

Alkylation of the Carbohydrates

III. From Test Tube to Pilot Plant

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The pioneer work in the alkylation of the carbohydrates, as far as can be ascertained, was initiated by Emil Fischer in 1895 (1). At that time he treated D⁺-glucose with absolute methyl alcohol in the presence of a trace of dry hydrogen chloride (0.25%), and obtained a mixture of the two monomethyl derivatives which have since come to be known as the *alpha* and *beta*-methyl glucosides. This work appears the more significant today, forty-five years later, because of the known tendency of both plants and animals to detoxicate poisonous products with which they come in intimate contact by glycoside formation. Recent studies by Denny and Miller, for example, indicate that when potato tubers and gladiolus corms are treated with ethylene chlorohydrin, the foreign chemical is converted to a gentiobioside (2).

The foundation laid by Emil Fischer was soon taken advantage of by Irvine and Purdie. They treated the methyl alpha-D⁺-glucoside of Fischer with methyl iodide in the presence of silver oxide by refluxing the mixture together for a number of hours, and obtained methyl 2,3,4,6-tetramethyl-alpha-D⁺-glucoside, which they reported in 1903 (3). This suggested to them the possibility of using the alkylated sugars in structural studies and ushered in a research program which, in the hands of numerous investigators, has clarified materially the structure of the so-called simple sugars.

Haworth, a product of the Irvine school, sought a more economical and simpler method of effecting alkylation, and was able to report in 1915 that the alkylated derivatives of the glycosides could be obtained quite readily by the use of alkyl sulfates. (4) He treated methyl glucoside, for example, simultaneously with methyl sulfate and concentrated sodium hydroxide by the dropwise addition of the reagents to a solution of the glucoside, under vigorous agitation, at a temperature of about 80° C., until alkylation was fairly complete. The resulting mixture was extracted with chloroform, the extract dried, the solvent evaporated, and the residue realkylated under similar conditions until analysis showed complete alkylation.

The Haworth method was developed by Green and Lewis who, in 1928, reported that they had treated methyl alpha-D⁺-mannoside with methyl sulfate in the presence of sodium hydroxide to give methyl 2,3,4,6-tetramethyl-alpha-D⁺-mannoside (5). They perfected a detailed procedure, furthermore, for the hydrolysis of the mannoside to 2,3,4,6-tetramethyl-D⁺-mannose and for the purification of the latter product by continuous extraction with petroleum ether.

Six years later (1934) West reported that a method had been introduced whereby the sugars instead of the glycosides could be used

as the starting materials for these alkylations (6). He and his co-workers treated D⁺-glucose with a carbon tetrachloride solution of methyl sulfate and then with an aqueous solution of sodium hydroxide at a temperature of about 60° C. to effect glucoside formation. By continued treatment, then, by the procedure of Haworth they effected complete methylation to give methyl 2,3,4,6-tetramethyl- α -D⁺-glucoside. Subsequent acid hydrolysis of this product yielded 2,3,4,6-tetramethyl-D⁺-glucose.

In the same year (1934) Muskat reported that the alkylation of the carbohydrate materials could be effected with methyl sulfate in liquid ammonia (7).

Up to this point in this summary, attention has been given to the *methylation* of the carbohydrates only, but some progress had already been made with respect to *ethylation*. In 1925 Hess and Salsman reported the preparation of octaethylcellobiose (8). Coles, in 1932, reported that 2,3,6-triethyl-D⁺-glucose could be obtained from triethylcellulose, and indicated that an impure form of 2,3,4,6-tetraethyl-D⁺-glucose had been obtained (9). Two years later (1934) Muskat prepared and identified 3-ethylacetone-D⁺-glucose.

In 1936 Degering and Padgett produced methyl 2,3,4,6-tetraethyl- α -D⁺-glucoside by repeated ethylation of methyl α -D⁺-glucoside by the method of Haworth and subsequent treatment by the method of Irvine and Purdie (10). Acid hydrolysis of this product gave 2,3,4,6-tetraethyl-D⁺-glucose, which was described as white, slender needles, m.p. 80-2° C., with a specific rotation in ethyl alcohol of $(\alpha)_{\text{D}}^{20} = 95.9^{\circ}$, and soluble in water, chloroform, ethyl alcohol, and ethyl ether. Starting with D⁺-glucose, by use of the West procedure, Degering, Binkley, and Sprang subsequently obtained ethyl 2,3,4,6-tetraethyl- α -D⁺-glucoside, and starting with methyl mannoside they obtained methyl 2,3,4,6-tetraethyl-D⁺-mannoside, as described in the following detailed procedure.

Preparation of Ethyl 2,3,4,6-Tetraethyl- α -D-Glucoside Directly from D-Glucose

Twenty-five grams of D-glucose is dissolved in 15 ml. of water and added to a three-liter round-bottom flask which is equipped for vigorous agitation. Then 125 ml. of ethyl sulfate, dissolved in 125 ml. of carbon tetrachloride, is added to the glucose solution. Vigorous agitation is begun and the temperature of the bath raised to 65° C. Aqueous sodium hydroxide (8.5 N) is introduced dropwise from the dropping funnel until the carbon tetrachloride distills. This operation usually requires one and one-half hours. Sufficient sodium hydroxide (five hundred ml. of 8.5 N) is added then to neutralize the 220 ml. of ethyl sulfate which is to be added later. The temperature of the bath is raised to 80° C. and the ethyl sulfate introduced not faster than two drops per second. When the addition of ethyl sulfate is completed, the temperature of the water bath is raised to boiling and held there for thirty minutes, and the bath is then allowed to cool.

The mixture is extracted with six 100 ml. portions of chloroform, and the extracts dried with anhydrous sodium sulfate, decolorized by treatment with Norite, and filtered. The chloroform is removed by distillation under diminished pressure, and a light yellow sirup of crude ethyl 2,3,4,6-tetraethyl- α -*D*-glucoside is obtained. The sirup may be rectified in a modified Podbielniak column to give a colorless liquid which boils at 99.8° C. at 0.2 mm. Its refractive index is 1.4462 at 25° C. The average yield is seven grams. This product, when subjected to hydrolysis, gives the 2,3,4,6-tetraethyl-*D*-glucose described by Degering and Padgett.

The optimum conditions for the second step in the ethylation of *D*-glucose were determined by making a study of the ethylation of methyl- α -*D*-glucoside with ethyl sulfate in the presence of aqueous sodium hydroxide. The methods of both West and Haworth were studied. The average of the best results of these studies are presented in Table I.

TABLE I. Optimum Concentration of Alkali for Alkylation

Experiment	Bath		Base Used	Yield	% Yield
	Temperature	Method of			
1	80°C.	West	8.5 N NaOH	17g.	39.4
2	80°C.	West	12.5 N NaOH	10g.	23.2
3	80°C.	West	24.5 N NaOH	3g.	6.9
4	80°C.	Haworth	12.5 N NaOH	9g.	18.6
5	80°C.	Haworth	8.5 N NaOH	16g.	37.1

It may be concluded from Table I that, for the second step in the ethylation of *D*-glucose at about 80°C., 8.5 N approaches the most suitable concentration for the sodium hydroxide.

In 1929 Lewis and Greene succeeded in preparing crystalline 2,3,4,6-tetramethyl-*D*-mannose in pure form. The alkylation of sugars has now been extended by the authors of this paper to include the *ethylation* of methyl α -*D*-mannoside, by the procedure just cited for the ethylation of D^+ -glucose.

The Commercial Application

The year 1936 saw the first commercial application of alkylation to the carbohydrate series when the Dow Chemical Company began producing ethyl cellulose on a pilot plant scale. This product is now available under the trade name of Ethocel, and looks to a promising future in the fiber, film, and plastic trades. Little did the early workers in this tedious field realize that their efforts would be rewarded some day by the application of their art to the commercial production of alkylated derivatives of cellulose.

Some work has been carried on during this period in an attempt to alkylate starch, and studies are still in progress. The methyl, ethyl, and propyl starches have been obtained and their properties are being studied.

What more the future has in store, in the alkylation of the carbohydrates, remains to be unveiled by the research workers of tomorrow.

Bibliography

1. Fischer, E., 1895. *Über die Verbindungen der Zucker mit den Alkoholen und Ketonen*, **28**:1151.
2. Private communication of Dr. F. E. Denny to Ed. F. Degering.
3. Irvine, J. C., and Purdie, T., 1903. The alkylation of sugars, *Journ. Chem. Soc.*, **93**:1021; 1904, **85**:1061.
4. Haworth, W. N., 1915. A new method of preparing alkylated sugars, *J. Chem. Soc.*, **107**:8.
5. Green, R. D., and Lewis, W. L., 1928. Reactivity of methylated sugars, III. *Journ. Am. Chem. Soc.*, **50**:2813-25.
6. West, E. S., and Holden, R. F., 1934. Methylated Sugars, I. Preparation of Tetramethylglucose, *Journ. Am. Chem. Soc.*, **56**:930-2.
7. Muskat, I. E., 1934. Reactions of carbohydrates in liquid ammonia, *Journ. Am. Chem. Soc.*, **56**:693-5, 2449-54.
8. Hess, K., and Salsmann, G., 1925. Octaethylcellobiose and its acetolysis in comparison with cellobiose and octaacetylcellobiose, *Annalen*, **445**:111-22.
9. Coles, H. W., 1932. The literature of alkylated carbohydrates. Tri-, tetra-, and penta-alkylated glucose derivatives. *Iowa State College Journal of Science*, **VI**:43-64.
10. Degering, Ed. F., and Padget, A. R., 1936. The preparation of methyl 2,3,4,6-tetraethylalphy-D+-glucoside, *Journ. Org. Chem.*, **1**:4, 336-8.