ON THE STRUCTURE OF THE SO CALLED 5-METHYL GLUCOSE OF OHLE AND VON VARGHA

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(Received for publication, June 21, 1932)

In continuation of the work on the nature of the glycoside formation in the partially substituted sugars, a study of the 5-methyl glucose described by Ohle and von Vargha was undertaken by us. On the basis of previous experience, a substance of this structure was expected to form but one glucoside, the furanoside, and it was therefore surprising to find indication of the formation of two glucosides. These were formed, moreover, at approximately the same rates as in the case of unsubstituted glucose. The formation of two glucosides from 5-methyl glucose would require either the existence of glucosides with ring structures other than <1, 4> and <1, 5>, or else the migration of the methyl group in the course of glucoside formation. Further study, however, has convinced us that no irregularity had occurred but that instead an incorrect structure has been assigned by Ohle to his substance, which in reality is 6-methyl glucose.

The following observations led to this conclusion. The osazone of the substance described by Ohle has a melting point (180–185°) which is very close to that last reported for 6-methyl glucosazone (184–187° corrected). The rotation of the osazone of the “5-methyl” glucose was reported as −101.9° in pyridine, and this we have confirmed. However, in alcohol the “5-methyl” glucosazone has initial and final rotations of −70° and −44° respectively. These values are practically identical with those reported by

Helferich and Günther\(^4\) and by Ohle and von Vargha\(^4\) for 6-methyl glucosazine; namely, initial \(-70.3^\circ\) and \(-69.6^\circ\), and final, \(-46.9^\circ\) and \(-46.4^\circ\).

Methylation of the methylglucoside resulting after long heating of a solution of Ohle's "5-methyl" glucose in methyl alcohol containing hydrogen chloride, gave a tetramethyl methylglucoside which was hydrolyzed to a tetramethyl glucose. This was crystallized and found to have the properties of 2,3,4,6-tetramethyl glucose. The tetramethyl glucose was further identified by conversion to the anilide, identical with that from 2,3,4,6-tetramethyl glucose. From 5-methyl glucose this substance could have been formed only by actual migration of the methyl group from position (5), an improbable assumption. Moreover, this possibility is contradicted by the curves of lactone formation of the "5-methyl" gluconic acid which indicate two lactones, formed at rates which are close to those found for the corresponding lactones of unsubstituted glucose. As the lactone formation was measured at room temperature and in only slightly acid solution, migration of a methyl group would appear most unlikely.

For further evidence, the monomethyl glucose was converted to the tetracetate, and through the acetobromo derivative, to the triacetate methyl methylglucoside. Both of these derivatives were found to have the properties reported by Helferich and Günther for the corresponding derivatives of 6-methyl glucose.

All of these results lead to the conclusion that the crystalline "5-methyl" glucose described by Ohle and von Vargha\(^4\) is the 6-methyl glucose, previously obtained by Helferich and Becker,\(^5\) though in amorphous state. As a consequence of this conclusion, the structure of the "trimethyl glucose" of Pácsu,\(^6\) shown by Shinle\(^7\) to be a monomethyl glucose, was in need of reinvestigation inasmuch as the 5-methyl structure was excluded by Shinle on the basis of the claims of Ohle. However, it will be shown in a subsequent publication that the assumption of Shinle is probably correct.

Work on the synthesis of 5-methyl glucose is now in progress.

EXPERIMENTAL

*Methyl Monoacetone Glucose*—6-Tolylsulfo monoacetone glucose was prepared from monoacetone glucose following the procedure of Ohle and von Vargha. In general the yields were not quite as high as those reported by them.

The 6-tolylsulfo monoacetone glucose was converted to the methyl monoacetone glucose by a slight modification of Ohle's procedure, the isolation of the anhydromonoacetone glucose being omitted. 50 gm. of tolylsulfo monoacetone glucose were dissolved in 100 cc. of methyl alcohol, cooled in an ice-salt mixture, and added with vigorous shaking to a solution of 3.75 gm. of metallic sodium in 100 cc. of methyl alcohol similarly cooled in an ice-salt mixture. The product was allowed to stand 20 minutes in the freezing mixture and an ice-cold solution of 7.5 gm. of metallic sodium in 125 cc. of methyl alcohol was then added with shaking. A separation of sodium toluenesulfonate occurred immediately. The mixture was allowed to stand at room temperature with occasional shaking for 2 days and was then cooled in ice water. Hydrochloric acid was added until the solution became just acid to phenolphthalein (pH about 7.6). 2 volumes of ether were added and the precipitate was filtered off and washed with more ether. The filtrate and washings were combined and concentrated under reduced pressure to a syrup which was taken up in chloroform. The chloroform solution was washed twice with water, dried with sodium sulfate, and concentrated under reduced pressure to a syrup. This was taken up in ether and the solution was cooled in the refrigerator. Pentane was added just to turbidity and the mixture was seeded. The seed crystals were obtained by distilling a portion of the material under greatly diminished pressure as described by Ohle. The yield of crude crystalline product was 19 gm. and after one recrystallization from ether-pentane, 15 gm.

Several lots of the methyl monoacetone glucose were combined and recrystallized as above.

The substance had the composition of a methyl monoacetone hexose.

4.595 mg. substance: 8.635 mg. CO₂ and 3.225 mg. H₂O
3.385 " " 3.475 " AgI
234.1 Found. " 51.24, " 7.85, " 13.51
Structure of 5-Methyl Glucose

The product sintered at about 70° and then melted at 71-72°. It had a rotation, in chloroform, of $[\alpha]_{D}^{20} = \frac{-0.24 \times 100}{2 \times 2.0} = -6.0°$. Ohle and von Vargha² give 71-72° as the melting point and -6.4° as the rotation.

*Monomethyl Glucose*—The methyl monoacetone glucose described above was hydrolyzed exactly as described by Ohle and von Vargha² and the product was recrystallized twice from absolute alcohol. The composition corresponded to a monomethyl hexose.

\[
\begin{align*}
4.725 \text{ mg. substance:} & \quad 7.511 \text{ mg. CO}_2 \text{ and } 3.040 \text{ mg. H}_2\text{O} \\
5.891 \text{ " } & \quad 7.435 \text{ " AgI} \\
\text{C}_7\text{H}_{14}\text{O}_6. \text{ Calculated. C 43.28, H 7.27, OCH}_3 15.93 \\
194.1 \text{ Found. } & \quad 43.34, \text{ H 7.19, } \text{ OCH}_3 16.66
\end{align*}
\]

The substance had a melting point which varied greatly with the rate of heating. If kept at 138° for several minutes it melted to a clear liquid, but if heated rapidly, it softened at 150° and melted at 153-154°. Ohle and von Vargha² reported 143-144° as the melting point. The optical rotation in water of our product was 101.8° 1 minute after dissolving, 86.0° at 30 minutes, 59.5° at 3 hours, and 56.0° at 5 and at 24 hours. A second sample had an initial rotation of 104.5° and an equilibrium rotation, after 5 hours, of 58.5°. Ohle and von Vargha² reported 101.2° 3 minutes after dissolving, and 59.92° at equilibrium after 3 hours.

*Methyl Glucosazone*—0.5 gm. of the methyl glucose was converted to the osazone exactly as described by Ohle and von Vargha.² The product, which formed readily, was recrystallized from alcohol, in which it was fairly soluble.

The analysis corresponded to a methyl hexosazone.

\[
\begin{align*}
4.880 \text{ mg. substance:} & \quad 0.651 \text{ cc. N (28° and 761 mm.)} \\
4.650 \text{ " } & \quad 3.070 \text{ mg. AgI} \\
\text{C}_{12}\text{H}_{24}\text{O}_{14}\text{N}_4. \text{ Calculated. N 15.06, OCH}_3 8.33 \\
372.2 \text{ Found. } & \quad 15.14, \text{ OCH}_3 8.72
\end{align*}
\]

On heating the recrystallized material, it contracted at 180°, melted at 183°, and decomposed at 192°. Ohle and von Vargha² had reported 180° with decomposition as the melting point of their material. Helferich and Günther³ gave 184-187° (corrected) as the melting point of the pure 6-methyl glucosazone, and Ohle and
von Vargha found 178° as the melting point of the osazone of 6-methyl glucose prepared through isodiacetone glucose.

The rotation of the product, in pyridine, was −102° initial, and −28° at equilibrium after 24 hours. Ohle and von Vargha reported −101.9° initial, but were unable to observe the end value due to coloration of the solution. Our own solution darkened only slightly in 6 days. The rotation of our product in absolute alcohol was −70° 5 minutes after dissolving and −44° at equilibrium after 24 hours. Helferich and Günther reported −70.3° initial and −46.9° at equilibrium for the rotations, in alcohol, of the osazone of 6-methyl glucose, and Ohle and von Vargha reported −69.6° initial and −46.4° at equilibrium for the osazone of 6-methyl glucose prepared from methyl isodiacetone glucose.

**Tetracetylg-Methyl Glucose**—3 gm. of the "5-methyl" glucose were acetylated according to the procedure described by Helferich for the 6-methyl glucose. The product crystallized easily and was twice recrystallized from a little absolute alcohol. The composition corresponded to a tetracetyl methyl hexose.

4.695 mg. substance: 8.568 mg. CO₂ and 2.550 mg. H₂O
6.075 “ “ “ : 4.001 “ AgI

C₁₅H₂₉O₁₈. Calculated. C 49.70, H 6.12, OCH₃ 8.55

The melting point was 95–96° and the rotation, in chloroform, was \([\alpha]_{D}^{0} = \frac{+0.86° \times 100}{2 \times 2.0} = +21.5°\). Helferich reports 91–93° (corrected) as the melting point and +20.9° as the rotation, in chloroform, for β-tetracetyl-6-methyl glucose.

**Triacetyl-6-Methyl-β-Methylglucoside**—The syrupy tetracetate from 9.5 gm. of the "5-methyl" glucose was treated with 50 cc. of a saturated solution of hydrogen bromide in glacial acetic acid without preliminary attempts at crystallization. After standing for 2 hours at room temperature the mixture was poured onto ice, ice water was added, and the solution was extracted three times with chloroform. The extracts were washed three times with ice water, dried with sodium sulfate, and concentrated under reduced pressure to a thick syrup. This was taken up in 100 cc. of dry methyl alcohol, cooled to 10°, and 10 gm. of dry silver oxide were added. The mixture was shaken vigorously. A test after 10
minutes indicated that practically no bromide remained. The mixture was filtered, then refiltered with charcoal, and concentrated under reduced pressure to a syrup. This was dissolved in ether and cooled. Pentane was added just to turbidity. On standing overnight in the ice box the material crystallized. A second crop was obtained on concentrating the mother liquors. The total yield was 12.4 gm. The material was recrystallized twice from absolute alcohol and once from ether.

The composition corresponded to a triacetyl methyl methylhexoside.

\[ \text{5.001 mg. substance: 9.195 mg. CO}_2 \text{ and 2.920 mg. H}_2\text{O} \]
\[ \text{4.775 \ " \ " : 6.685 \ " \ \ \ \ \ \text{AgI} } \]
\[ \text{C}_9\text{H}_{18}\text{O}_6. \ \text{Calculated. C 50.27, H 6.64, OCH}_3 18.55 \]
\[ \text{334.2 \ Found. \ " 50.17, " 6.53, " 18.48 } \]

The product melted at 104-105° and had a rotation, in chloroform, of \[ [\alpha]^{29}_D = \frac{-0.58^\circ \times 100}{2 \times 2.0} = -14.5^\circ. \] Helferich and Günther\(^3\) give a melting point of 107-108° and a rotation of -12.4° for the triacetyl-\(\beta\)-methylglucoside of the 6-methyl glucose.

**Methyl Methylglucoside**—5 gm. of the monomethyl glucose were dissolved in 250 cc. of dry methyl alcohol containing 0.5 per cent hydrogen chloride. The solution was sealed in a round bottom flask and heated in a bath of boiling carbon tetrachloride for 43 hours. The specific rotation of the solution, after cooling, was +115°. The hydrogen chloride was removed with silver oxide and the silver precipitate was washed with warm methyl alcohol. The methyl alcohol solution and washings were combined and concentrated under reduced pressure to a syrup. Of this syrup 0.4 gm. were removed for analysis and dried over phosphorus pentoxide under greatly reduced pressure. Although not a pure product, the composition corresponded fairly well to a methyl methylhexoside.

\[ \text{3.452 mg. substance: 5.700 mg. CO}_2 \text{ and 2.500 mg. H}_2\text{O} \]
\[ \text{3.710 \ " \ " : 9.170 \ " \ \ \ \ \text{AgI} } \]
\[ \text{C}_9\text{H}_{18}\text{O}_6. \ \text{Calculated. C 46.15, H 7.76, OCH}_3 29.81 \]
\[ \text{208.1 \ Found. \ " 45.02, " 8.10, " 32.62 } \]

**Tetramethyl Methylglucoside**—The product prepared above was methylated by the Purdie method with 45 cc. of methyl iodide as the solvent. The solution was initially turbid. The product was
isolated in the usual manner by repeated extraction with hot chloroform. The solution was concentrated under reduced pressure to a syrup and this was redissolved in 45 cc. of methyl iodide, giving a clear solution. After remethylation the product was isolated in the same manner. The chloroform extract was concentrated under reduced pressure to a syrup and this was distilled under greatly reduced pressure. Yield 4.2 gm. The product had a rotation, in alcohol, of $[\alpha]_D^{20} = +101^\circ$, and a refractive index of $n_D = 1.4413$. The composition corresponded to a tetramethyl methylhexoside.

5.980 mg. substance: 11.455 mg. CO$_2$ and 4.685 mg. H$_2$O
4.670 " " : 21.311 " AgI

C$_{11}$H$_{22}$O$_5$. Calculated. C 52.76, H 8.86, OCH$_3$ 61.95
250.2 Found. " 52.24, " 8.76, " 60.23

Tetramethyl Glucose—3.8 gm. of the above product were dissolved in 75 cc. of 1.5 N hydrochloric acid and heated on the steam bath for 7 hours. The hydrochloric acid was removed with silver oxide and the silver salts were extracted once with warm water and twice with boiling acetone. The combined extracts were concentrated under reduced pressure to a syrup. On seeding with a crystal of 2,3,4,6-tetramethyl glucose, the syrup crystallized immediately. The product was twice recrystallized from pentane containing 0.5 per cent of ether. It melted at 88–90° and had a specific rotation, in alcohol, of 102° 2 minutes after dissolving, and 83.5° at equilibrium after 48 hours. The melting points recorded in the literature range from 88–104°. The rotation in alcohol is reported as 104.9° initial, and 83.9° at equilibrium.

Tetramethyl Glucose Anilide—0.5 gm. of the above tetramethyl glucose was dissolved in 2 cc. of absolute alcohol, 0.58 cc. of freshly distilled aniline (3 mols) were added, and the mixture was refluxed on the steam bath for 3 hours. On cooling, the product crystallized. It was filtered off, washed with a little absolute alcohol, and recrystallized from absolute alcohol. It melted at 137–138° and had a rotation, in methyl alcohol containing 0.001 per cent hydrochloric acid, of $+64.0^\circ$ at equilibrium. Greene and Lewis$^8$ report a melting point of 138° and a final rotation of $+59^\circ$ in methyl alcohol containing 0.001 per cent hydrochloric acid.

758 Structure of 5-Methyl Glucose

*Methyl Gluconic Acid and Lactone Formation*—To 5 gm. of the methyl glucose in 90 cc. of water, was added a solution of 12.5 gm. of iodine and 25 gm. of barium iodide in 60 cc. of water. The mixture was stirred mechanically and 300 cc. of 0.5 N barium hydroxide solution were dropped in, 20 minutes being required for the addition. The mixture was stirred for an additional 15 minutes and then acidified with sulfuric acid. Sulfur dioxide was passed in until the iodine was exactly reduced, and the halide was removed by adding moist silver carbonate. Acid was added as required to keep the mixture acid to Congo paper. The silver precipitate was filtered off, resuspended in dilute sulfuric acid, refiltered, and washed with dilute sulfuric acid. The combined filtrates were saturated with hydrogen sulfide, and aerated to remove the excess. A warm saturated solution of barium hydroxide was added to a pH of 8.5 and the mixture of silver sulfide and barium sulfate was filtered off and washed with water. The combined filtrate and wash water were concentrated under reduced pressure to about 100 cc., readjusted to pH 8.5, and filtered with charcoal. This filtrate was concentrated to a thick syrup and then dried over phosphorus pentoxide to a glassy solid. This was powdered and redried to constant weight. Yield 6.7 gm. The composition corresponded to a barium salt of a methyl hexonic acid.

<table>
<thead>
<tr>
<th>Time (min.)</th>
<th>α (degrees)</th>
<th>Time (hrs.)</th>
<th>α (degrees)</th>
<th>Time (hrs.)</th>
<th>α (degrees)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1½</td>
<td>0.00</td>
<td>1</td>
<td>0.54</td>
<td>72</td>
<td>1.10</td>
</tr>
<tr>
<td>3</td>
<td>0.09</td>
<td>1½</td>
<td>0.53</td>
<td>144</td>
<td>1.27</td>
</tr>
<tr>
<td>8</td>
<td>0.18</td>
<td>3</td>
<td>0.57</td>
<td>288</td>
<td>1.24</td>
</tr>
<tr>
<td>15</td>
<td>0.35</td>
<td>6</td>
<td>0.61</td>
<td></td>
<td></td>
</tr>
<tr>
<td>32</td>
<td>0.45</td>
<td>23</td>
<td>0.85</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

8.530 mg. substance: 7.315 mg. AgI

12.090 " " ; 5.490 " BaSO₄

(C₇H₁₅O₇)₂Ba. Calculated. OCH₃ 11.16, Ba 24.74

555.6 Found. " 11.31, " 26.72
The rotation, in water, was $\left[ \alpha \right]_{D}^{25} = \frac{+1.06^\circ \times 100}{2 \times 2.0} = +26.5^\circ$.

0.250 gm. of this product was dissolved in water, 0.97 cc. (2 mols per mol of Ba) of 1.0 N hydrochloric acid was added, the mixture was diluted immediately to a volume of 5.0 cc., and the rotation

![Graph](image_url)

**Fig. 1.** Optical rotation during lactone formation at 25°

![Graph](image_url)

**Fig. 2.** Optical rotation during glucoside formation at 25° and at 76°. Glucose and methyl glucose.

was measured in a 2 dm. tube with sodium (D) light. The observed rotations are given in Table I and the specific rotations (calculated on the basis of barium salt) are plotted in Fig. 1.

*Glucoside Formation*—The methods and technique have been
Structure of 5-Methyl Glucose

previously described and need not be repeated in detail here. A 0.344 molal solution of the sugar in dry methyl alcohol containing 0.5 per cent of dry hydrogen chloride was used. Experiments were made at room temperature, and in sealed tubes heated in a bath of boiling carbon tetrachloride. The rotations were measured at 20° with sodium (D) light. 4 dm. tubes were used for the room temperature experiments and 2 dm. for the others. The specific rotations calculated from the data are plotted in Fig. 2. The corresponding curves for glucose are reproduced from an earlier paper for purposes of comparison.

| TABLE II |

Glucoside Formation at 25° from Reduction Determinations

<table>
<thead>
<tr>
<th>Time (hrs.)</th>
<th>Cc. 0.01 N thiosulfate</th>
<th>Mg.</th>
<th>Free sugar, per cent</th>
<th>Distribution of sugar, per cent</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before hydrolysis</td>
<td>After hydrolysis</td>
<td>Before hydrolysis</td>
<td>After hydrolysis</td>
</tr>
<tr>
<td>0</td>
<td>10.88</td>
<td>7.03</td>
<td>10.55</td>
<td>6.82*</td>
</tr>
<tr>
<td>1</td>
<td>7.86</td>
<td>6.93</td>
<td>7.62</td>
<td>6.73*</td>
</tr>
<tr>
<td>3</td>
<td>4.32</td>
<td>6.90</td>
<td>4.19</td>
<td>6.70*</td>
</tr>
<tr>
<td>7</td>
<td>2.80</td>
<td>6.74</td>
<td>2.72</td>
<td>6.54*</td>
</tr>
<tr>
<td>24</td>
<td>2.39</td>
<td>8.82</td>
<td>2.32</td>
<td>8.55</td>
</tr>
<tr>
<td>48</td>
<td>2.47</td>
<td>7.64</td>
<td>2.40</td>
<td>7.41</td>
</tr>
</tbody>
</table>

* The total sugar present in these samples was 6.67 mg. In all the others it was 10.0 mg.

In order to determine analytically the character of the glucosides which were formed, the method previously developed was used. This consisted in determining the amount of reducing sugar present in a particular sample, before and after hydrolysis with dilute acid. The difference is assumed to represent the amount of γ-glucoside present in the sample. The limitations of the method, as well as the necessary corrections, have been previously discussed in detail.

The micro Willstätter method was used without modification. This was found to give practically theoretical values for the

methyl glucose both before and after heating with acid, so that no correction was required. A sample of the glucoside which had been formed by heating the acid methyl alcohol solution at 76° for 8 hours was hydrolyzed with 0.1 N hydrochloric acid at 100° for 10 minutes and then analyzed for reducing sugar. The amount present was, within the limits of experimental error, no more than before the hydrolysis so that this correction was likewise omitted.

The data, and the amounts of $\gamma$-glucoside, normal glucoside, and free sugar, calculated from them are given in Table II. Comparison with the results on glucose in the earlier papers\(^1\) shows that the rates of formation of the $\gamma$-glucosides are closely alike in the two sugars, as are those for the normal glucosides.
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J. Biol. Chem. 1932, 97:751-761.

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