Summary

2,5 - Dianilino -3,6 - dihydroxy - *p* - benzoquinone and its mono-anil are described. They are obtained by the action of aqueous alkali on 2,5-dianilino-3,6-dibromo-*p*-benzoquinone.

SCHENECTADY, N. Y.

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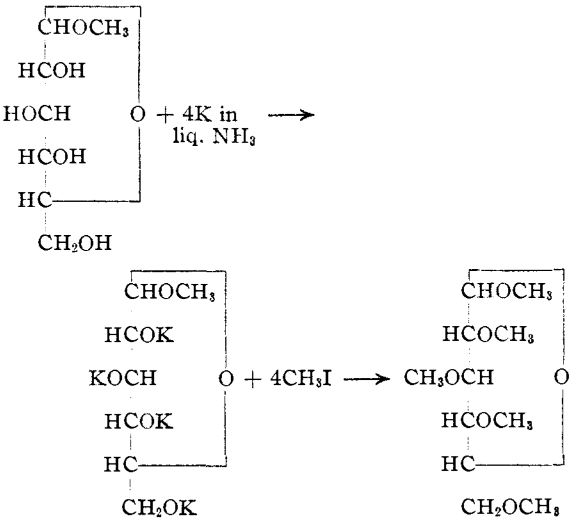
Reactions of Carbohydrates in Liquid Ammonia: Preliminary Paper

BY IRVING E. MUSKAT[1]

The recent advances in the chemistry of carbohydrates are due in a large measure to the introduction of the method of preparation of their methyl ethers. Two methods of methylation are in general use; one introduced by Purdie and his collaborators[2] consists of treating the sugar with silver oxide and methyl iodide, while the other, introduced by Haworth,[3] uses methyl sulfate as the methylating reagent. Either method is time consuming, and it is usually necessary to repeat the process a number of times to ensure complete methylation. It is presumably not possible to control either method so as to methylate a specified number of hydroxyl groups; all free hydroxyl groups are attacked. Neither method is well suited to the use of small quantities of material. In addition, the Purdie method is rather expensive, since it is customary to use five times the theoretical quantity of silver oxide and seven to ten times the theoretical quantity of methyl iodide for each methylation.

It has been known for some time that some alcohols will react with sodium or potassium in liquid ammonia solution to form salts. Kraus, White and their collaborators[4] have treated these salts in liquid ammonia with alkyl halides and thus formed the corresponding ethers. It was therefore considered possible that this general reaction might be introduced into sugar chemistry with considerable advantage. Thus, for example, if methylglucoside were soluble in liquid ammonia, it could be treated with sodium or potassium to form the salt which, in turn, could be made to react with methyl iodide, for instance, to give the methylated derivative.



A preliminary investigation has shown that such salts of carbohydrates are formed, and the behavior of these salts opens a new field for the study of the mechanism of carbohydrate reactions and the synthesis of derivatives hitherto difficult to prepare, or unobtainable. Some of the possibilities and limitations of the method as revealed in this preliminary study are presented here.

Apparatus and Procedure

The apparatus and experimental method employed in this work are essentially those described by Johnson and Fernelius[5] in their recent review on the chemistry of liquid ammonia. Complete detailed directions are given in this review for obtaining the liquid ammonia from the commercial supply tanks and purifying it, as well as the description of the apparatus and technique for working with ammonia both at its boiling point (−33.4°) and at room temperature under pressure (the vapor pressure of liquid ammonia at ordinary temperature is about 8.5 atm.). The method described by Johnson and Fernelius is used for those reactions where the alkali metal salt must be freed from ammonia before coupling with any other reagent which would react with the ammonia. However, in those cases, such as alkylations, where the entire re-

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(1) National Research Fellow in Chemistry.

(2) Purdie and Irvine, *J. Chem. Soc.*, **83**, 1021 (1903); Purdie and Bridgett, *ibid.*, **83**, 1037 (1903); *et seq.*

(3) Haworth, *ibid.*, **107**, 8 (1915).

(4) Kraus and White, THIS JOURNAL, **45**, 768 (1923); White, *ibid.*, **45**, 779 (1923); White and Knight, *ibid.*, **45**, 1780 (1923); Kraus and Kawamura, *ibid.*, **45**, 2756 (1923); White, Morrison and Anderson, *ibid.*, **46**, 961 (1924).

(5) Johnson and Fernelius, *J. Chem. Ed.*, **6**, 441 (1929).

action is carried out in liquid ammonia, the method may be simplified by condensing the liquid ammonia directly in the Dewar flask, and adding sufficient sodium or potassium to react with the moisture in the liquid ammonia and impart a faint blue color to the ammonia solution.[6] The Dewar flask can be connected to a gasometer in order to collect any gases which may be liberated during the course of the reaction. However, it is very important that in all cases the reactions must be carried out under absolutely anhydrous conditions.

Either sodium or potassium can be used in this work; potassium is frequently used because of its greater solubility—1.25 moles of potassium is soluble in 100 g. of liquid ammonia as compared with 1.07 moles of sodium. The choice between sodium and potassium also depends on the solubilities of their halides in the various solvents which may be used in the purification of the reaction products.

Solubility of Carbohydrates in Liquid Ammonia.[7]—All of the ordinary sugars, their methylated, acetylated and acetone derivatives are quite soluble in liquid ammonia. The polysaccharides are also quite soluble in liquid ammonia. With the exception of the free sugars, which will be discussed in the following paragraph, liquid ammonia is without effect on these carbohydrates and their derivatives, and they may be recovered unchanged on evaporation of the ammonia. In addition some of the alkali metal salts of the carbohydrates are soluble in liquid ammonia.

Reaction of Free Sugars in Liquid Ammonia.—The free sugars, that is, those containing potential aldehyde or ketone groups, dissolve in liquid ammonia and react to form the corresponding amines.[8] The amines may be isolated in pure form by allowing the ammonia to vaporize under anhydrous conditions.

Glucose (5 g.) was dissolved in a small quantity of liquid ammonia. The ammonia was allowed to vaporize and the residual sirup was triturated with absolute alcohol. The white crystalline material obtained was washed with absolute alcohol, and dried in a vacuum desiccator. A quantitative yield of 1-aminoglucose was isolated as shown by its analysis and physical constants.

Anal. 1-Aminoglucose: N, 7.8; m. p. 121°; $[\alpha]_D$ $+19.5°$ (in water). Found: N, 7.51; m. p. 121°; $[\alpha]_D^{26°}$ $+17.6°$ (0.048 g. in 5.00 cc. of water).

Preparation of Alkali Metal Salts of Carbohydrates.—As stated above, both the sodium and potassium salts of the carbohydrates can be prepared. However, in most of the work reported herein the potassium salts were used. These salts may be prepared by the following methods.

(1) The substance is first dissolved in liquid ammonia and the calculated amount of potassium is added in small pieces. The course of the reaction may be followed by the blue color which the alkali metal in solution imparts to the ammonia; loss of the blue color indicates that the potassium has reacted completely. In this way it is possible to "titrate" the sugar with potassium. In some instances the surface of the potassium becomes covered with the reaction products and thus the reaction stops before completion. In those cases the reaction may be carried out by adding a solution of potassium in liquid ammonia to a solution of the sugar in liquid ammonia.

(2) The calculated amount of potassium is dissolved in liquid ammonia and the sugar or a solution of the sugar in liquid ammonia is added. This method can be used where an excess of potassium is not undesirable.

(3) In those cases where the potassium would reduce the sugar or react with any groups already substituted in the sugar molecule (acyl groups), the potassium salt is prepared by treating the sugar with potassium amide in liquid ammonia. The potassium amide is made directly in the reaction vessel by dissolving a calculated amount of potassium in liquid ammonia and placing a rusty iron nail in the solution to catalyze the formation of the amide. The formation of the potassium amide is complete when the blue color disappears. The sugar may then be added to the potassium amide solution or *vice versa.*

In order to increase the solubility of the organic compounds in the liquid ammonia it is sometimes desirable to add ether or benzene to the liquid ammonia. The potassium salts of the sugars vary considerably in their solubility in liquid ammonia. Some are quite soluble, while others are practically insoluble. The subsequent reactions of these salts depend to a considerable degree on their solubility in this medium.

It is possible by these methods to substitute a limited number of hydrogen atoms from the hydroxyl groups with potassium. In this manner, partially substituted derivatives of carbohydrates may be prepared directly. It is of considerable interest to determine which of the hydroxyl groups in the sugars react preferentially. This work is now in progress.

Alkylations

The potassium salts of carbohydrates, prepared as described above, may be treated with any appropriate alkyl halide. A 5% excess over the calculated amount of the alkyl halide is added to the liquid ammonia solution of the salt. Reaction usually occurs in several minutes. In some cases the potassium salt of the carbohydrate is too insoluble or not sufficiently reactive to combine with the alkyl halide. In those cases the ammonia may be removed, and the remaining salt suspended in an organic solvent and then refluxed with the alkyl halide. In some cases where it is desired to introduce a larger number of alkyl groups, it is better to form the potassium salt and alkylate it, in two or more steps. Thus, if four methyl groups are to be introduced, the dipotassium salt could be formed and methylated, and then two more equivalents of potassium added and again methylated. A number of alkylations were carried out in order to test the general applicability of this reaction.

α-Methylmannoside (3.88 g.—0.02 mole) was dissolved in anhydrous liquid ammonia, and 3.1 g. (0.08 mole) of potassium added in small pieces. That all of the potassium reacted was indicated by the disappearance of the blue color from the liquid ammonia solution. The tetrapotassium salt of the sugar remained in suspension in the liquid ammonia. Twelve grams of methyl iodide (slight excess over 0.08 mole) was then added slowly. Reaction

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(6) Most commercial liquid ammonia is quite pure and practically anhydrous.

(7) The author wishes to express his appreciation to Mr. Joseph Lender for his assistance in the experimental work.

(8) Further work has shown that the aldehyde ammonia addition product is first formed. This will be reported in a later paper.

occurred quite rapidly and the liquid ammonia solution became clear. The ammonia was allowed to vaporize and the residue was extracted several times with chloroform. The chloroform extract was dried over anhydrous sodium sulfate, filtered, and the solvent removed under diminished pressure. The light-colored residual oil distilled almost entirely at 110–115° under 0.2 mm. pressure, which is the boiling point of tetramethyl-α-methylmannoside. The oil crystallized on standing. The yield of the methylated sugar was 4.6 g., or 92% of the theoretical yield. Its analysis and physical constants proved it to be the tetramethyl-α-methylmannoside.

Anal. 2,3,4,6-Tetramethyl-α-methylmannoside: OCH_3, 62.0; m. p. 40°; $[\alpha]_{\rm D}$ +43.5° in water; $n_{\rm D}^{16^\circ}$ 1.4494. Found: OCH_3, 62.5; m. p. 39–40°; $[\alpha]_{\rm D}^{26^\circ}$ +46.58° (0.1610 g. in 5.00 cc. of water); $n_{\rm D}^{26^\circ}$ 1.4445.

Monoacetone glucose (2.20 g.—0.01 mole) was dissolved in anhydrous liquid ammonia, and 1.17 g. (0.03 mole) of potassium added in small pieces. After all of the potassium had reacted, slightly more than 0.03 mole of methyl iodide was added, and the product worked up as described above. A light yellow oil (2.5 g.) distilled over at 90–95° under 0.05 mm. pressure; this corresponds to a 95% yield of trimethyl-monoacetone glucose.

Anal. 3,5,6-Trimethyl-monoacetone glucose: OCH_3, 35.5; $[\alpha]_{\rm D}$ −29.5° in methyl alcohol; $n_{\rm D}^{23^\circ}$ 1.44914. Found: OCH_3, 34.6; $[\alpha]_{\rm D}^{26^\circ}$ −28.6° (0.147 g. in 5.00 cc. of methyl alcohol); $n_{\rm D}^{26^\circ}$ 1.4492.

Diacetone glucose (5.20 g.—0.02 mole) was dissolved in anhydrous liquid ammonia, and 0.78 g. of potassium (0.02 mole) was added in small pieces. The monopotassium salt of diacetone glucose is quite soluble in liquid ammonia. Slightly more than 0.02 mole of methyl iodide was added, and the product worked up as described above. A 96% yield of methyl-diacetone glucose was isolated.

Anal. 3-Methyl-diacetone glucose: OCH_3, 11.0; b. p. 105° (0.3 mm.); $[\alpha]_{\rm D}$ −32.17° in alcohol; $n_{\rm D}^{17^\circ}$ 1.4518. Found: OCH_3, 11.09; b. p. 105° (0.3 mm.); $[\alpha]_{\rm D}^{26^\circ}$ −34.6° (0.101 g. in 5.00 cc. of absolute alcohol); $n_{\rm D}^{24^\circ}$ 1.451.

A γ-sugar, acetone methylrhamnoside (γ), was methylated in identically the same manner. No change occurred in the ring structure, and a 92% yield of the methylated product was isolated. In order to show that this method was applicable to the alkylation of the disaccharides, sucrose was completely methylated to the octamethyl derivative. Further work on the methylation of carbohydrates and the introduction of various alkyl groups is now in progress.

Arylation

Preliminary studies have already shown that certain of the aryl halides react with the potassium salts of carbohydrates in liquid ammonia solution. However, in order to obtain a good yield of the product it may be necessary in some cases to remove the ammonia, suspend the salt in an organic solvent, and reflux with the aryl halide; or the reaction may be carried out under pressure and at room temperature in liquid ammonia solution.

Acylation

Since the acyl halides react with ammonia, the potassium salts of the carbohydrates must be freed from this medium before the acylating reagent is added. This is accomplished by allowing the ammonia to vaporize under strictly anhydrous conditions. The dry salt is suspended in anhydrous ether (or any other appropriate anhydrous organic solvent) and a slight excess of the acyl halide is added. The reaction products may be worked up in a manner entirely analogous to that described above for alkylation.

α-Methylmannoside (3.88 g.—0.02 mole) was dissolved in anhydrous ammonia, and 3.1 g. (0.08 mole) of potassium was added in small pieces. After all of the potassium had reacted, the ammonia was removed by vaporization under anhydrous conditions. Dry ether was added to the salt which remained, and slightly more than 0.08 mole of acetyl chloride was added. The reaction was quite vigorous. The product was worked up as described above. An almost quantitative yield of the tetracetyl derivative of α-methylmannoside was isolated.

Anal. Tetracetyl-α-methylmannoside: C, 49.72; H, 6.07; m. p. 65°; $[\alpha]_{\rm D}^{20^\circ}$ +49.1° (in chloroform). Found: C, 49.45; H, 5.81; m. p. 63°; $[\alpha]_{\rm D}^{24^\circ}$ +48.0° (0.100 g. in 5.00 cc. of chloroform).

Introduction of Phosphorus and Sulfur

An investigation has shown that potassium salts of carbohydrates, suspended in ether, react with phosphorus oxychloride, thionyl chloride and sulfur monochloride to give the corresponding esters. The preparation of these esters as well as those containing such elements as arsenic and antimony is now being studied.

The author wishes to express his appreciation to Dr. P. A. Levene for his many helpful suggestions during the progress of this work.

Summary

A new method for the introduction of alkyl, aryl and acyl groups, phosphorus and sulfur, into the carbohydrate molecule by means of the preparation of the alkali metal salts of the carbohydrates in liquid ammonia solution, has been described.

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