4. Similar resinous products result if other polyhydric alcohols are substituted for glycerol, or if other polybasic acids are substituted for phthalic anhydride.

5. At whatever temperature the glycerol–phthalic anhydride reaction is carried out, gelation occurs before the esterification has an opportunity to complete itself.

SCHENECTADY, NEW YORK

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, IOWA STATE COLLEGE]

STRUCTURE OF BETA-GLUCOCHLORALOSE[1]

BY H. W. COLES, L. D. GOODHUE AND R. M. HIXON

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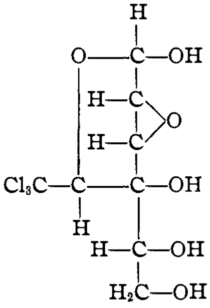
Two crystalline chloral derivatives of glucose were reported by Heffter[2] in 1889 but were not named. More detailed studies of the chloral derivatives of the various carbohydrates have been made by Hanriot[3] and his associates, by Meunier,[4] by Petit and Polonowski,[5] and by Pictet and Reichel.[6] The most recent formula for the β-glucochloralose is that of Pictet and Reichel (Formula III). Most of the standard handbooks give the older formula of Hanriot (Formula I) or of Polonowski (Formula II).

The evidence regarding the structure of β-glucochloralose is conflicting. The absence of reducing properties, the failure to combine with hydroxylamine and phenylhydrazine and the resistance of the compound to hydrogenation all indicate that the free aldehyde groups of both the glucose and the chloral have been modified in their union. The formation of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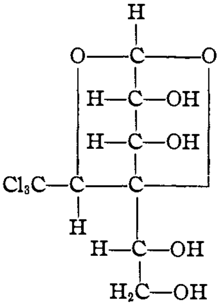
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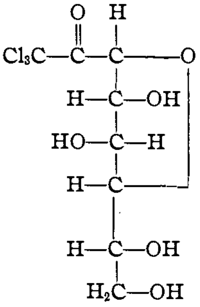
III

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[1] This compound is also called "Parachloralose."

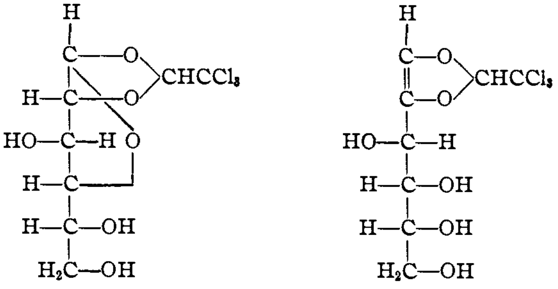
[2] Heffter, *Ber.*, **22**, 1050 (1889).

[3] Hanriot and Richet, *Compt. rend.*, **116**, 63 (1892); **117**, 734 (1893); **122**, 1127 (1896); *Bull. soc. chim.* [3], **9**, 947 (1893); [3], **11**, 37, 258, 303 (1894); Hanriot, *Ann. chim. phys.*, **18**, 466 (1909); Hanriot and Kling, *Compt. rend.*, **152**, 1398, 1596 (1911); **156**, 1380 (1913).

[4] Meunier, *Ann. chim. phys.*, [6] **22**, 413 (1906).

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

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



IV V

Formulas for β-glucochloralose.

tetra-derivatives and the fact that the carbohydrate chain can be oxidized by nitric acid without rupture of the glucose–chloral linkage have been used as evidence for the above formulas. The essential points which these formulas depict are: (a) a carbon–carbon linkage between the chloral and glucose radicals and (b) the presence of four free hydroxy groups.

On the other hand, the chloral condensation products with glycerin[7] and with the α-hydroxy acids[8] have been considered to have acetal linkages analogous to the other aldehyde and ketone condensation products with the poly-alcohols. Similar structures are also assumed to be present in the dichloral glucoses.[9] The reaction reported by Hanriot and Kling[10] would be highly indicative that this is also the case in β-glucochloralose. The reaction was accordingly duplicated for confirmation. β-Glucochloralose was reduced by means of aluminum amalgam to dechloro-β-glucochloralose (glucose-dichloroacetaldehyde). This compound was hydrolyzed by refluxing with dilute hydrochloric acid. The dichloro-acetaldehyde was distilled out and converted to both the oxime and osazone of glyoxal for identification. The glucose was isolated as the osazone. It seems improbable that the removal of one chlorine atom would render the linkage shown in either Formula I, II or III as labile as this reaction would indicate.

The conversion of β-glucochloralose to two different dichloralglucoses identical with those previously reported in the literature would appear to harmonize with only this acetal type of structure. There would appear to be no logical explanation for the condensation of chloral with β-glucochloralose as represented by any of the proposed formulas containing four free hydroxy groups, to give a dichloralglucose containing but one free hydroxy group. The only formula that suggests itself as being in harmony with these facts is an acetal type of linkage in the β-glucochloralose,

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[7] Yoder, THIS JOURNAL, **45**, 475 (1923).

[8] Böeseken, *Verslag Akad. Wetenschappen Amsterdam*, **35**, 1084 (1926).

[9] Ross and Payne, THIS JOURNAL, **45**, 2363 (1923).

[10] Hanriot and Kling, *Bull. soc. chim.*, [4] **11**, 207 (1912).

with a keto–enol isomerization similar to that shown in Formulas IV and V to explain the formation of tetra-derivatives.

The linkage shown in IV is that of the 1,2-monochloralglucose. This structure presumably belongs to the compound reported in this paper as being formed by the condensation of chloral with 3,5,6-trimethylglucose obtained from the corresponding mono-acetone glucose. This compound is not identical with the trimethyl-β-glucochloralose obtained by direct methylation of β-glucochloralose. The two isomeric trimethylchloralglucoses are very similar in solubilities. The 3,5,6-trimethylmonochloralglucose gives no reaction for an active hydrogen with the Zerewitinoff test.[11] The trimethyl-β-glucochloralose not only gives this test but forms a monoacetyl derivative.[12]

Evidence regarding the positions of the methyl groups in trimethyl-β-glucochloralose was sought by removing both one and two of the chlorine atoms and hydrolyzing the reduced chloral group to give the free trimethylglucose. The dichloro-acetaldehyde was easily characterized by its oxime and osazone but sufficient monochloro-acetaldehyde was not obtained to be certain of its identity. In both derivatives the strength of acid necessary to hydrolyze the compounds was so strong (about 1 *N*) that partial decomposition of the methylated sugar resulted. The impure sirup obtained by vacuum distillation resembled the 3,5,6-trimethylglucose in its instability toward acids and in being levorotatory.

Experimental Part

Preparation of β-Glucochloralose.—The following method of preparation of β-glucochloralose was found most satisfactory: 300 g. of chloral hydrate and 400 cc. of concd. sulfuric acid are cooled in running water to 12–15°. As soon as the chloral layer begins to separate, 200 g. of glucose is stirred in using a strong mechanical stirring apparatus, the blades of which should be near the bottom of the beaker to prevent clogging with the floating cakes of material. After stirring for ten to twelve hours at 12–15°, the reddish, viscous mass, which should show no evidence of charring, is poured slowly with violent stirring into 4 liters of cold water. The white precipitate of dichloralglucoses is allowed to settle. The mother liquor is decanted, brought to a boil and allowed to cool slowly. The β-glucochloralose which separates at this point is recrystallized from alcohol, several recrystallizations being necessary for absolute purity; yield, 60 g.

Separation of the Dichloralglucoses.—The precipitate of dichloralglucoses obtained in the above procedure is heated with 500 cc. of water and small portions of sodium hydroxide are added until the excess chloral is driven off and the mixture becomes slightly alkaline. The crude product is filtered off and washed; yield, about 100 g.

A hot alcoholic extract of this product yields the dichloralglucose of m. p. 225° frequently reported in the literature. Only one recrystallization is necessary for purification.

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[11] Zerewitinoff, *Ber.*, **40**, 2023 (1907); *Z. anal. Chem.*, **68**, 321 (1926).

[12] This compound will be reported in a later paper. Attempts to introduce a fourth methyl group have as yet proved negative.

Evaporation of the alcoholic mother liquor leaves a sirup which is taken up in hot carbon tetrachloride and filtered from insoluble materials. Cooling and concentrating this solution yields the dichloralglucose, m. p. 135°, frequently described in the literature. The yield of the two dichloralglucoses is about equal.

It is possible that other dichloralglucoses can be isolated from this mixture, as further information regarding their specific solubilities becomes available. At times a compound of m. p. 188° is obtained with the latter fraction mentioned above.

Conversion of β-Glucochloralose into Two Different Dichloralglucoses.—Twenty g. of β-glucochloralose was treated with 100 g. of chloral hydrate and 100 cc. of sulfuric acid as described for glucose. After the precipitation with water and washing free from acid as in the previous directions, the dichloralglucoses were separated from the unchanged compound by taking up in acetone. The mixture of the two dichloralglucoses is thrown out of the acetone as a white powder by adding water until it is turbid and allowing to stand for two or three hours. The powder (about 10 g.) is dried at 70° until the odor of chloral is no longer noticeable and is then extracted with 200 cc. of hot benzene.

One of the dichloralglucoses (m. p. 268°) is insoluble in benzene and remains as a residue (about 3 g.). Acetylation yielded the mono-acetate (m. p. 198°) as reported by Ross and Payne.[9] Both of these compounds were also checked by chlorine analysis.

Slow evaporation of the benzene solution yields about 6 g. of an isomeric dichloralglucose (m. p. 225°). This compound was checked by a mixed melting point with the dichloralglucose isolated as a by-product in the preparation of the β-glucochloralose. Acetylation yielded the mono-acetate (m. p. 126°), as reported by Ross and Payne.[9]

Trimethyl-β-Glucochloralose.—It was found impossible to methylate β-glucochloralose by either the silver oxide method of Purdie and Irvine[13] or by the original dimethyl sulfate reaction proposed by Haworth.[14] The following modification of the latter method was found quite successful: 5 to 7 g. of finely powdered β-glucochloralose is placed in a three-necked flask provided with a condenser and a mercury-sealed mechanical stirrer; 100 cc. of dimethyl sulfate is added and the mixture is warmed to 60° until nearly all of the compound is in solution. The water-bath is removed and 25 g. of sodium hydroxide in pieces the size of a pea is added. If the mixture is kept dry the reaction is slow but as the reaction proceeds it becomes more rapid and care must be taken to prevent too high temperature. The excess dimethyl sulfate is destroyed by adding sodium hydroxide in 3 g. portions until the reaction mixture becomes basic. Small amounts of water are added as the mixture becomes too thick to stir.

The reaction mixture is extracted repeatedly with chloroform, the chloroform extract concentrated to a sirup, the sirup taken up in methyl alcohol and crystallized by careful addition of water; yield, 4 g. After recrystallization from petroleum ether the melting point remains constant at 109–110°.

Anal. (Carius). Calcd. for $C_{11}H_{17}O_6Cl_3$: Cl, 30.28. Found: Cl, 30.44, 30.42.

The trimethyl-β-glucochloralose showed little or no rotation in methyl alcohol (concd. 2.2% in a decimeter tube). The crystals are soluble in hot water, glacial acetic acid and ethyl acetate. Repeated methylation by the above method did not change the compound.

Trimethyl Monodechloro-β-glucochloralose (Trimethylglucose-dichloro-acetaldehyde).—Seven g. of trimethyl-β-glucochloralose was dissolved in 250 cc. of alcohol containing 5 cc. of concd. hydrochloric acid. The solution was diluted with water until precipitation just began. This solution is held at 50–60° under reflux for twenty-four

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[13] Purdie and Irvine, *J. Chem. Soc.*, **83**, 1021 (1903); **85**, 1049 (1904).

[14] Haworth, *ibid.*, **107**, 8 (1915).

hours while an excess of aluminum amalgam is added in small portions. If the amalgam is added in one portion, it tends to become inactive. As the reaction becomes alkaline, acid is added. The alcohol is distilled out under reduced pressure and the residue is extracted with ether. The oil obtained from the ether is difficult to obtain crystalline, the best method being to precipitate it carefully from alcoholic solution by slowly adding water; m. p. 68°; yield, 3 g.

Anal. Calcd. for $C_{11}H_{18}O_6Cl_2$: C, 41.63; H, 5.72; Cl, 22.37. Found: C, 41.78, H, 5.75; Cl, 22.33, 22.57.

Acid hydrolysis of 5 g. of this compound in 30 cc. of water and 7 cc. of hydrochloric acid (concd.) at boiling temperatures under reflux for six hours yielded positive tests for the dichloro-acetaldehyde (osazone of glyoxal) but the sugar resinified.

Lower concentrations of acid caused only slight hydrolysis. Several attempts were made to purify the methylated sugar by vacuum distillation but in no case was it possible to free the sirup from chlorine. The sirup was slightly levorotatory.

Trimethylbidechloro-β-glucochloralose (Trimethylglucose Monochloro-acetaldehyde).—The trimethyl-β-glucochloralose was reduced with sodium amalgam under various conditions. The reduced compounds would not crystallize so they were subjected to vacuum distillation. A clear sirup which partially crystallized came over at 155–160° (bath temp.) under 4 mm. The chlorine analysis was slightly low for the monochloro compound (calcd., 12.8; found, 11.72). Hydrolysis of the sirup yielded results similar to those described for the preceding compound.

Mono-acetone glucose has been prepared by partial hydrolysis of diacetoneglucose in water solutions.[15] A more convenient method has been found by taking advantage of the insolubility of the mono-acetoneglucose in ethyl acetate as compared to the solubility of the diacetoneglucose. Fifty g. of diacetoneglucose is dissolved in 400 cc. of ethyl acetate containing 4 cc. of concentrated nitric acid. The solution is heated to boiling and then cooled. The mono-acetoneglucose separates at once and is pure after one recrystallization from either water or neutral ethyl acetate.

3,5,6-Trimethylmonochloralglucose.—Five g. of 3,5,6-trimethylglucose, prepared from mono-acetoneglucose, was added to 40 cc. of sulfuric acid and 30 g. of chloral hydrate cooled in an ice-bath and mechanically stirred. After four hours the solution was stirred into 400 cc. of ice water. The separated gummy mass was taken up in chloroform and washed with sodium hydroxide solution to free it from sulfuric acid. After the evaporation of the chloroform the sirup was allowed to crystallize from alcohol and was then recrystallized from petroleum ether. The melting point gradually changed from 109 to 120° after many recrystallizations; yield, 2 g.

Anal. Calcd. for $C_{11}H_{17}O_6Cl_3$: Cl, 30.28. Found: Cl, 30.54. *Rotation.* Soln. 0.8413 g.; chloroform, 9.998 cc. (by wt.). $\alpha^{25}_{D} = -2.44°$ in a decimeter tube; $[\alpha]^{25}_{D} = -29.01°$.

The compound does not react with methylmagnesium iodide, which would indicate the absence of free hydroxyl groups. The solubilities are about the same as for the isomeric compound obtained by methylation of β-glucochloralose.

Summary

1. Trimethyl-β-glucochloralose is reported from the methylation of β-glucochloralose. Attempts to introduce a fourth methyl group have proved negative although an acetyl group can be introduced.

2. 3,5,6-Trimethylmonochloralglucose is reported from the condensation of chloral with 3,5,6-trimethylglucose.

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[15] Irvine and Macdonald, *J. Chem. Soc.*, **107**, 1701 (1915).

3. β-Glucochloralose condenses with chloral to yield two dichloralglucoses identical with those previously reported in the literature.

4. It is pointed out that the present formulas for β-glucochloralose cannot explain the formation of the dichloralglucoses. The reaction reported by Hanriot and Kling by which both the aldehyde and glucose are identified would indicate an acetal rather than a carbon–carbon linkage.

AMES, IOWA

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE STATE COLLEGE OF WASHINGTON]

ORIENTATION IN THE BENZENE RING. THE BROMINATION OF 2-AMINORESORCINOL DIMETHYL ETHER[1]

BY ARTHUR A. LEVINE AND HOOPER LINFORD

RECEIVED SEPTEMBER 25, 1928 PUBLISHED FEBRUARY 5, 1929

It has been shown in preceding papers[2] that the 2,6-dimethyl ether of pyrogallol gives on halogenation in an anhydrous medium a monohalogen substitution product in which the halogen atom has substituted meta to the hydroxyl group. The bromination of 2-aminoresorcinol dimethyl ether, which has an analogous structure, has been investigated in order to determine the mechanism of the reaction. Two courses are open for the entering halogen atom, it may substitute directly in the ring or else replace one of the amino hydrogens and subsequently migrate to the ortho-ortho-para positions as shown by Chattaway and Orton[3] in case of acetanilide. It may be assumed that in 2-aminoresorcinol the bromine atom enters the amino group and subsequently migrates to the para position, but such is not the case, apparently, since the product obtained has the bromine atom in the meta position to the amino group. It has not been possible to prepare the N-bromo derivative and actually determine whether the bromine atom migrates to the meta position. Every effort gave oxidation products.

The acetanilide of 2-aminoresorcinol dimethyl ether was brominated with a calculated quantity of bromine in acetic acid as a solvent. Numerous attempts have been made to brominate the free base in an anhydrous medium. Satisfactory results have been obtained on bromination of the free base in glacial acetic acid containing a small quantity of acetic anhydride. The product obtained, however, was the corresponding monobromo-acetanilide. The formation of the acetanilide is rather unusual, taking place with the utmost ease at room temperature, while Kauffmann

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[1] Abstracted from a thesis by Hooper Linford, presented to the Graduate Faculty of the State College of Washington in partial fulfilment of the requirements for the degree of Master of Science.

[2] (a) Levine, THIS JOURNAL, **48**, 2719 (1926); (b) **49**, 797 (1927).

[3] Chattaway and Orton, *Ber.*, **32**, 3573, 3635 (1899).