[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

Acetylation of Carbohydrates by Ketene

BY CHARLES D. HURD, S. M. CANTOR AND ARTHUR S. ROE

Van Alphen's is the only recorded experiment[1] dealing with the behavior of ketene toward simple sugars. He used pyridine as solvent and concluded that acetoglucose was not formed. In the present investigation this work was repeated and extended.

The reaction between ketene and glucose in pyridine yielded a yellow sirup which gave an acetyl value approximating that of triacetylglucose. No crystalline glucose pentaacetate was obtainable, however, by treatment of this sirup with acetic anhydride. Possibly a pyridine–ketene complex inhibited the crystallization.

Wollenberg[2] has described a crystalline substance, $C_{13}H_{11}O_3N$, melting at 204° which was formed by reaction of ketene and pyridine. The structure was not determined, but its formula suggests the combination of one mole of pyridine and four of ketene, with elimination of one mole of water. In repeating this work we were able to obtain a small amount of the 204°-material. Neither of the polymers of ketene, namely, acetylketene or dehydroacetic acid, produced this substance on reaction with pyridine, which suggests that it must arise by reaction of ketene itself with pyridine. Dehydroacetic acid was formed in quantity in pyridine from both ketene and acetylketene.

There was no reaction between ketene and glucose when the latter was suspended in hot acetone or hot dioxane. Derivatives of glucose wherein the 1-hydroxyl was blocked underwent acetylation smoothly, however, in these solvents. α-Methyl 6-triphenylmethylglucoside changed to α-methyl 2,3,4-triacetyl-6-triphenylmethylglucoside, and 1,2-glucose dimethylketal (monoacetone glucose), yielded 3,4,6-triacetyl-1,2-glucose dimethylketal. Only three acetyl groups were introduced into α-methyl glucoside by ketene but the fourth could be inserted by further acetylation at 0° with acetic anhydride and pyridine.

In view of the known catalytic effect of sulfuric acid on acetic anhydride in acetylations, such for example as in the conversion of tartaric acid to diacetyltartaric anhydride,[3] it seemed reasonable to believe that it would be an effective catalyst also in acetylations by ketene. Such proved to be the case. The effect of a trace of sulfuric acid in bringing about a reaction between ketene and a suspension of glucose in acetone was striking. Acetylation progressed nearly to completion, analysis showing 4.6 acetyl groups per molecule instead of the theoretical 5.0. The product, however, possessed a brown color which resisted clarification. *p*-Toluenesulfonic acid could not be substituted for sulfuric acid in this reaction.

Sulfuric acid was effective in catalyzing the reaction between ketene and α-methyl glucoside. The product was a sirup which contained 3.94 acetyl groups per molecule. This closely approximates α-methyl tetraacetylglucoside. Without the catalyst it was possible to introduce only three acetyl groups.

In earlier work it has been shown[4] that ketene is absorbed by sulfuric acid with the formation of a mixed acid anhydride. The latter may function as the reactive substance in the acetylation process, sulfuric acid being regenerated.

Experimental Part

To prepare ketene acetone vapor was passed over a platinum filament[5] electrically heated to about 750°. The stream of ketene gas was used directly in a flow of about 0.14 mole per hour.

Ketene and Glucose

In Acetone (Sulfuric Acid).—A drop of concd. sulfuric acid was added to a suspension of 3.6 g. of anhydrous glucose in 50 cc. of dry acetone. Ketene was passed through the mixture for an hour and a half. Enough heat was developed to keep the acetone refluxing gently. The reaction mixture slowly turned yellow, and finally dark red. When the mixture was poured into water a red oil separated. The latter was desiccated *in vacuo* to a glass. Treatment of an alcoholic solution of the material with activated charcoal was ineffective in removing the color. The substance could not be crystallized from benzene, toluene, alcohol, or acetone–water even when the solution was seeded with crystalline pentaacetylglycose. The material was finally dried in a vacuum desiccator over sulfuric acid, and the red glassy solid was analyzed for its acetyl content by the method of Freudenberg.[6] The material contained 4.59 acetyl groups per molecule.

(1) Van Alphen, *Rec. trav. chim.*, **43**, 823 (1924).
(2) Wollenberg, *Ber.*, **67**, 1675 (1934).
(3) Wohl and Oesterlin, *ibid.*, **34**, 1144 (1901).
(4) Hurd and Dull, THIS JOURNAL, **54**, 3428 (1932).
(5) Hurd and Williams, *ibid.*, **58**, 965 (1936).
(6) Freudenberg, *Ann.*, **433**, 230 (1923).

In Dioxane (*p*-Toluenesulfonic Acid).—Ketene was passed for two hours through a suspension of 7.2 g. of glucose in 50 cc. of dry dioxane. The dioxane contained 0.01 g. of *p*-toluenesulfonic acid. None of the glucose dissolved during this period. On evaporation of the dioxane, a water-soluble residue was left which pointed to negligible acetylation. These results were obtained both at 25° and at 100°.

In Pyridine.—Two grams (0.011 mole) of anhydrous glucose was dissolved in 50 cc. of anhydrous pyridine and ketene was passed through it for one hour. The mixture was thrown into chloroform, and the chloroform solution washed with dilute hydrochloric acid, dilute sodium carbonate solution and finally water to remove the excess pyridine and ketene. Distillation of the solvent left a yellow sirup which did not respond to decolorization with Norit or to crystallization from alcohol, ether or a mixture of ether, and petroleum ether. Left in water over a four-day period, it did not solidify as glucose pentaacetate usually will. Part of the material was desiccated by phosphorus pentoxide *in vacuo* to a glass: $[\alpha]^{20}D$ in chloroform, +39.5°; mol. wt. (cryoscopically in camphor), 295; % acetyl, 45.3, 46.1. The results approach triacetylglucose (mol. wt., 306; % acetyl, 42.2).

The remaining sirup was placed with an excess of acetic anhydride and pyridine and left for twelve hours at 0° but the reaction product again would not crystallize. The specific rotation of the glassy solid obtained on desiccation was +48.8° (in chloroform). Specific rotations for α- and β-glucose pentaacetates are 101.6 and 3.8°.

Ketene and α-Methyl Glucoside

In Dioxane.—Ketene was passed for an hour into the suspension of 2 g. (0.01 mole) of α-methyl glucoside in 100 cc. of pure dioxane at 70–80°, during which time complete solution occurred. A sirup was left on evaporation of the dioxane which analyzed 40.6% acetyl. α-Methyl triacetylglucoside contains 42.4% acetyl.

After standing for twenty-four hours at 0° with 18 g. of acetic anhydride and 22 g. of dry pyridine, the sirup yielded crystalline α-methyl tetraacetylglucoside. It was recrystallized from ether; yield, 0.5 g., m. p. and mixed m. p. 100–101°.

In Acetone with Sulfuric Acid.—Ketene was passed for ninety minutes into a refluxing suspension of 4.75 g. of α-methyl glucoside in 50 cc. of dry acetone which contained a drop of concd. sulfuric acid. A yellow color developed. The mixture was poured into water. The yellow oil which separated contained 3.94 acetyl groups per molecule but it would not crystallize, nor could the yellow color be removed with activated charcoal.

α-Methyl 6-Triphenylmethylglucoside

Acetylation by Acetic Anhydride.—α-Methyl glucoside was converted to the 6-trityl ether according to the directions of Helferich and Becker.[7] It was changed readily into α-methyl 6-triphenylmethyl-2,3,4-triacetylglucoside, m. p. 136°, by reaction at 0° for three hours with acetic anhydride and pyridine. Helferich found the specific rotation of this material to be +136.9° in pyridine.

Acetylation in Acetone by Ketene.—One gram (0.0024 mole) of the above trityl ether was dissolved in 100 cc. of acetone and ketene was introduced for thirty minutes. Isolation of the sirup and crystallization from alcohol yielded 1.3 g. of crystals, m. p. 80–83°, $[\alpha]^{20}D$ in chloroform +120°. This was chiefly α-methyl 6-triphenylmethyl-2,3,4-triacetoglucoside. It was converted to the pure triacetate, m. p. 136°, by treatment with acetic anhydride and pyridine.

Glucose 1,2-Dimethylketal

Acetylation by Acetic Anhydride.—Acetylation of 1 g. of glucose 1,2-dimethylketal ("monoacetone glucose"), m. p. 159–160°, by acetic anhydride and pyridine at 0° yielded 1.6 g. of triacetylglucose 1,2-dimethylketal, m. p. 73–74°. Ohle and Spencker[8] report a melting point of 75° and $[\alpha]^{20}D$ +24.6° in chloroform.

Acetylation in Acetone by Ketene.—One gram of glucose 1,2-dimethylketal (0.0046 mole) was dissolved in 200 cc. of acetone, and ketene was passed through the solution for ninety minutes. Isolation of the sirup and crystallization from ether and petroleum ether gave 1.45 g. of impure triacetylglucose 1,2-dimethylketal, m. p. 60–63°, $[\alpha]^{20}D$ +17.1° in chloroform. Treatment of these crystals with the acetylating mixture of acetic anhydride and pyridine raised the melting point to 74°.

Ketene and Pyridine

Ketene was passed for four hours into a solution of 7.9 g. of pyridine in 5 cc. of dioxane. Heat was developed and the reaction mixture turned first yellow, then red. When no more heat was evolved the reaction was stopped. On cooling, about 0.05 g. of crystals separated, m. p. 199–200°. Wollenberg[2] reported a melting point of 204°.

From the residual liquid, there was obtained 10.2 g. of pure dehydroacetic acid, m. p. 109°.

Acetylketene and Pyridine

A solution of 3.9 g. of pyridine (0.05 mole) in 10 cc. of dioxane was prepared, to which 8.4 g. (0.1 mole) of acetylketene was added. The solution was soon boiling and changed in color to brown. No crystals appeared on cooling. Evaporation of the solution yielded some crystals of dehydroacetic acid, m. p. 106–109°. Recrystallization from water yielded 6.8 g., m. p. 109°.

Dehydroacetic Acid and Pyridine

No reaction was observed when a solution of 8.4 g. of dehydroacetic acid (0.03 mole) and 3.9 g. of pyridine (0.05 mole) in 15 cc. of dioxane was allowed to stand for three days. Evaporation yielded some crystals (dehydroacetic acid) which when washed with hydrochloric acid and dried weighed 7.6 g., m. p. 108°.

Summary

A trace of sulfuric acid is effective in catalyzing the reaction between ketene and a suspension of glucose in acetone.

Direct action of ketene and α-methyl glucoside yielded α-methyl triacetylglucoside. Acetylation of α-methyl 6-triphenylmethylglucoside and glucose 1,2-dimethylketal progressed more nearly to completion. When a trace of sulfuric acid

(7) Helferich and Becker, *Ann.*, **440**, 7 (1924).

(8) Ohle and Spencker, *Ber.*, **59**, 1845 (1926).

was present in the reaction of α-methyl glucoside and ketene, acetylation progressed nearly to completion.

Pyridine is not a satisfactory solvent for the glucose–ketene reaction. Wollenberg's compound, $C_{13}H_{11}O_3N$, formed by reaction of ketene and pyridine, is not formed by reaction of pyridine with either acetylketene or dehydroacetic acid.

EVANSTON, ILLINOIS RECEIVED NOVEMBER 25, 1938

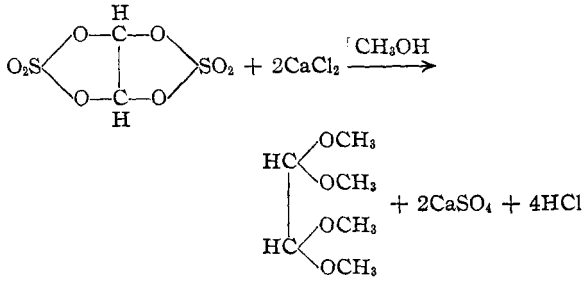
[CONTRIBUTION FROM THE RESEARCH LABORATORY OF ORGANIC CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY, NO. 179]

The Preparation and Estimation of Glyoxal Tetramethyl Acetal

BY D. H. GRANGAARD AND C. B. PURVES

Although the tetraethyl acetal of glyoxal has been synthesized in various ways,[1-3] the tetramethyl acetal apparently has never been isolated in a pure condition.[2] We required a specimen of the latter for reference purposes[4] and to obtain it we adapted the synthesis used by Baker and Field[3] for the former.

Acetylene tetrachloride and 65% oleum readily gave the white, insoluble sulfate of glyoxal in about 30% yield.[5] A reaction occurred when this was heated in absolute methyl alcohol containing calcium chloride and the result was a nearly quantitative formation[6] of glyoxal tetramethyl acetal.



This method was also valid for other acetals in the series.

Glyoxal tetramethyl acetal was a mobile, colorless liquid, b. p. 159°, with the interesting solubility and volatility characteristics described in the experimental portion. The acetal was easily and quantitatively hydrolyzed to glyoxal by hot, dilute mineral acid and was therefore estimated readily as glyoxal *bis*-2,4-dinitrophenylhydrazone.[7] Smaller amounts could be determined colorimetrically, also as glyoxal, by a method involving Benedict's uric acid reagent (arsenophosphotungstic acid),[8] provided certain precautions were taken. The pure acetal served as an excellent source for standard glyoxal solutions, since it was easy to prepare and its aqueous solutions were stable for months.

Experimental

Glyoxal Tetramethyl Acetal.—The glyoxal sulfate was used without further purification. One mole (30.8 g.) was dissolved in 800 cc. of cold absolute methanol containing two moles (31.4 g.) of anhydrous calcium chloride. After boiling for three hours under a reflux condenser, the solution was set aside for about twelve hours to allow the very finely divided precipitate of calcium sulfate to settle. The decanted mother liquor, together with the methanol washings from the precipitate, was made slightly alkaline with sodium methylate solution and then diluted with an equal volume of water. When this aqueous alcoholic system was fractionally distilled through an efficient column, the methyl alcohol volatilized without carrying over any of the product, which was recovered in the first 750 cc. of the aqueous fraction. Sodium chloride (225 g.) was dissolved in this fraction prior to a twelve-hour extraction with ether in an efficient continuous extractor. The ethereal extract was dried over anhydrous magnesium sulfate, the solvent evaporated, and the slightly yellow liquid residue (16.7 g. or 79%,[9] $n^{20}D$ 1.3998) distilled under diminished pressure. The pure acetal boiled at 98–100° (110 mm.).

Anal. Calcd. for $C_2H_2(OCH_3)_4$: C, 47.97; H, 9.39; OCH_3, 82.61; mol. wt., 150.1; *MR*, 36.48. Found: C, 48.04, 47.96; H, 9.44, 9.33; OCH_3, 82.08, 81.98; mol. wt. (dioxane), 145, 146; *MR*, 36.72.

(1) Pinner, *Ber.*, **5**, 151 (1872).

(2) Harris and Temme, *ibid.*, **40**, 171 (1907). From sodium ethoxide and the diethyl acetal of dichloracetaldehyde. The two corresponding methyl derivatives gave a product so volatile that it could not be separated from the excess methyl alcohol.

(3) Baker and Field, *J. Chem. Soc.*, 86 (1932).

(4) We have been studying the isolation of glyoxal, as the tetramethyl acetal, from various oxy-starches and oxycelluloses for the past eighteen months. In the meantime, Davidson [*J. Text. Inst.*, **29**, T 215–218 (1938)] has independently developed our exact line of thought in this connection.

(5) Ruggli and Henzi, *Helv. Chim. Acta*, **12**, 362 (1929); M. A. Perkins, U. S. Patent 1,999,995 (1935); British Patent 447,135 (1936).

(6) *Cf.* the 13% yield of the tetraethyl acetal obtained by Baker and Field[3] without the calcium chloride. These authors preferred the structural formula used here for glyoxal sulfate.

(7) (a) Glasstone and Hickling, *J. Chem. Soc.*, 824 (1936); (b) Neuberg and Simon, *Biochem. Z.*, **256**, 485–491 (1932).

(8) Ariyama, *J. Biol. Chem.*, **77**, 359 (1928).

(9) Some of the product was lost in the dry-ice traps.