

[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE STATE
UNIVERSITY OF IOWA]

STRUCTURE OF METHYLATED SUGARS. I. PRELIMINARY PAPER

BY CARRELL H. WHITNAH

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The recognized conflict of the results obtained by C. S. Hudson,¹ by comparing differences of optical rotations of sugars, with the results of W. N. Haworth and co-workers² from the properties of methylated sugars, suggests the possibility that the ring structure of glucose may be changed by the processes used to establish it.

The possibility of variation of the ring structure of methylated sugars with the temperature and alkalinity of methylation is suggested by the convincing evidence that "normal" or "abnormal" glucoside rings are formed on condensation of sugars with alcohol containing small amounts of hydrogen chloride at high³ and low⁴ temperatures, respectively.

The production of "normal" glucoside at low temperature in alcohol containing more acid⁵ indicates the importance of the alkalinity factor.

The care deemed necessary by Hibbert⁶ in drawing conclusions as to carbohydrate structure from methylation experiments, carried out in "slight hydrogen-ion concentrations," and the indications⁷ that more than one ring structure is formed on methylation of galactose and arabinose with methyl sulfate and sodium hydroxide, justify the attempt to find conditions under which glucose will yield a methylated product of unusual structure.

Experimental Part

Twenty grams of glucose was dissolved in 25 cc. of water and placed in a bath at thirty degrees. The solution was made alkaline with sodium hydroxide and then fifteen to twenty cc. of methyl sulfate added. Thirty per cent. sodium hydroxide was then added a drop at a time so as to maintain the solution alkaline to brom thymol blue but acid to phenolphthalein. One cc. of 30% sodium hydroxide eventually neutralized about an equal volume of methyl sulfate. The alkalinity was determined by dropping a drop of the reaction mixture into a drop of indicator on a spot-plate. A much more sensitive and convenient indicator of alkalinity was a simple potentiometer attached to a cell made by suspending in the reaction mixture electrodes of platinum and antimony. The potentiometer determinations required occasional checking against the determina-

¹ C. S. Hudson, *THIS JOURNAL*, **48**, 1434 (1926).

² (a) E. L. Hirst, *J. Chem. Soc.*, 350 (1926); (b) W. N. Haworth and C. W. Long, *ibid.*, 345 (1929); (c) W. N. Haworth and S. Peat, *ibid.*, 350 (1929).

³ (a) E. Fischer, *Ber.*, **28**, 1145 (1895); (b) T. S. Patterson and J. Robertson, *J. Chem. Soc.*, 300 (1929).

⁴ E. Fischer, *Ber.*, **47**, 1980 (1914).

⁵ E. Fischer, *ibid.*, **26**, 2400 (1893).

⁶ H. Hibbert and N. M. Carter, *THIS JOURNAL*, **51**, 1601 (1929).

⁷ E. L. Hirst and G. J. Robertson, *J. Chem. Soc.*, **127**, 358 (1925).

tions with color indicators, as the potential corresponding to a given alkalinity changed slowly with the composition of the solution.

More methyl sulfate was added from time to time so that there was an excess of at least 10 cc. over the sodium hydroxide added.

From 30 to 35 cc. of sodium hydroxide was added during from eight to ten hours before the mixture ceased to reduce Fehling's solution. The alkalinity and temperature were then somewhat increased and thereby the rate of methylation. The reaction was stopped when 100 cc. of methyl sulfate had been used up and the bath finally was heated to about 70° to insure destruction of all of the methyl sulfate. Tests for active sugar have not been obtained from any experiment in which the final destruction of methyl sulfate was carried out in a boiling water-bath.

After cooling, the sugar solution was extracted with chloroform, the extract dried over calcium chloride, the chloroform evaporated and the residue distilled at about 2-mm. pressure and at temperatures always over 100°. The distillate when dissolved in water, acidified with hydrochloric acid and treated with barium chloride, showed no trace of sulfate even after standing for several days.

The first test used to demonstrate the presence of active glucoside was to decolorize a few drops of dilute permanganate with a few drops of the product dissolved in water. One-tenth gram of methylated sugar would completely decolorize three drops of permanganate within one minute, while a similar solution of ordinary methylated glucose retained the color of one drop of permanganate for several minutes. A more definite comparison of rates of oxidation is indicated by Table I and the curves of Fig. 1.

TABLE I
EXPERIMENTAL DATA

Time, min.	Subs. obs.				Time, min.	Subs. obs.			
	A	B	C	D		A	B	C	D
Used, g.	0.090	0.060	0.150	0.096	Used, g.	0.090	0.060	0.150	0.096
	0.067 N KMnO ₄ per 0.100 g. of subs., cc.					0.067 N KMnO ₄ per 0.100 g. of subs., cc.			
1				0.21	36		1.00		
2				.42	37.5			2.60	
3		0.05			40				4.75
4	0.17	.09			44		1.21		
6.5			0.20		46			2.66	
7		.13	.27	1.60	48				5.16
8.5	.25				50.5		1.39		
11			.54	2.63	55			2.70	
14				3.07	58		1.60		5.56
15			.95		68.5		1.81		
18	.33		1.42	3.54	72				6.13
21			2.03		77.5		2.00		
22				3.82	81				6.51
24		.55	2.26		90		2.25		6.91
26		.60			97.5		2.45		
29		.83			104		2.78		7.44
32			2.53		118		0.79 (interpolated)		
31				4.31	307		1.66 (not completely reduced)		

The substances examined include (A) a stable methylated glucoside obtained by methylating at 60° in a solution of about 0.025 N sodium hydroxide; (B) glucose; (C) the methylated glucoside prepared above; and (D) a solution made by hydrolyzing this glucoside in 0.10 N hydrochloric acid and then neutralizing with sodium hydroxide.

The weight of the substance indicated was dissolved in 50 cc. of water and made neutral to litmus. The permanganate solution was then added as required. Except for the last observation on substance (A), each addition of permanganate was one drop as soon as the solution failed to depolarize a cell made by inserting electrodes of silver and platinum in the solution.⁸

Other tests to prove the existence of active sugar depend on the possibility of hydrolysis with dilute hydrochloric acid. Ready hydrolysis in a boiling water-bath was indicated by the increase of specific rotation of 1.2 g. of substance in 15.00 cc. of 0.10 *N* hydrochloric acid, from 32.7° to 65° in three hours.

On standing overnight at room temperature after two hours in a boiling water-bath, the specific rotation rose from 61.7° to 90.8°. The final value at room temperature, after the rotation in a boiling water-bath became constant at 67.8°, was 112.5°.

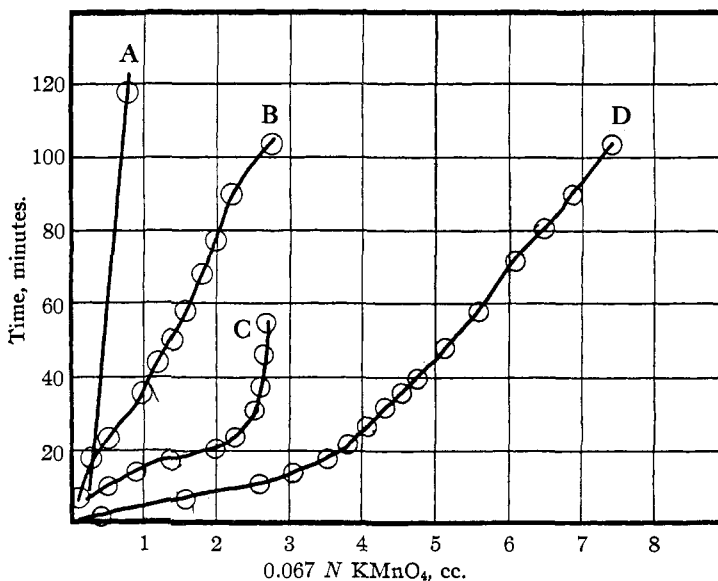


Fig. 1.

Hydrolysis at 60° was indicated by the fact that 1 g. of substance in 10 cc. 0.10 *N* hydrochloric acid increased its capacity for oxidation by iodine⁹ from an initial value of 0.24 g. of iodine to 1.10 g. after three and one-half hours and to 1.37 g. after twenty-one hours. Corresponding values for α -methylglucoside were from an initial value of 0.187 g. of iodine to 0.382 g., after three and one-half hours, and 0.536 g. after twenty-one hours.

For both glucosides, hydrolysis with 8% or 2.14 *N* hydrochloric acid finally produced a decreasing iodine capacity. The values for the active glucoside were 0.64 g. of iodine after one and seven-tenth hours, 0.312 g. after three and one-half hours and 0.147 g. after twenty-one hours.

The relative rates of hydrolysis at 60° were also indicated by the fact that the above solution of active methylated glucoside after hydrolysis with 0.10 *N* hydrochloric acid had to be diluted about nine times as much as the similar solution of α -methylglucoside

⁸ B. F. Brann and M. H. Clapp, *THIS JOURNAL*, 51, 39 (1929).

⁹ H. Sobotka, *J. Biol. Chem.*, 69, 267 (1926).

in order that equal volumes of the two solutions would completely reduce equal volumes of Fehling's solution.

Summary

Methylation of glucose with methyl sulfate and sodium hydroxide at a temperature of 30° in a solution kept alkaline to brom thymol blue and acid to phenolphthalein resulted in a product which definitely gave a positive response to several common tests for an active or gamma sugar.

MANHATTAN, KANSAS

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

THE PREPARATION OF TRIPHENYLMETHYLMAGNESIUM CHLORIDE

BY HENRY GILMAN AND E. A. ZOELLNER

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Introduction

In connection with studies¹ involving triphenylmethylmagnesium chloride, it was necessary to develop a procedure for the preparation of this Grignard reagent in consistently high yields. We have had indifferent success, for some time, in preparing this reagent by methods commonly employed for the preparation of typical RMgX compounds.

The method described at this time gives excellent yields (96% and higher). These yields have been checked by different workers in this Laboratory so that the preparation is not as erratic as formerly. Our acid method of titration was used in determining the optimal factors reported at this time. The method of titration is very probably sound, and the high yields are unquestionably real because carbonation of the triphenylmethylmagnesium chloride has given yields of triphenylacetic acid as high as 91%.²

Experimental Part

The general procedure followed was that described recently by Gilman, Zoellner and Dickey³ for the determination of yields of a variety of Grig-

¹ (a) Gilman and Jones, *THIS JOURNAL*, 51, 2840 (1929); (b) Gilman and Fothergill, *ibid.*, 51, 3149 (1929).

² Unlike some other directions on optimal conditions for the preparation of unusual Grignard reagents reported from this Laboratory [such as allylmagnesium bromide by Gilman and McGlumphy, *Bull. soc. chim.*, 43, 1322 (1928), and *tert.*-butylmagnesium chloride and *tert.*-amylmagnesium chloride by Gilman and Zoellner, *Rec. trav. chim.*, 47, 1058 (1928)], considerable work has been done by others on triphenylmethylmagnesium chloride, particularly in connection with free radicals. Among such earlier work are the following important references: Schmidlin, *Ber.*, 39, 628, 4183 (1906), and Chichibabin, *ibid.*, 40, 3965 (1907); *ibid.*, 42, 3469 (1909). These authors have reported unusually high yields of products from triphenylmethylmagnesium chloride.

³ Gilman, Zoellner and Dickey, *THIS JOURNAL*, 51, 1576, 1584 (1929).