular in character. The intermediate steps in this reaction are not indicated by the data at hand, but it is safe to conclude that whatever mutarotation reactions take place are so rapid that their effects on the velocity constant are negligible. That the mutarotation rates are not the determining factors in the reaction velocity is seen from the fact that the mutarotation of the hydrazone is not a unimolecular reaction while the half-life period of the α-*d*-glucose of 3.1 minutes, as compared to the half-life period of eight minutes for α-*d*-glucose phenylhydrazone in Table II, shows that glucose mutarotation cannot be the controlling factor, and even indicates that glucose mutarotation does not take place to any great extent.

The results of experiment 2 indicate that the reversal of the rotation observed by Frèrejacque was probably caused by the adsorption of *d*-glucose from solution by phenylhydrazine oxalate. This conclusion finds support in that the value of "*K*" in Table II increases toward the end of the reaction, this increase being due to the removal of the positive rotatory *d*-glucose from solution. Again, although the hydrolysis of the hydrazone seems to be complete, the concentration of sugar in the final solution was rarely more than 80% of that theoretically possible, although in much more dilute solutions concentrations of sugar as high as 90% of the theoretical were obtained before precipitation of the phenylhydrazine oxalate began.

It is concluded from the preceding discussion that no information of value concerning either the structures of the *d*-glucose phenylhydrazones or their relationships to the isomers of *d*-glucose can be obtained from hydrolysis studies of the hydrazones.

The Reaction of Phenylhydrazine with the Isomeric *d*-Glucoses

Procedure 1.—4.913 g. of *d*-glucose was dissolved in 15 cc. of distilled water. To this was added a solution of 2.401 g. of phenylhydrazine dissolved in 15 cc. of alcohol, and the resulting solution was then thoroughly mixed and diluted to 50 cc. with alcohol, which required an additional 16.5 cc. of alcohol. The course of the reaction at 30° was then followed polarimetrically. The rotations were taken for the mercury line at 5461 Å. Figure 2 shows a graph of the observed rotations multiplied by ten (α·10) against time in minutes for typical runs with α- and with β-*d*-glucose. Figure 3 shows a comparison of two runs of α-*d*-glucose with two runs of β-*d*-glucose.

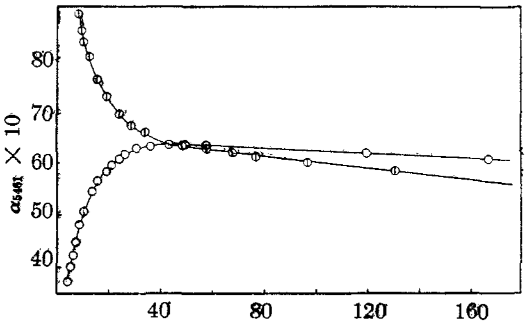

Fig. 2.—The change of rotation with time of solutions of α-*d*-glucose (⦶) and of β-*d*-glucose (○) with phenylhydrazine in a 65% alcohol–water mixture showing the relative reaction rates of α-*d*-glucose and β-*d*-glucose with phenylhydrazine.

Procedure 2.—The experimental detail was the same as that for procedure 1, except that the 4.913 g. of glucose was dissolved in 15 cc. of 0.0244 molar aqueous hydrochloric acid instead of 15 cc. of water. Figure 4 shows a graph of the observed rotations times ten against time in minutes for typical runs with α-*d*-glucose and with β-*d*-glucose. The solutions at equilibrium had a yellow color which did not change during a period of two weeks. There was no indication of osazone formation such as the orange color which developed rapidly when the reaction was catalyzed with acetic acid. Furthermore, the addition of an amount of acetic acid equivalent to that of the hydrochloric acid used in these experiments was followed in about twenty-four hours by a heavy precipitation of osazone.

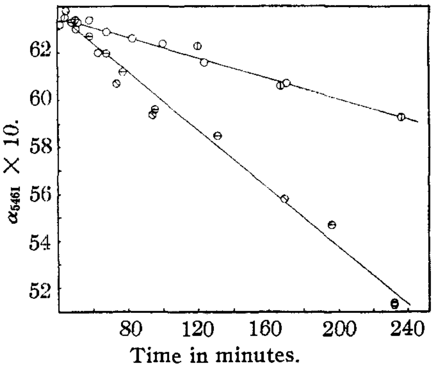

Fig. 3.—The relative reaction rates of α-*d*-glucose (⊗, ⊖) and β-*d*-glucose (○, ⦶) with phenylhydrazine in neutral solution after mutarotation is complete.

Discussion

Since the rate of hydrazone formation, as seen in Fig. 2, is very small compared to the mutarotation rate of glucose, the observation, as seen by comparing the tangents of the curves in Figs. 2 and 3, that the hydrazone formation rate is about twice as fast when α-*d*-glucose is the starting material as when β-*d*-glucose is used, would have to be explained by assuming that the mutarotation equilibrium mixture formed from β-glucose differs from that formed from α-glucose. This assumption is not supported by any other evidence and seems quite improbable.

A more feasible explanation of this discrepancy is that a small amount of some catalyst was present in the α-glucose used. A determination of its mutarotation rate failed to indicate any appreciable amount of such an impurity. In procedure 2 a definite amount of hydrochloric acid was added with the hope that, if the discrepancy were due to catalysis, the difference in the reaction rates would disappear when an amount of catalyst large compared to the impurity present in the α-glucose was added. The results shown graphically in Fig. 4 indicate that the reaction rates are in reality the same. Since the α-glucose used was recrystallized from acetic acid, it seems probable that the complete removal of the acetic acid is not easily accomplished, since to this end the α-glucose was washed many times with ammoniacal alcohol, but apparently without success. It is concluded, therefore, that no measurable difference exists between the reaction rates of α- and β-*d*-glucose with phenylhydrazine, since the mutarotation of the glucose is too rapid to permit such a comparison in alcohol–water solutions, and that the observed difference is due to the presence of traces of acetic acid, which is known to catalyze the reaction.

The formation of both hydrazone and osazone when acetic acid is used, and of the hydrazone alone when hydrochloric acid is used, is of special interest. It is frequently stated that hydrazones do not form in the presence of strong mineral acids. The results presented here show that hydrazone formation does proceed, but that the oxidation of the hydrazone does not, which prevents the formation of osazone. Calculations made from the rotation of the equilibrium mixture of hydrazone and glucose taken from Fig. 4 show that 68.5% of the glucose is transformed into hydrazone.

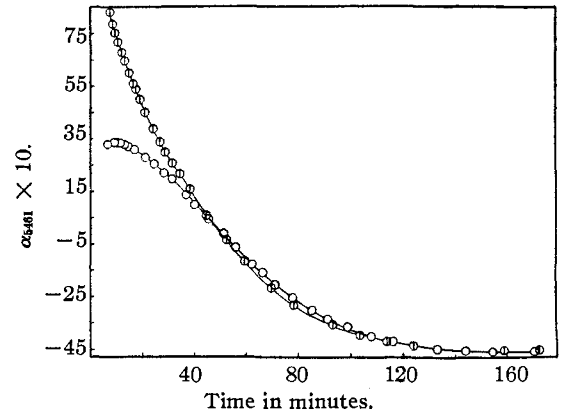

Fig. 4.—A comparison of the rates of reaction of α-*d*-glucose (⦶) and β-*d*-glucose (○) with phenylhydrazine in the presence of 0.0073 molar HCl.

The writer wishes to express his gratitude to Dr. H. T. Briscoe for his help and encouragement during the progress of this study.

Summary

1. A method for the preparation of pure α-*d*-glucose phenylhydrazone has been described.

2. The mutarotation of this hydrazone has been examined in aqueous solution and shows that at least three forms of *d*-glucose phenylhydrazone exist.

3. The hydrolysis of α-*d*-glucose phenylhydrazone in the presence of oxalic acid has been found to be pseudo-unimolecular.

4. Increases in the velocity constant toward the end of the hydrolysis have been explained as being due to the adsorption of *d*-glucose from solution by phenylhydrazine oxalate.

5. It is concluded that hydrolytic studies of hydrazones can yield no information of value concerning the structures of the hydrazones or their relationships to the isomers of *d*-glucose.

6. The reactions of the two isomers of *d*-glucose with phenylhydrazine have been followed polarimetrically.

7. The more rapid reaction rate of the alpha form has been explained by assuming a small undetectable amount of catalyst to be present as an impurity in the α-glucose, since the rates in the presence of hydrochloric acid were found to be identical for the alpha and beta forms.

8. It has been shown that strong acids, contrary to general belief, catalyze hydrazone formation, although they fail to catalyze appreciably the formation of osazone.

RECEIVED FEBRUARY 17, 1934

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT AT THE OHIO STATE UNIVERSITY]

The Preparation of Thiophene and its Homologs from 1,3-Diolefins and Sulfur

BY A. F. SHEPARD, A. L. HENNE AND THOS. MIDGLEY, JR.

Thiophene and its homologs can be synthesized from conjugated diolefins and sulfur. The reaction is general and the yields range from 6 to 50%.

The procedure consists in dropping the liquid diolefin into or bubbling the gaseous diolefin through a vessel containing sulfur kept at about 350°, collecting the materials distilling from the vessel and subsequently effecting their separation. The operation is especially smooth with isoprene or dimethylbutadiene and it affords a 47% yield of 3-methylthiophene or a 31% yield of 3,4-dimethylthiophene. Thiophene is obtained from butadiene with a 6% yield, and 2,3-dimethylthiophene from 3-methyl-1,3-pentadiene with a similarly low yield.

The thiophene derivative produced is not contaminated by isomers, nor does it contain a dihydrothiophene, although the formation of the latter compound could have been expected as a primary result of the linking of the sulfur to the diolefin. By-products of the reaction are hydrogen sulfide, carbon bisulfide and non-volatile materials.

Acetylene, mono-olefins[1] and hydroaromatic compounds are not converted by sulfur into thiophene homologs except in traces. Acetylene and heated pyrites[2] give a good yield of thiophene but diolefins[3] and pyrites yield only small quantities of thiophene derivatives.

Experimental

The reaction vessel was a 1.5-liter iron pot with a lid which could be sealed with Wood's metal. An inlet tube and a thermometer extended through this lid. A broad (15 mm.) outlet at the top of the side wall of the pot led through an air condenser to one receiver chilled with ice and to a second kept at −78°. Glass equipment was unsuitable because of the difficulty of removing sulfur residues.

3-Methylthiophene.—After sweeping out the reaction vessel with carbon dioxide, 200 cc. of crude 50% isoprene was dripped into 800 g. of sulfur at 350 ± 10° at a rate of 5–10 cc. per minute. The combined contents of the receivers, after evaporation of the hydrogen sulfide, were then fractionally distilled, a yield of 30 g. (30%) of crude 3-methylthiophene being obtained. The recovered isoprene was immediately and repeatedly re-treated until no more methylthiophene was obtained, the final yield being 46 g. (47%). The low boiling fraction (50 cc.) was carbon disulfide and a mixture of amylenes originally present in the crude isoprene. 3-Methylthiophene possessing the following constants was obtained from the crude in 86% yield by a single fractional distillation: boiling point 114.9–115.4° (corrected) at 748 mm.; freezing point −55.8 to −56.2°; density d_4^{25} 1.009; refractive index n_D^{25} 1.5169; molecular refraction observed 29.4 (calculated 30.1).[4] It gave a pure blue indophenin reaction and formed an iodo compound when treated with iodine and mercuric oxide. From it were prepared chloromercuri-3-methylthiophene melting at 128° (alone and in a mixture with authentic material) and 3-methylthiophene-mercurithiocyanate melting at 167–168° with decomposition;[5] the mother liquor from the chloromercuri compound yielded no 2-methylthiophene-mercurichloride.

---

[1] Meyer and Sandmeyer, *Ber.*, **16**, 2176 (1883).

[2] Steinkopf, *Ann.*, **428**, 123 (1922).

[3] Steinkopf, *ibid.*, **403**, 11 (1914).

[4] St. Opolski, *Chem. Centr.*, II, 1797 (1905).

[5] Steinkopf, *Ann.*, **424**, 33 (1921).