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BENZOPHENONE DERIVATIVES OF HEXITOLS IN
THE CARBOHYDRATE SERIES

BY
SISTER M. FIDES PAULL, O.S.F.

A THESIS

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OMAHA, AUGUST, 1948

DEDICATED

TO

MY MOTHER

78841

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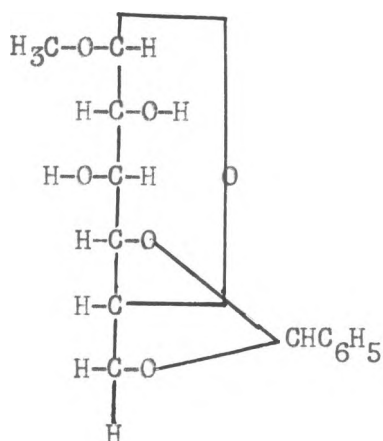
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INTRODUCTION

It is known that hydroxyl groups in sugars have been blocked by various methods to facilitate analytical, synthetic and structural problems. Benzoates, methyl groups, acetal groups, etc. have been used for this purpose.

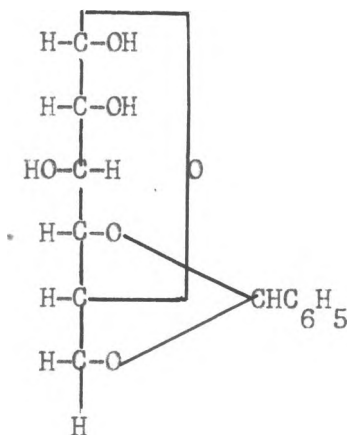
For example, compounds of glucosides with aromatic aldehydes were synthesized by Ekenstein and Blanksma.¹ These compounds were of interest because the aromatic group can be easily split off from their acetal unions through catalytic reaction. The aromatic glucosides with their partially concealed hydroxyl groups proved to be valuable and interesting material for synthetic reactions among the sugars.

Zervas² proved that benzylidene compounds were more useful. He synthesized the alpha-benzylidene-glucose from grape sugar with benzaldehyde in presence of zinc chloride. The structure proved to be 4,6-benzylidene alpha-d-glucose. Besides the pure material there were other isomers and stereoisomers. Phenylhydrazone as well as osazones were formed. Consequently the OH on carbon 1 and 2 were free. With alkali and dimethylsulfate in cold temperature he synthesized a benzylidene-methyl-glucoside.



4,6-benzylidene-beta-d-methyl-glucoside, the product of Freudenberg, Toepffer, and Anderson.³

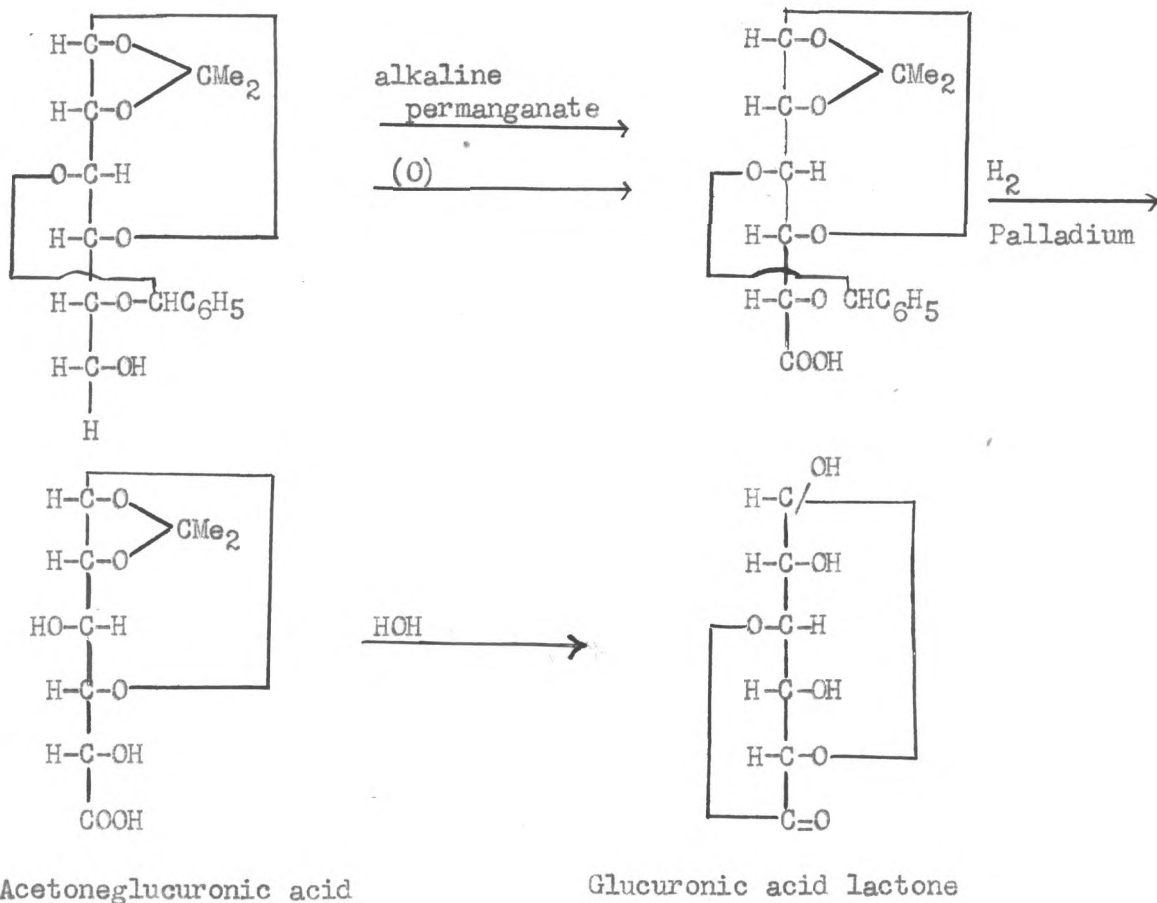
This proved the structure of 4,6-benzylidene-alpha-d-glucose:



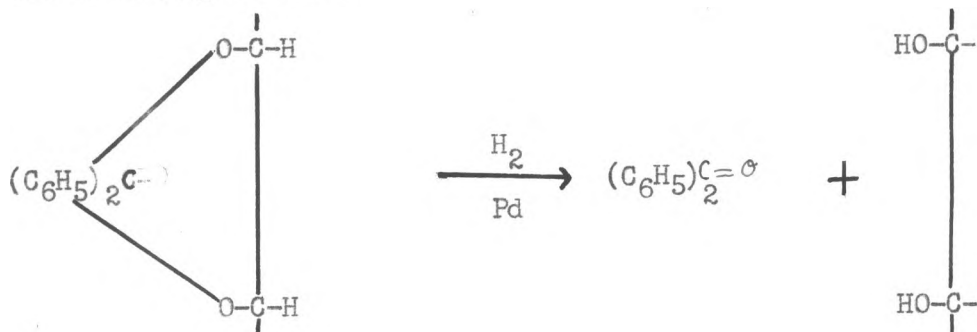
By acetylating this compound a mixture of alpha and beta triacetyl compounds were formed. The benzylidene radical was easily removed with catalytic hydrogenation and a tri-acetyl-glucose resulted. By again acetylating it he synthesized the penta-acetyl-beta-glucose. The benzylidene radical had proved

a good blocker and could be removed easily.

Benzaldehyde was also used with acetone glucose to synthesize d-glucuronic acid. These two were combined in presence of phosphorus pentoxide and resulted in a good yield of crystals of acetone-benzylidene-glucose that melted sharply at 150°. The structure proved to be 1,2-monoacetone,3,5-benzylidene- α -d-glucofuranose. This blocked all the hydroxyls except that of the carbon 6. Upon oxidizing it with KMnO_4 in a weak alkali solution, it was converted to a carboxyl group of 1,2-monoacetone-3,5-benzylidene- α -d-glucuronic acid. The benzylidene radical was removed with a catalyst and the resulting compound was monoacetone-glucuronic acid. Equations for the work of Zervas and Sessler⁴ are given below -



Papadakis⁵ prepared 1,2-monoacetone-5,6-benzophenone- α -d-glucofuranose by treating 1,2-monacetoneglucose and benzophenone-chloride in presence of pyridine and showed that by catalytic hydrogenation the aromatic residue could be removed as shown by the following scheme.



This presented another method analogous to Zervas. The compound was crystalline but the pyridine method gave low yields due to the formation of a red substance as a by-product.

Papadakis⁶ later prepared benzophenone-ascorbic acid by heating ascorbic acid with benzophenone chloride in dry toluene instead of pyridine. This method did not give the red material and the yields were good. The object of the formation of benzophenone ascorbic acid was to afford a tubercular patient the benefit of both benzophenone and ascorbic acid by slow hydrolysis in the system. Benzophenone is known to have a bacteriostatic effect on tubercle bacilli.

From the standpoint of carbohydrate chemistry it seemed important to find out whether benzophenone chloride will react with sugars or sugar derivatives which have secondary hydroxyl groups free.

OBJECT OF RESEARCH

The object of the present research is:

- a) To test this method, namely the preparation of aromatic ketals by treating benzophenone chloride in toluene with sugar or sugar derivatives,
- b) To extend the work of sugar alcohols of the hexitol series, and
- c) To find out whether the benzophenone chloride can react also with two secondary hydroxyl groups.

METHOD

Papadakis'⁶ work on benzophenone-ascorbic acid was repeated using the toluene method and found to give good results. On treating plain glucose, the results were negative perhaps due to the facts a) that in the pyranose ring numbers 1 and 5 carbons are joined by an oxygen bridge and b) to the bulkiness of the benzophenone molecule itself. It may be necessary to investigate this case further.

Next the reaction of benzophenone chloride with mannitol was tried according to the method described in detail in the experimental part. The open chain hexitols afford six hydroxyl groups and therefore a possibility of a reaction of three benzophenone chlorides. Because of structural considerations in the case of tri-benzophenone derivative, one of the benzophenone chlorides would necessarily have to react with secondary hydroxyl groups. Should this be the case, it would answer the third objective of the present investigation. The results of the benzophenone chloride with mannitol as shown in the experimental part of this investigation prove that a tri-benzophenone derivative has been formed.

The compound formed was a white powdered substance which under the microscope showed that it was crystalline in structure. The crystals are insoluble both in hot water and hot alcohol. m.p. 161-162°.

It would be interesting as a further research in the future to try the rate of hydrolysis of the benzophenone residues of the tri-benzophenone mannitol. Intermediate products of the hydrolysis may help to elucidate the structure of the original tri-benzophenone-d-mannitol.

The structure of tri-benzophenone-d-mannitol has not yet been proved experimentally. Theoretically the following isomeric compounds are possible;

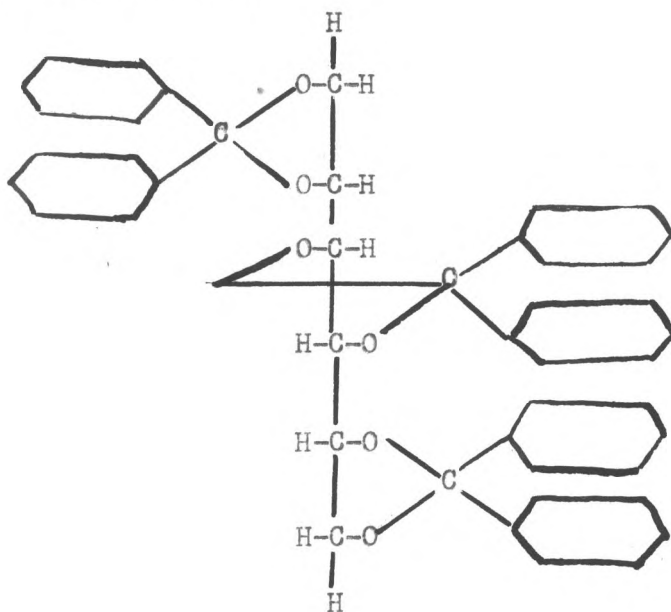
1,2 : 3,4 : 5,6 - tri-benzophenone-d-mannitol;

1,2 : 3,5 : 4,6 - tri-benzophenone-d-mannitol;

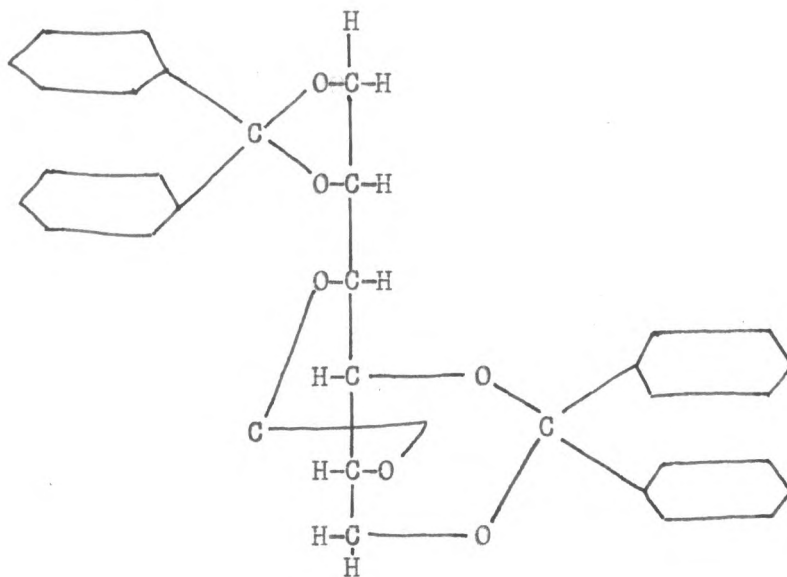
1,3 : 2,4 : 5,6 - tri-benzophenone-d-mannitol.

The graphical structure of these isomers is shown below.

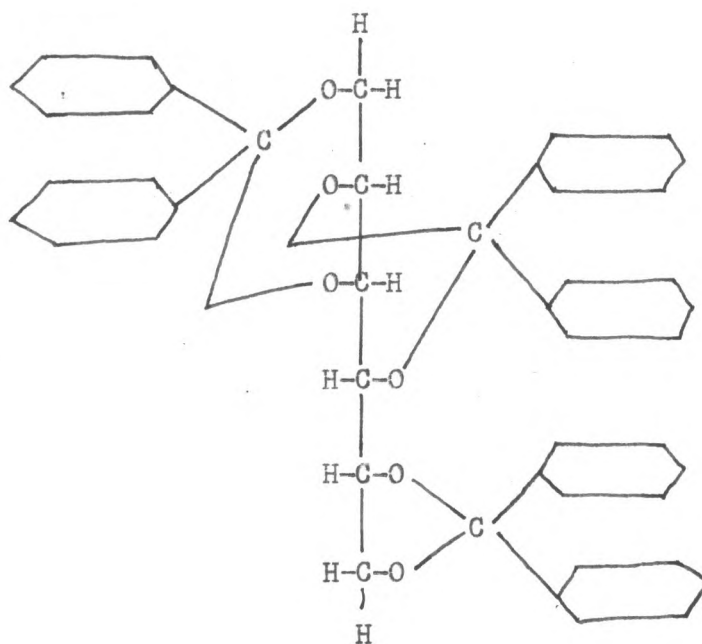
Further work on partially hydrolyzed intermediates will be necessary to elucidate this structure.



1,2 : 3,4 : 5,6 - Tri-benzophenone-d-mannitol



1,2: 3,5: 4,6: - Tri-benzophenone-d-mannitol



1,3: 2,4: 5,6 - Tri-benzophenone-d-mannitol

EXPERIMENTAL

Benzophenone Chloride. - The method used for the preparation of benzophenone chloride is essentially the same as that of Kekule and Franchimont.⁷ An equivalent amount of benzophenone and phosphorus-pentachloride was placed in a flask under a reflux condenser. The temperature of the oil bath was kept from 145-150°. The temperature of the refluxing material was kept around 90°. It was refluxed from one to two hours. The product was fractionated twice.

Benzophenone Ascorbic Acid. - The method used for the preparation of benzophenone ascorbic acid was essentially the same as that of Papadakis with some modifications.

Benzophenone chloride (12.5g.) was carefully added to ascorbic acid (9.2g.) in dry toluene and heated under a reflux condenser until no more HCl was coming off. Oil bath temperature was kept between 85-90°. After filtering the compound was treated with ice water that had a small amount of NaHCO₃ to remove any unreacted ascorbic acid and HCl, then with benzene to remove any benzophenone formed. It was finally recrystallized from methyl alcohol. m.p. 207-208°. The substance is insoluble in water but soluble in ethyl and methyl alcohol.

Benzophenone Mannitol. - Benzophenone chloride (32.5g.) was carefully added to mannitol (22.5g.) in dry toluene and

and heated under a reflux condenser. A mechanical stirrer was used. The temperature of the oil bath was started at ninety and was gradually raised so that the HCl was dispelled. The reactants were refluxed from 12 to 15 hours. The temperature of the oil bath was 125-130° during the latter part of the process. The product was carefully washed with ice water to remove any unreacted mannitol, then with benzene to remove the unreacted benzophenone. The resulting product was insoluble in hot water and in hot alcohol. Mannitol is soluble in cold water and benzophenone is very soluble in alcohol but not in water. Judging from the solubility standpoint a new product was formed. This was refluxed with methyl alcohol, filtered hot by suction and dried in vacuo. The melting point of the product did not differ much from that of the original mannitol. m.p. product was 161-162°; m.p. of mannitol 166-168°. The crystals were set aside until the following summer. Again the product was insoluble both in hot water and in hot alcohol. The substance was again washed with boiling methyl alcohol. After drying the melting point of substance was found to be the same.

Anal. Calcd. for $C_{45}H_{38}O_6$:

C, 80.08; H, 5.68

Found

C, 80.06; H, 5.73

SUMMARY

1. Papadakis' work on benzophenone-ascorbic acids using the toluene method was repeated and found successful.

2. Aromatic ketals of hexitols were formed by heating benzophenone chloride and mannitol in dry toluene with stirring until no more HCl was given off.

3. The formation of a tri-benzophenone derivative of mannitol indicates that one of the benzophenone chlorides has reacted with secondary hydroxyl groups.

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