[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE COLLEGE OF LIBERAL ARTS, NORTHWESTERN UNIVERSITY]

# THE REACTIVITY OF THE METHYLATED SUGARS. III. THE ACTION OF DILUTE ALKALI ON TETRAMETHYL-*d*-MANNOSE

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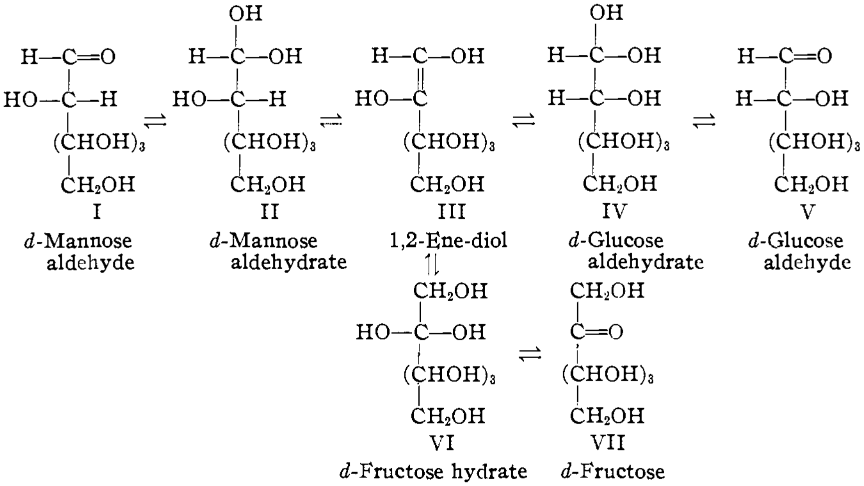
Attention has already been directed[2] to the fact that the methylated sugars offer excellent opportunities for testing experimentally the validity of certain of the theories developed to explain the reactivity of the simple sugars.

The interconversion of sugars by alkalies, first studied by Lobry de Bruyn,[3] and explained by him and also by Fischer[4] and by Wohl,[5] was exhaustively studied by Nef[6] and his students. Nef's study of the action of alkalies and alkaline oxidizing agents on the sugars led him to interpret the reactions on the basis of the formation of intermediate ene-diols. Thus the obtaining of isomeric hexoses from *d*-glucose in alkaline solution and of acids of from one to five carbon atoms by alkaline oxidation was readily explained by assuming progressive enolization. It is this theory of enolization and, more especially, the actual mechanism of enol formation when methylated mannose is treated with alkali, that is our chief concern here. Nef[6,7] explained enol formation by assuming that a given sugar can selectively add and lose water in such a way as to produce ene-diols, and from them various isomeric sugars.

On the basis of Nef's explanation the interconversion of *d*-mannose into *d*-glucose and *d*-fructose may be illustrated as follows



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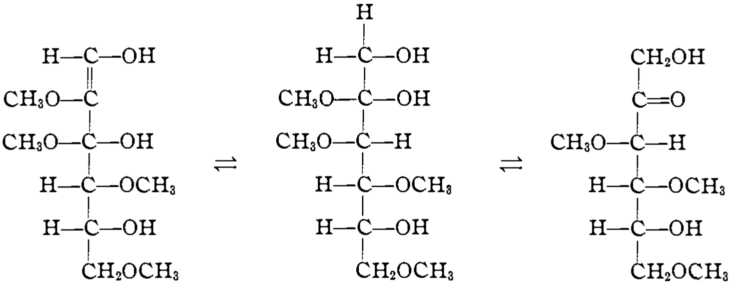
[1] Abstracted from a dissertation submitted by Richard D. Greene to the Graduate

By assuming that enolization continues down the carbon chain, Nef accounted for the formation of other products, as *d*-glutose and *d*-pseudofructose. If Nef's theory of enol formation is entirely correct, we can make certain predictions as to the behavior of the methylated sugars with alkali. Thus 2,3,4,6-tetramethyl-*d*-mannose should add water to form its aldehydrate, which would then lose water to form the 1,2-monomethyl ene-diol. This, in turn, by selective loss and addition of water, might form 2,3,4,6-tetramethyl-*d*-glucose. It might, however, equally well form an unstable hemi-acetal (IX), which would undoubtedly lose methyl alcohol to form 3,4,6-trimethyl-*d*-fructose.



VIII IX X

This trimethylfructose (X) would then be subject to a repetition of the same process of enolization and demethylation, and in the presence of oxidizing agents should yield fragments of from one to five carbon atoms (in the chain) just as in the case of the unmethylated sugars.

Actually the facts are not consistent with such behavior. The resistance of the methylated sugars to mineral acids and to fermentation is well known. It has been shown that they are much less reactive with Fehling's solution[8] than are the unmethylated sugars. The oxidation of tetramethyl-*d*-glucose with alkaline hydrogen peroxide[2a] yielded predominantly formic and carbonic acids with a methylated five carbon acid, whereas Nef's difficulty in obtaining any five carbon acid from unmethylated glucose is historic. It was further shown that tetramethyl-*d*-glucose[2b] under the action of dilute alkali yields a mixture of methylated glucose and mannose with a certain amount of the ene-diol common to them.

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School of Northwestern University, in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

[2] (a) Gustus and Lewis, THIS JOURNAL, **49**, 1512 (1927); (b) Wolfrom and Lewis, *ibid.*, **50**, 837 (1928).

[3] Lobry de Bruyn and Van Ekenstein, *Rec. trav. chim.*, **14**, 156, 203, 213 (1895).

[4] Fischer, *Ber.*, **28**, 1149 (1895).

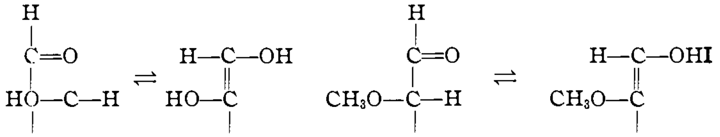
[5] Wohl and Neuberg, *Ber.*, **33**, 3099 (1900).

[6] Nef, *Ann.*, **357**, 214 (1907); **376**, 1 (1910); **403**, 204 (1914).

[7] Spoehr, *Am. Chem. J.*, **43**, 228 (1910).

[8] Purdie and Irvine, *J. Chem. Soc.*, **85**, 1060 (1904); Irvine, *ibid.*, **85**, 1077 (1904).

The conclusion from these facts must be that enolization is definitely blocked at carbon 2 when the labile hydrogen of the sugar is replaced by the non-polar methyl group. Nef's theory as it stands does not account for the behavior of the methylated sugars and so must not be an entirely correct explanation of the reactivity of the simple sugars. By a simple modification, however, it can be made to fit all the facts. If the concept of enolization by addition and loss of water be modified in favor of a simple keto-enol tautomerism, we can harmonize the behavior of the substituted and unsubstituted sugars perfectly.



$$\begin{array}{c}\text{H}\\|\\\text{C=O}\\|\\\text{HO—C—H}\\|\end{array}\rightleftharpoons\begin{array}{c}\text{H—C—OH}\\\|\\\text{HO—C}\\|\end{array}\qquad\begin{array}{c}\text{H}\\|\\\text{C=O}\\|\\\text{CH}_3\text{O—C—H}\\|\end{array}\rightleftharpoons\begin{array}{c}\text{H—C—OH}\\\|\\\text{CH}_3\text{O—C}\\|\end{array}$$

We can now understand their difference in reactivity for we would not suspect that, under our conditions, methyl should go from oxygen to carbon. It seems highly reasonable then, that tetramethyl-*d*-mannose with alkali should produce a system containing only tetramethylated glucose and mannose.

In the further verification of this principle it was first necessary to find conditions under which mannose would produce a system containing considerable amounts of glucose and fructose, with minimum secondary effects. Having then applied identical conditions to the methylated sugar, we should be in a position to generalize correctly from the results.

A solution molar in mannose and 0.035 *N* in calcium hydroxide held at 35° for 200 hours fulfilled the above requirements. Tetramethyl-*d*-mannose, which had been obtained crystalline for the first time, was subjected to similar conditions. In the analytical investigation of the action of alkali on tetramethylmannose it was found that the specific rotation increased from +2.4° to an equilibrium value of +42°. This is precisely the value obtained from a synthetic mixture of equal quantities of tetramethylmannose and tetramethylglucose. Determination of total methylated aldoses by iodine titration gave the surprising result of apparently increased aldose content. This is ascribed to the presence of a certain amount of the ene-diol, common to the two sugars, which seems to possess unusual stability. This view is confirmed by the fact that treatment with acid restores the original iodine value. Investigation of the alkaline solution of mannose did not show the presence of an unmethylated ene-diol of any stability.

The separation of the two tetramethyl sugars from the reaction mixture was accomplished by their conversion to the anilides, which were separated on the basis of their solubility in aniline, tetramethylglucose anilide being much the more insoluble.

This investigation, in showing that tetramethyl-*d*-mannose with alkali gives no methylated ketose and an undiminished amount of methylated aldose, affords direct evidence that the process of enolization involves the movement of hydrogen atoms rather than selective hydration and dehydration. In addition, the general enol explanation of sugar reactivity finds further support. While this work does not involve, and therefore does not answer, the question of the absolute ring structures of the two tetramethyl sugars dealt with, yet their interconvertibility indicates that they possess the *same* ring structure.

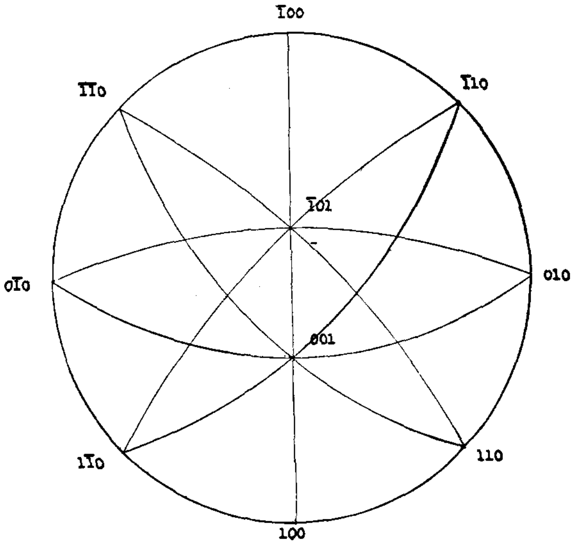


Fig. 1.—Stereographic projection of tetramethylmannose. Crystallography of tetramethylmannose.* Monoclinic. Resembles orthoclase, Fig. 767, p. 457, Dana's "Mineralogy," 3d ed., W. E. Ford. Some crystals have (100) also slightly developed. $110 \wedge 1\bar{1}0 = 89^\circ\ 1'$; $100 \wedge 010 = 45^\circ\ 39'$; $100 \wedge 001 = 55^\circ\ 30'$; $100 \wedge 101 = 55^\circ\ 11'$; $001 \wedge 101 = 69^\circ\ 19'$. Cleavage: (100) perfect. Optically. Birefringence fairly strong, $(\gamma - \alpha) = 0.023$. $\alpha = 1.475$, $\beta = 1.495$, $\gamma = 1.498$. Ax. Pl.||(010). Extinction parallel. Dispersion, $p < v$.

* Acknowledgments are here made to A. J. Walcott, Department of Mineralogy, Northwestern University, for directing the crystallographic determinations.

## Experimental Part

**The Preparation of Crystalline Tetramethylmannose.**—$\alpha$-Methylmannoside was prepared from vegetable ivory nuts by the method of Hudson;[9] the yield was about 50%

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[9] Hudson, "Organic Syntheses," John Wiley and Sons, Inc., New York, **7**, 64 (1927).

of the weight of vegetable ivory used. From the mannoside so obtained the completely methylated mannoside was prepared by the method of Haworth.[10] The tetramethyl-α-methylmannoside was a limpid, colorless liquid; b. p. 116° at 2 mm. It later solidified to a mass of prisms, m. p. 39–40°. The specific rotation in water was $[\alpha]_D$ = +43.5° (*c* = 5). The mannoside was hydrolyzed with hydrochloric acid and the tetramethylmannose was isolated according to the method of Irvine.[11] Vacuum distillation had been employed by previous workers in the purification of tetramethylmannose, but with quantities not exceeding 30 to 40 g., perhaps. An attempt at vacuum distillation (2–5 mm.) of 258 g. of tetramethylmannose resulted in complete decomposition, with the formation of some tetramethylglucose and a large amount of partially demethylated products. A similar attempt at distillation of 633 g. promised the same result and the method of purification by distillation was abandoned.

Extraction with petroleum ether (b. p. 40–50°) was tried on a freshly prepared sample of tetramethylmannose as a means of removing the small amount of unhydrolyzed mannoside present. Equal volumes of the petroleum ether and tetramethylmannose were heated at about 55° in order to produce gentle refluxing, while the mixture was stirred vigorously. After one hour the mixture was allowed to demulsify and cool and the solvent layer was decanted. This treatment was repeated. The residual sirup (90% of the original) was almost entirely freed from solvent *in vacuo*. After several days standing the sirup crystallized completely. The large lot of undistilled material above (633 g.) crystallized largely after seeding. It was now possible to purify the sugar by recrystallization, as with tetramethylglucose. This operation was carried out in a continuous siphon extractor. In this way 270 g. of pure crystalline tetramethylmannose was obtained. The yield was not calculated because of the previous treatment of the material. Methoxyl was determined by the modified Zeisel method.[12]

*Anal.* Subs., 0.1492, 0.1209: AgI, 0.5862, 0.4762. Calcd. for $C_6H_8O_2(OCH_3)_4$:-$OCH_3$, 52.5. Found: 51.9, 52.1.

The constants of the sugar were as follows

| Recrystallization | $[\alpha]^{20}_D$ ($c$ = 5 in all cases) | | | |
|---|---|---|---|---|
| | $H_2O$ | $CH_3OH$ | $CHCl_3$ | M. p. |
| First | +2.4° | +27.6° | +23.0° | 50–51° |
| Second | +2.4° | +27.6° | +23.0° | 50.5–51.5° |

The preparation of the tetramethylglucose and tetramethylfructose referred to in the course of this work is described by M. L. Wolfrom.[2b]

**Preparation of Tetramethylmannonic Lactone from Crystalline Tetramethylmannose.**—Ten g. of crystalline tetramethylmannose was oxidized with bromine according to the method of Purdie and Irvine.[13] The crude lactone was purified by the sodium salt method of Haworth.[14] The pure lactone was a colorless sirup, which showed no tendency to crystallize. Mol. wt. by titration, 235. Calcd. for $C_{10}H_{18}O_6$: 234. $OCH_3$, calcd., 53.0. Found, 52.2. A solution of the lactone in water (*c* = 2.97) changed in specific rotation $[\alpha]_D$ from +136.4° to +62.8° in six days. This agrees with the data of Upson and Whitnah[15] and confirms the conclusion of Haworth[14] that

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[10] Haworth, *J. Chem. Soc.*, **107**, 8 (1915).

[11] Irvine and Moodie, *ibid.*, **87**, 1465 (1905).

[12] Hewitt and Moore, *ibid.*, **81**, 318 (1902).

[13] Purdie and Irvine, *ibid.*, **83**, 1033 (1903).

[14] Charlton, Haworth and Peat, *ibid.*, **128**, 89–101 (1926).

[15] Whitnah, "Dissertation," Nebraska University, **1925.**

the tetramethylmannonic lactone prepared from "normal" tetramethylmannose is an "unstable" one.

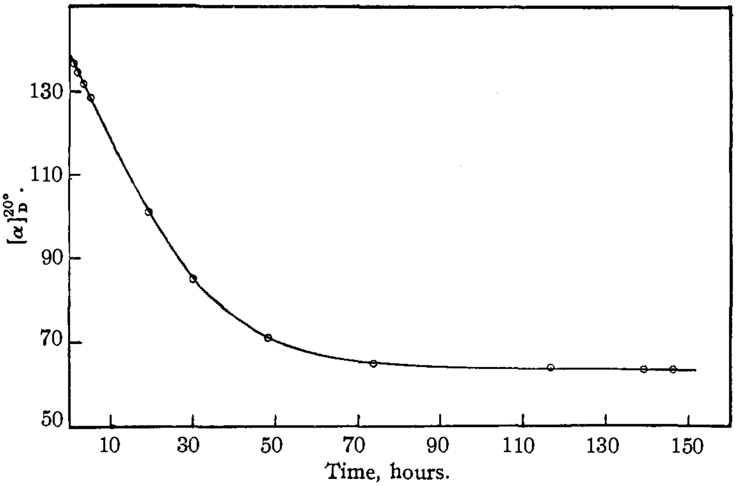

Fig. 2.—Change in specific rotation of tetramethylmannonic lactone in water ($c$ = 2.969).

**The Action of Dilute Alkali on Mannose.**—It was proposed to find the optimum conditions for the interconversion of mannose and then to apply these to tetramethylmannose. A solution molar in mannose and 0.342 $N$ in calcium hydroxide was allowed to stand at 35° for 200 hours. During this period the specific rotation changed from +14.3° to +0.6° (constant) and the solution had become neutral to phenolphthalein.

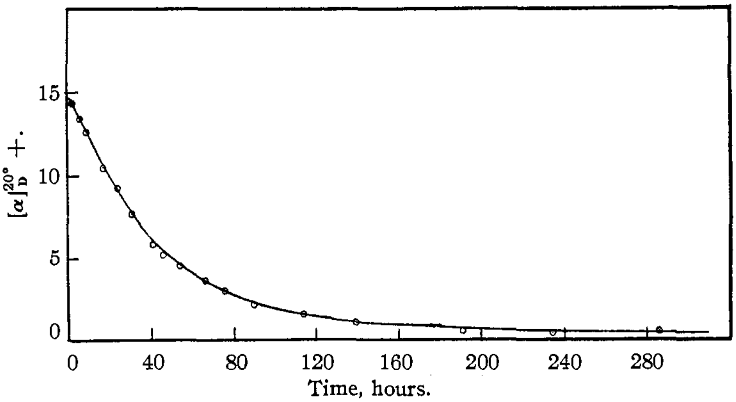

Fig. 3.—Change in specific rotation of mannose and alkali.

The amounts of glucose, mannose and fructose were determined periodically and finally. The percentages of the three sugars were calculated from the determination of reducing sugar by the Munsen-Walker method, aldoses by iodine titration[16] and mannose as

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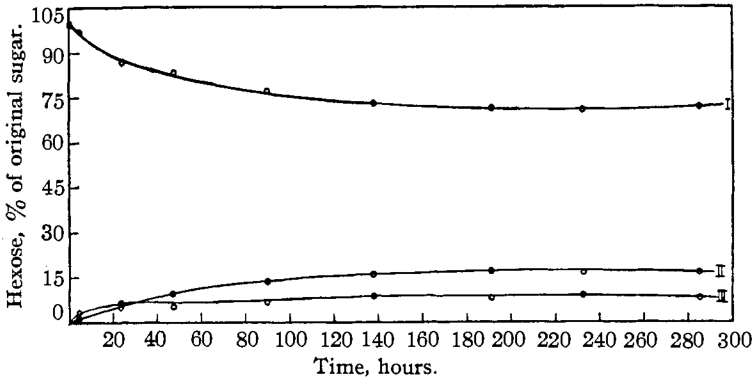
[16] Cajori, *J. Biol. Chem.*, **54**, 617 (1922).

the phenylhydrazone.[17] The applicability of these methods had been tested on known solutions of the three sugars. The final percentages so determined were: mannose 71.7, glucose 8.9, fructose 16.9, non-sugar bodies, probably saccharinic acids (by diff.) 2.5. The polarimetric reading calculated from these percentages and the accepted specific rotations of the three sugars was −0.6° as against the observed value +0.6°. This is nearly as close agreement as the analytical determinations warrant.

In view of the evidence of the apparent stability of the methylated ene-diol, the reaction solution of the *unmethylated* sugar was tested. Iodine titration and Fehling's solution gave identical values with and without acidification, indicating no more than a transient existence of the simple ene-diol.

**Preliminary Study of the Action of Alkali on Tetramethylmannose.**—The action of 0.034 *N* calcium hydroxide on mannose had produced a considerable degree of interconversion and it seemed probable that the same conditions would be applicable to tetramethylmannose. Solutions of tetramethylmannose were made up molar in the sugar and with alkalinity of 0.03 *N* barium hydroxide, 0.035 *N* calcium hydroxide, 0.04 *N* barium hydroxide and 0.056 *N* barium hydroxide. Little or no specificity in the two alkalies was observed. These solutions were held at 35° and polarimetric observations were made at intervals. The specific rotations increased from the initial value of +2.4°, respectively, to +38.9°, +41.5°, +41.8° and +41.8° in about 200 hours. The alkalinity gradually decreased until the solutions were almost neutral. It is clear that a true equilibrium is involved since further increase of alkali beyond a certain point does not increase the specific rotation. The result has further interest, in view of the statement appearing frequently in sugar texts that rotation drops in alkaline solution.



I, mannose; II, fructose; III, glucose.

Fig. 4.—Formation of glucose and fructose from mannose and alkali.

The nature of this change was investigated by the method of iodine titration. This method was used in the determination of methylated aldoses in a known mixture of tetramethylmannose, tetramethylglucose and tetramethylfructose and found to be perfectly applicable.[2b] Determinations of the iodine values of the equilibrated solutions yielded results from 117 to 152% of the original, varying with the strength of alkali. This was taken as indicating the presence of a certain amount of the stable monomethyl ene-diol, which was capable of reacting with more iodine than the sugar. Treatment of the equilibrated solutions with acid caused a return to the original value

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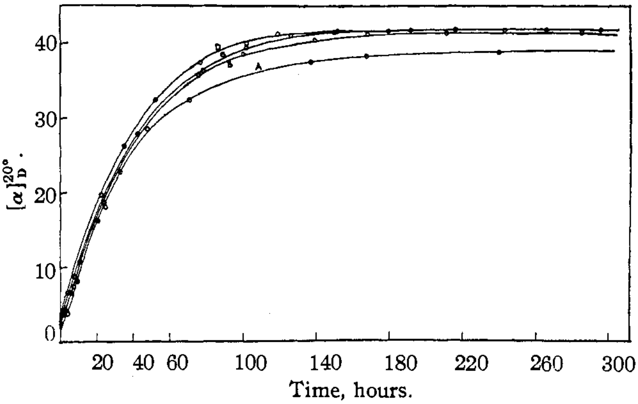
[17] Sherrard and Blanco, *J. Ind. Eng. Chem.*, **15**, 612 (1923).

of 100% tetramethyl aldohexose, indicating the absence of tetramethylfructose. The specific rotation of +42° was not appreciably altered by such treatment. Reference to the specific rotations of tetramethylmannose (+2.4°) and tetramethylglucose (+82°), shows that a mixture of equal quantities of the two sugars would have a specific rotation of +42°. Treatment of a mixture of equal quantities of the two sugars with 0.035 *N* alkali gave a constant specific rotation of +42°. The presumption of the presence of equal amounts of the two sugars in the equilibrated mixture is confirmed by the actual isolation of their anilides.



*A*, 0.03 *N* $Ba(OH)_2$; *B*, 0.035 *N* $Ca(OH)_2$; *C*, 0.04 *N* $Ba(OH)_2$; *D*, 0.056 *N* $Ba(OH)_2$.

Fig. 5.—Action of different strengths of alkali on tetramethylmannose.

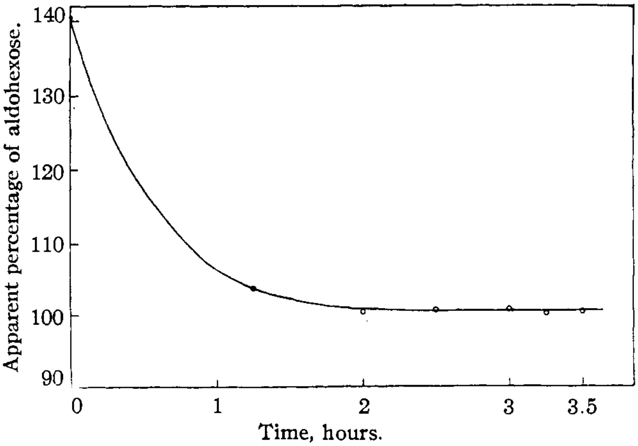


Fig. 6.—Rate of de-enolization of tetramethylmannose.

**Optimum Conditions for De-enolization.**—The complete reconversion of the enediol to sugar required a surprisingly strong acid treatment. Three *N* hydrochloric acid at 35° reduced the iodine from 152 to 100% apparent aldohexose in four hours. Since sulfuric acid could be removed more readily (as barium sulfate) it was substituted.

A portion of a reaction solution from 0.035 *N* calcium hydroxide was made 3 *N* in sulfuric acid and *M*/2 in sugar and held at 35° with the following results.

| Interval, hours | (Original) | 0 | 1.25 | 2 | 2.5 | 3 | 3.25 | 3.5 |
|---|---|---|---|---|---|---|---|---|
| $I_2$ value, % app. aldohex. | 140.4 | 103.7 | 100.4 | 100.8 | 100.7 | 100.1 | 100.3 | |

Further work showed that weaker acid at a higher temperature would render de-enolization complete. A solution 0.02 *N* in sulfuric acid and *M*/5 in sugar was heated at 95°. In fifteen minutes the iodine value dropped from 140.4 to 100.5% apparent aldohexose. In actual practice it was thought better to employ a temperature of 50° and a longer time.

**Quantitative Recovery of the Sirup.**—This phase of the work presented difficulties as serious as they were unexpected. Originally it was taken for granted that the sugar could be recovered quantitatively from the equilibrated solution without any special difficulty. While their known greater stability gave them an apparent advantage over the simple sugars, nevertheless the methylated sugars seem to possess a degree of volatility which necessitated the utmost care in their isolation from aqueous solution. After de-enolization of the equilibrated solution with sulfuric acid, the acid was removed by the addition of 0.1 *N* barium hydroxide drop by drop, until just faintly acid, and barium carbonate for the remainder of the acid. After removal of the barium sulfate by filtration, the water was evaporated at 25 mm. and 45–50°. The residual sirup was taken up in alcohol and finally in ether, any precipitate being removed before evaporating the solvent *in vacuo*. In this way but an 80–85% recovery of sirup was possible. The use of alcohol and ether was then discarded as unnecessary and the water was removed at 35° instead of at 45–50°. After these modifications a yield of 93.5% of sirup was obtained.

**Methods of Separation and Identification.**—Tetramethylglucose was established qualitatively as a product of the interconversion of tetramethylmannose, as follows. The equilibrated sirup from the experiment with 0.056 *N* alkali was seeded with tetramethylglucose. Crystallization occurred and the crystals were freed from sirup and recrystallized from petroleum ether. The following constants were obtained: $[\alpha]^{20}_{D}$ in water ($c = 1.14$) $+ 83.7°$; m. p. 89–90°; identical with those of pure tetramethylglucose. Both equilibrated sirups and synthetic mixtures of equal amounts of the two sugars actually exhibited spontaneous crystallization of tetramethylglucose, in nearly equal amounts (10–15%) of the tetramethylglucose present. In this way substantial confirmation of the presence of equal amounts of the two sugars in the equilibrated solution was afforded. Attempts were made to separate the sugars as such quantitatively by crystallization and by the use of solvents, without success. Of their known compounds the anilides[18] appeared promising, being nicely crystalline and quantitative in formation. The two anilides were prepared

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[18] Irvine, *J. Chem. Soc.*, **93**, 95 (1908); **97**, 1449 (1910).

by heating for three hours at 100° a mixture of 8 moles of aniline with a 30% solution of the sugar in absolute alcohol. After recrystallization from absolute alcohol both anilides were obtained in a high degree of purity, with the following constants.

$[\alpha]_D^{20°}$ in Ethyl Alcohol with 0.001% Hydrochloric Acid ($c$ = 5)

| Anilide | Initial | Final | M. p. |
|---|---|---|---|
| Tetramethylglucose | +230° | +59° | 138° |
| Tetramethylmannose | Variable | −8.5° | Variable |

These anilides exhibit mutarotation with definite and reproducible equilibrium values, just as the sugars do. The tetramethylglucose anilide has a constant melting point, indicative of one solid form.

The original workers[18] had recorded such a wide variation in the case of hydrolysis of the two anilides that it seemed to promise a method of separation. This variability in case of hydrolysis was not confirmed, but the relative insolubility of the tetramethylglucose anilide in aniline was successfully utilized.

A trial separation was made on the anilides prepared from a mixture of equal amounts of the two sugars. Seven g. each of tetramethylmannose and tetramethylglucose was dissolved in 42 cc. of alcohol (absolute) and 42 cc. (8 moles) of redistilled aniline was added. The mixture was heated at 100° for three and one-half hours. After standing for eighteen hours the mass of crystals which had formed was filtered off. After removal of the alcohol a crop of crystals came out of the aniline and was filtered off. The aniline was completely removed from the remaining solution by distillation *in vacuo* and the mixed anilides were separated on the basis of fractional solubility in aniline. The more insoluble portions, high in tetramethylglucose anilide, were recrystallized from absolute alcohol. A melting point of 137–139° was taken as the criterion of purity. As the tetramethylmannose anilide content of the remainder was increased, crops were removed by crystallizing from alcohol. The purity of the tetramethylmannose anilide was later ascertained by determination of the specific rotation and that of the tetramethylglucose anilide also was confirmed in this way. Out of a calculated weight of 18.45 g. of mixed anilides, 7.59 g. of pure tetramethylglucose anilide and 8.02 g. of pure tetramethylmannose anilide were isolated. In addition to this a crystalline residue of 1.5 g. of mixed anilides remained, making 17.11 g. of crystalline anilides (92.8% calcd.) remaining at the end of the separation. In addition 0.8 g. of very dark, tarry matter remained. The enormous number of leachings with aniline and its subsequent removal induce progressive tar formation.

**Tetramethylmannose with 0.0325 *N* Barium Hydroxide.**—Tetramethylmannose (35.424 g.) was dissolved in an amount of 0.0407 *N* barium hydroxide sufficient to make a volume of 150 cc. This solution, 1 *M* in sugar, 0.0325 *N* in alkali (sp. gr., 1.043;

22.65% sugar) was kept at 35°. The specific rotation at 182 hours was +41.3°, indicating 49.5% tetramethylglucose and 50.5% tetramethylmannose. The iodine value was 125% of the original and the color of the solution was slightly yellow. The solution, now 139.8 cc. containing 33.02 g. of sugar, was combined with 185 cc. of 0.1 *N* sulfuric acid and 374 cc. of water. This solution, *M*/5 in sugar and 0.02 *N* in acid, was kept at 50° for four hours in order to de-enolize it. The iodine value was then 103.5%, indicating almost complete conversion of the enol.

The de-enolized solution, 701.8 g. containing 32.81 g. of sugar, was neutralized by the dropwise addition of 130 cc. of 0.1 *N* barium hydroxide at 40°. The slight acidity left was removed by the addition of 0.4 g. of barium carbonate. After removal of the barium sulfate the iodine value of the solution was found to be 103.4%.

The amber colored solution, 1090 g. containing 32.66 g. of sugar, was evaporated *in vacuo* at 25 mm. and 35°. The evaporation was carried out in a one-liter Claisen flask with a removable glass column. The receiver was kept ice-cold. The flask was weighed every two hours after the removal of nearly all the water, and was found to reach constant weight after twenty hours of distillation. The residual brown sirup weighed 30.85 g., a yield of 94.5%. This, however, contained a slight dark-brown residue, which was separated in the subsequent removal of the sirup preparatory to making the anilides. By decanting the alcohol solution of the sirup, 0.32 g. of the dark residue remained, leaving 30.53 g., net, of sirup, or 93.5%. This residue was not investigated beyond ascertaining that it was soluble in water, insoluble in alcohol, was mainly organic and gave a test for barium. The iodine value of the sirup was 107.3%, a slight increase over the value previously obtained on the solution. The specific rotation was +40.4°. The iodine value of the aqueous distillate indicated the presence of 0.39 g. of sugar. Reckoning this in the yield, the total weight accounted for is 95.7% of the original.

After the removal of 3.83 g. of sirup as a specimen, the remaining 26.70 g. was dissolved in 82 cc. of absolute alcohol and 82 cc. of water white aniline was added. The mixture was heated in a glycerol bath at 100° for 3.2 hours, using an air condenser. After standing for two days, the solution had failed to yield any crystals. One-tenth of the solution (2.67 g. of sugar) was evaporated *in vacuo* and efforts were made to obtain crystals from it. A small amount of crystalline material was obtained, but it appeared that the formation of the anilides had been quite incomplete, perhaps because of the presence of moisture from the original sirup. The test portion was kept separate and the main lot (24.03 g. of sugar) was freed from alcohol and partly from aniline, in order to eliminate any possible water. The solution was then restored to the original concentrations of aniline and alcohol and heated at 100° for two hours. Now, after cooling, a reasonable crystallization occurred.

The reaction mixture at this stage was very black and from previous experience it seemed highly desirable to remove the crystalline mixed anilides from the dark material before attempting their separation. By progressive concentration of the alcohol solution 26.18 g. (83%, calcd.) of crystalline anilides was obtained. At this point it was necessary to precipitate some of the tar by dissolving the residue in alcohol–ether and adding petroleum ether (40–50°). Crystallization following this step raised the total to 90%. Some more tar was removed from the residue at this point by steam distillation. The light-colored, water-soluble portion (3 g.) was heated with 9 cc. of absolute alcohol and 9 cc. of aniline at 100° for three hours. By crystallization as before, in a desiccator held at 5°, the total weight of crystalline anilides was raised to 29.74 g., or 93.9% of the calculated weight (31.67 g.).

The mixed anilides were repeatedly leached with aniline, the undissolved portions being recrystallized from absolute alcohol (generally 1:5) to obtain pure tetramethylglucose anilide, m. p. 137–139°. As the remaining material increased in tetramethylmannose anilide content, it was also crystallized out. In the later work a superior method was developed. This consisted in dissolving the mixed anilides in 3 parts of aniline and allowing almost pure tetramethylglucose anilide to crystallize.

In this way 12.50 g. of tetramethylglucose anilide of m. p. 137–139° was obtained in 11 portions. A composite melting point with pure tetramethylglucose anilide showed no depression. The specific rotation ($CH_3OH$, $c = 2.36$) decreased from +228.7° to +58.9° on the addition of 0.001% of dry hydrogen chloride. A slightly greater amount of tetramethylmannose anilide, 12.79 g., was obtained in 6 lots, a composite of which yielded a specific rotation ($CH_3OH$, 0.0001%, hydrogen chloride, $c = 4.93$) of −8.5°, in agreement with the accepted value. A crystalline residue of 0.37 g. gave a specific rotation of +31.9° in the same solvent, indicating that this unseparated portion contained 60% of tetramethylglucose anilide and 40% of tetramethylmannose anilide. A tarry residue of 2.08 g. raises the total residual weight to 27.74 g., a loss of 2.00 g. in manipulation. The enormous number of transfers and lengthy treatment with aniline make this appear not unreasonable.

Reviewing the significant steps of the process, 32.66 g. of tetramethylmannose after treatment with alkali yielded 30.53 g. of recovered sirup, or 93.5%. Of this 30.53 g. of sirup, 24.03 g. (net) was converted to the anilides. Out of a possible 31.67 g. of anilides, 29.74 g. of crystalline material, or 93.9%, was obtained. From these mixed anilides 25.29 g. of the pure anilides was separated, a yield of 85%.

The nature of the processes and the yields obtained, along with the analytical data, justify the conclusion that the action of dilute alkali on tetramethylmannose, followed by suitable acid treatment, produces a mixture of equal amounts of tetramethylmannose and tetramethylglucose. From this we can only conclude that the interconversion of sugars is an enolic process involving migratory hydrogen atoms.

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## Summary

1. The action of dilute alkali on mannose was investigated and conditions were found for conversion to glucose and fructose with minimum saccharinic acid formation. The composition of the solution at equilibrium was determined.

2. Tetramethylmannose was obtained in crystalline form for the first time.

3. On treating 100 g. of tetramethylmannose with dilute alkali, 93.5 g. of sugar was recovered. This yielded a weight of crystalline anilides equivalent to 87.8 g. of sugar. The weight of pure anilides separated from this was equivalent to 74.7 g. of sugar, of which 36.9 g. was tetramethylglucose and 37.8 g. was tetramethylmannose.

4. No methylated ketose was formed.

5. Evidence is presented for the presence of the monomethyl ene-diol common to tetramethylmannose and tetramethylglucose.

6. The ring structures of the normal forms of tetramethylmannose and tetramethylglucose are indicated to be identical.

7. The prediction of the ene-diol theory as applied to the action of dilute alkali upon tetramethylmannose has been confirmed.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF MIDDLEBURY COLLEGE]

# REACTIONS OF ALPHA, BETA-UNSATURATED DINITRILES

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Malononitrile, by virtue of its methylene group, readily condenses with carbonyl compounds to yield α,β-unsaturated dinitriles.[1] In several instances we obtained two products, the usual α,β-unsaturated dinitrile (I) and a dimer (II) whose structure we are still investigating.

$$C_6H_5CHO + CH_2(CN)_2 \longrightarrow \underset{\text{I}}{C_6H_5CH{=}C(CN)_2} \quad \text{also} \quad \underset{\text{II}}{C_{20}H_{12}N_4}$$

This paper deals with condensation products corresponding to I.

There is a close resemblance between the reactions of α,β-unsaturated dinitriles and those of α,β-unsaturated aldehydes and ketones, the resemblance being due to the presence in both classes of substances of a reactive conjugated system, $C{=}C(C{\equiv}N)_2$ and $C{=}C{-}C{=}O$, respectively.

We have studied this resemblance in four reactions which are typical of α,β-unsaturated aldehydes and ketones, namely, the reaction with sodium bisulfite, oxidation by permanganate, reversal of reaction of formation (aldol or ketol condensation) by means of sodium hydroxide and the addition of the elements of hydrocyanic acid.

Benzalmalononitrile (I) and similar substances dissolve in sodium bisulfite solution—slowly in the cold, rapidly when warmed. The product thus formed (III) resembles the sulfonates (IV)[2] obtained from the reaction

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[1] (a) Heuck, *Ber.*, **28**, 2251 (1895); (b) Walter, *Ber.*, **35**, 1320 (1902); (c) Hinrichsen, *Ann.*, **336**, 323 (1904); (d) Sachs and Appenzeller, *Ber.*, **41**, 102 (1908); (e) Heller and Wunderlich, *Ber.*, **47**, 1617 (1914); (f) Ostling, *Ofversich Finska Vetenskaps. Soc. Forhandl.*, **57A**, No. 11, 1 (1915); (g) Kauffmann, *Ber.*, **49**, 1324 (1916); (h) **50**, 526, 1618 (1917); (i) **52**, 1422 (1919); (j) Diels, Gärtner and Kaack, *Ber.*, **55**, 3439 (1922); (k) Diels and Conn, *Ber.*, **56**, 2076 (1923); (l) Rosenmund and Boehm, *Ann.*, **437**, 125 (1924); (m) Fischer and Nenitzescu, *Ann.*, **439**, 175 (1924).

[2] (a) Pinner, *Ber.*, **15**, 592 (1882); (b) Kerp, *Ann.*, **290**, 123 (1896); (c) Knoevenagel, *Ber.*, **37**, 4038 (1904); (d) Hofmann, *Ann.*, **201**, 81 (1880); (e) Harries, *Ann.*, **330**, 188 (1903); (f) Tiemann, *Ber.*, **31**, 3297 (1898); (g) **32**, 823 (1899); (h) **33**, 561 (1900); (i) Baeyer and Henrich, *Ber.*, **28**, 652 (1895); (j) Labbé, *Bull. soc. chim.*, [3] **23**, 280 (1900); (k) Looft, *Ber.*, **15**, 1538 (1882); (l) *Ann.*, **275**, 377 (1893).