[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, FORDHAM UNIVERSITY]

The Structure of β-Chloral Glucose

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The condensation products of chloral and *d*-glucose, commonly known as glucochloraloses[1] have not as yet been explained satisfactorily in their structure. To fill this gap β-chloral glucose (m. p. 227°) has been selected for investigation.

This compound exhibits a remarkable stability toward hydrolysis, unusual for condensation products of carbohydrates. As a consequence, Hanriot,[2] Pictet and Reichel[3] and Petit and Polonowski[4] suggested formulas connecting chloral with glucose by means of carbon–carbon linkages. Earlier experiments by Hanriot, consisting of partial dechlorination of β-chloral glucose and hydrolysis of the resulting compound, were repeated by R. M. Hixon[5] and co-workers. On the basis of these experiments, Hixon proposed an acetal connection between chloral and glucose.

The removal of chlorine by means of sodium amalgam, aluminum amalgam and alcoholic ammonia according to the procedures used in previous experiments is difficult and gives low yields. We have applied catalytic hydrogenation in weakly alkaline medium, using platinum oxide or Raney nickel as catalysts. After rapid absorption of approximately two moles of hydrogen a product could be isolated in good yields which was shown to be a monochloroethylidene glucose. It was hydrolyzed in acidic medium with formation of glucose and chloroacetaldehyde, isolated as glucosazone and chloroacetaldehyde-2,4-dinitrophenylhydrazone, respectively.

A sample of β-chloral glucose purified with particular care showed a specific rotation of −17.2° in pyridine and −3.6° in piperidine; it contained three active hydrogen atoms determined according to the Zerewitinoff method. Therefore, we find it impossible to interpret these experiments other than by postulating the presence of an acetal type of condensation between chloral and glucose, three free hydroxyl groups and a 1–4 or 1–5 lactol ring. All previous formulations, therefore, having four free hydroxyl groups must be incorrect.[2–4] The formation of a pentaacetyl derivative or, by starting with trimethyl-β-chloral glucose, of diacetyltrimethyl-β-chloral glucose, might well be explained in the light of results obtained recently by Montgomery, Hann and Hudson,[6] who showed that by the use of acetylation mixtures catalyzed by zinc chloride, complete rupture of hemiacetals under introduction of two additional acetyl groups might occur.

To prove the nature of the lactol ring, Criegee's[7] lead tetraacetate oxidation has been used. Just as in the case of monoacetone glucose, one mole of the oxidant is used in acetic acid (0.9 mole in six hours at 24°, 1 mole in one-half hour at 65–70°). The scission must have taken place between carbon atoms 5 and 6, since formaldehyde was one of the reaction products. Hence a furanoid system must be present in β-chloral glucose. The isolation of formaldehyde was accomplished by distillation from the reaction mixture into a solution of 2,4-dinitrophenylhydrazine in sulfuric acid. The isolated and recrystallized formal-2,4-dinitrophenylhydrazone was identical with a sample prepared under the same conditions from a formaldehyde–acetic acid solution.

These experiments account for the structure of chloral glucose, except for the second point of attachment of the chloral group. A decision in regard to this point could be reached by a synthesis of trimethyl-β-chloral glucose.

Monoacetone glucose (II) was methylated according to the method of West and Holden.[8] Two methylations were sufficient to obtain the permethylated product. The resulting 1,2-monoacetone-3,5,6-trimethylglucofuranose (III), upon acid hydrolysis, gave 3,5,6-trimethylglucose (IV). This was condensed with anhydrous chloral in the presence of sulfuric acid, at low temperatures, with formation of a crystalline product which after several recrystallizations proved to be identical

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(1) It is suggested to name these compounds simply chloral glucoses, in analogy to other carbonyl condensation products such as the acetone-, benzal- or ethylidene sugars. The prefix "β" obviously does not refer to a β-glucosidic structure; it has been retained in order to avoid conflict with the earlier nomenclature which denotes by α and β the difference between a low-melting monochloral glucose (187°) and the high-melting isomer (227°) which is being dealt with in this paper.

(2) Hanriot, *Ann. Chem. Phys.*, [8] **18**, 466 (1909).

(3) Pictet and Reichel, *Helv. Chim. Acta*, **6**, 621 (1923).

(4) Petit and Polonowski, *Bull. soc. chim.*, [3] **11**, 125 (1894).

(5) (a) Coles, Goodhue and Hixon, THIS JOURNAL, **51**, 519 (1929); (b) Goodhue, White and Hixon, *ibid.*, **52**, 3191 (1930); (c) White and Hixon, *ibid.*, **55**, 2438 (1933).

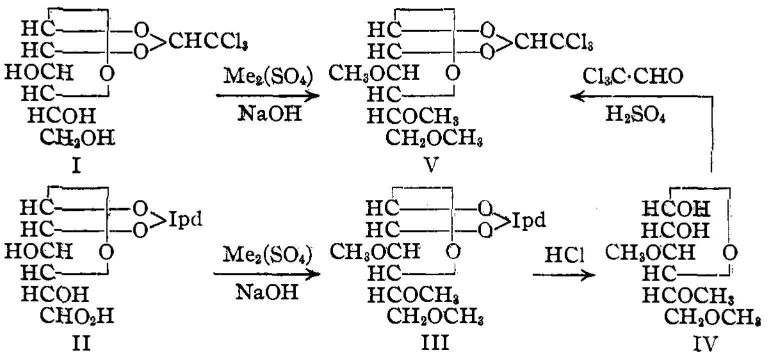
(6) Montgomery, Hann and Hudson, *ibid.*, **59**, 1124 (1937).

(7) Criegee, *Ber.*, **64**, 260 (1931).

(8) West and Holden, THIS JOURNAL, **56**, 930 (1934).

with trimethyl-β-chloral glucose (V), obtained on methylation of the original β-chloral glucose (I).

The synthesis of trimethyl chloral glucose by the condensation of 3,5,6-trimethylglucose with chloral is a repetition of the synthesis reported by Coles, Goodhue and Hixon.[5a] These investigators were not able to prove the identity of this compound with the derivative obtained by methylation of the β-chloral glucose, their failure possibly being due to incomplete methylation. This difficulty could be eliminated by the application of West and Holden's method of methylation.



Experimental Part

β-Chloral Glucose.—For the preparation, the directions of Hixon[5a] were followed, which were confirmed. The yields however were lower; they amounted to 35–40 g. from 200 g. of glucose and 300 g. of chloral hydrate as compared to Hixon's 60 g. A sample recrystallized three times had the constants: m. p. 237.5–238°; rotation, 0.1201 g. subst. in 4.4489 g. of piperidine; $l = 1$; $\alpha = -0.07°$; $[\alpha]^{20}\text{D}$ −3.60; 0.2588 g. subst. in 10.6301 g. of pyridine. $l = 2$; $\alpha = -0.81°$; $[\alpha]^{22}\text{D}$ −17.2°.

Anal. Calcd. for $C_8H_{11}O_6Cl_3$: C, 31.02; H, 3.58; Cl, 34.37; 3 active H atoms, 0.98. Found: C, 31.28; H, 3.70; Cl, 34.44; active H atoms 1.03, 1.03.

Dechlorination.—Removal of chlorine was effected by hydrogenation in acetic acid or ethyl alcohol, using either platinum oxide or palladium as catalysts. However, it was found that the less expensive Raney nickel was far more efficient and it was used exclusively thereafter.

A typical experiment follows: approximately 3 g. of nickel catalyst and 1.1 cc. of 50% sodium hydroxide (equivalent to slightly more than 2 moles of hydrochloric acid) were placed in a hydrogenation vessel and saturated with hydrogen. Then 2.5 g. of β-chloral glucose, dissolved in a minimum amount of hot ethyl alcohol, was introduced and shaken until approximately two moles of hydrogen were taken up. The absorption takes place with remarkable speed, approximately 500 cc. being absorbed within ten minutes. Complete removal of chlorine was found to be impossible; approximately one atom of chlorine remained. Hydrogen consumption: calcd., 362 cc.; found, 414 cc.

The contents of the shaker were then filtered from the catalyst, neutralized with hydrochloric acid and evaporated to dryness *in vacuo* at 40–45°. The residue was extracted three times with 20-cc. portions of hot ethyl alcohol, filtered from sodium chloride and concentrated to a small volume. Upon cooling, clusters of rods separated, melting at 165–166°; total yield of crude material approximately 1.35 g. (70%); recrystallized from alcohol, m. p. 168–170°.

Anal. Calcd. for $C_8H_{13}O_6Cl$: C, 39.91; H, 5.45; Cl, 14.74. Found: C, 40.78; H, 6.02; Cl, 13.87.

Repeated attempts to prepare a sample of this compound higher in chlorine and lower in carbon and hydrogen, failed. The deviations indicate that a mixture of monochloroethylidene glucose and ethylidene glucose was obtained. Continued hydrogenation in order to bring about complete dechlorination was unsuccessful. This preparation was used for the following hydrolysis.

Hydrolysis of Monochloroethylidene Glucofuranose.—Three-tenths gram of substance was dissolved in 15 cc. of 0.5 *N* hydrochloric acid and heated under reflux for about three hours. A sample of the solution now showed strong reduction toward Fehling's solution. The hot reaction mixture had a pungent odor. It was distilled under atmospheric pressure into a solution of 0.27 g. of 2,4-dinitrophenylhydrazine in 3 cc. of concd. sulfuric acid made up to 25 cc. with water. A copious crystalline precipitate was formed. After filtration and repeated washing with water, it was dried and analyzed, m. p. 149–151°.

Anal. Calcd. for $C_8H_7O_4N_4Cl$: N, 21.67. Found: N, 22.38.

The mother liquor was neutralized and upon reaction with phenylhydrazine and acetic acid, *d*-glucosazone could be isolated, m. p. 202°. *Anal.* Calcd. for $C_{18}H_{22}O_4N_4$: N, 15.63. Found: N, 15.26.

Trimethyl-β-chloral Glucose.—A suspension of 22.5 g. of finely powdered β-chloral glucose in 30 cc. of carbon tetrachloride was placed in a three-necked flask provided with a mercury-sealed stirrer, condenser and separatory funnel. This was methylated with 125 cc. of dimethyl sulfate and 130 cc. of 50% sodium hydroxide in the following manner. The mixture is brought to 55° in a water-bath, and 45 cc. of dimethyl sulfate in 50 cc. of carbon tetrachloride is introduced, all at once. Without further heating, the alkali is then introduced at first drop by drop, then as rapidly as possible without causing excessive foaming. During this time, about a half hour, the carbon tetrachloride distils over. When distillation has slackened the remaining alkali is added rapidly and the temperature of the bath raised to 70–75°. The remainder of the dimethyl sulfate is now added dropwise, once more taking care that the reaction does not become too violent. After all reactants are introduced, the bath is brought to 90–95° and maintained at that temperature for forty-five minutes. After cooling, the mixture is diluted with water to dissolve most of the separated sodium sulfate, extracted with chloroform, dried with anhydrous sodium sulfate, and concentrated to crystallization; yield 16.5 g. (83%).

Repeated recrystallization from ethyl–methyl alcohol (1:1) gave a product melting at 113–114°.

Anal Calcd. for $C_{11}H_{17}O_6Cl_3$: C, 37.55; H, 4.88; Cl, 30.26. Found: C, 37.75; H, 4.87; Cl, 30.36. Rotation: 0.2417 g. subst. in 8.4796 g. chloroform; $l = 2$; $\alpha = -2.35$; $[\alpha]^{22}_D$ −28.70.

Acetylation Experiments.—Four grams of trimethyl-β-chloral glucose was refluxed on the steam-bath for two hours with 25 cc. of acetyl chloride and 0.7 g. of fused zinc chloride. The reaction mixture began to darken within five minutes, finally becoming almost black. The excess acetyl chloride was removed *in vacuo*, the residue extracted with chloroform and the chloroform extract washed several times with water. Decolorization with charcoal was impossible. The dark viscous mass obtained on removal of chloroform could not be distilled.

In another experiment using acetic anhydride and zinc chloride, unchanged starting material was recovered upon pouring the reaction mixture into water and recrystallizing the insoluble substance which precipitated. Approximately 70% of original material could be recovered, m. p. 109–110°.

Lead Tetraacetate Oxidation.—A solution of 0.78 g. of β-chloral glucose in 200 cc. of glacial acetic acid was allowed to react with 1.05 g. of lead tetraacetate (1 mole) at room temperature for six hours. The course of the reaction was followed by titration of aliquot parts of the solution with 0.1 *N* sodium thiosulfate. The total volume of thiosulfate used was 42.1 cc. against 47.1 cc. calculated, which shows that 89.4% of the oxidant had reacted.

Similarly 1.0 mole of lead tetraacetate was used within thirty minutes when the reaction was carried out at 65–70°.

Isolation of Formaldehyde.—A third oxidation experiment was performed in order to isolate the volatile reaction product. β-Chloral glucose and lead tetraacetate were allowed to react in molar proportions at 60° in a well-stoppered flask. After attaching a condenser which led into a solution of 2,4-dinitrophenylhydrazine in sulfuric acid, the reaction mixture was boiled for a short time. A heavy, yellow, crystalline precipitate was formed, which after filtration and recrystallization from alcohol melted at 166–167°.[9] *Anal.* Calcd. for $C_7H_6O_4N_4$: N, 26.67. Found: N, 26.45.

A blank distillation with acetic acid alone produced no precipitate. If, however, a few drops of formalin solution were added, the identical formal-2,4-dinitrophenylhydrazone was obtained, m. p. 167–168°.

Synthesis of 1,2-Monoacetone-3,5,6-trimethylglucofuranose (III).—Diacetoneglucose[10] was hydrolyzed in aqueous acetic acid to monoacetone glucose.[11] The latter was methylated twice according to the method of West and Holden, yielding a colorless sirup, b. p. 117–119° at 0.7 mm., n_D 1.4467.

Anal. Calcd. for $C_{12}H_{22}O_6$: C, 54.92; H, 8.46. Found: C, 54.84; H, 8.43.

3,5,6-Trimethylglucofuranose (IV).—(III) was hydrolyzed by refluxing for two hours in (50%) aqueous alcohol containing 0.5% by weight of hydrochloric acid. The resulting colorless solution was neutralized with silver carbonate, filtered and concentrated *in vacuo* at 40–50°. The residue, a sirup, was extracted with ether, dried with "Drierite" and evaporated. This sirup was dried *in vacuo* over concd. sulfuric acid for eight hours.

Anal. Calcd. for $C_9H_{18}O_6$: C, 48.62; H, 8.17. Found: C, 49.30; H, 8.40, n_D 1.4590.

Trimethyl-β-chloral Glucose (V).—Four grams of 3,5,6-trimethylglucofuranose (IV) was condensed with 25 g. of anhydrous chloral and 30 cc. of concd. sulfuric acid by stirring for four hours at approximately 10–15°. Upon pouring into water a gummy mass separated, which was taken up in chloroform, the extract washed with dilute sodium hydroxide solution, dried with "Drierite" and concentrated finally to a very viscous sirup which crystallized on standing overnight at room temperature. After several recrystallizations from a 50% mixture of ethyl and methyl alcohol, crystals were obtained of m. p. 113–114°.

Anal. Calcd. for $C_{11}H_{17}O_6Cl_3$: C, 37.55; H, 4.88; Cl, 30.26. Found: C, 37.53; H, 4.89; Cl, 30.43. Rotation: 0.0985 g. subst. in 1.4889 g. chloroform; $l = 1$; $\alpha = -2.77$; $[\alpha]^{22}_D$ −28.08.

No depression was found upon mixed m. p. determination of a sample prepared by methylation of β-chloral glucose melting at 113–114°. The rotation likewise compares favorably with that of −28.70 found for the methylated β-chloral glucose.

The microanalyses reported in this paper were carried out by Mr. J. F. Alicino.

Summary

A proof of structure of β-chloral glucose is reported which is based on the following experiments: removal of chlorine by means of catalytic hydrogenation in weakly alkaline solution, and hydrolysis of the resulting monochloroethylidene glucose in acid medium to chloroacetaldehyde and glucose.

The number of active hydrogen atoms according to Zerewitinoff coincides with the free hydroxyl groups as determined by methylation.

The ring structure of β-chloral glucose is of the furanose type. Lead tetraacetate oxidation yields formaldehyde, which has been isolated.

A synthesis of trimethyl-β-chloral glucose in crystalline condition from 3,5,6-trimethylglucofuranose and anhydrous chloral, in the presence of concentrated sulfuric acid, is described.

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(9) Bryant, THIS JOURNAL, **54**, 3760 (1932).

(10) Freudenberg, *Ber.*, **59**, 107 (1926).

(11) Zervas and Sessler, *ibid.*, **66**, 1327 (1933).