2. Under similar conditions but using dilute hydrochloric acid at 100°, an equilibrium is obtained after about one hour in which the ratio of six- to five-membered acetal is 0.37:1.

3. The results indicate the ease of transformation of oxygen rings in cyclic acetals and, by analogy, point to similar conditions in the case of furanose and pyranose rings in carbohydrates, anhydro sugars and polysaccharides.

MONTREAL, CANADA

[COMMUNICATION FROM THE DEPARTMENT OF INDUSTRIAL AND CELLULOSE CHEMISTRY, McGILL UNIVERSITY]

STUDIES OF REACTIONS RELATING TO CARBOHYDRATES AND POLYSACCHARIDES. XXV. METHYLATION PROCESSES AND TENDENCY TOWARD RING SHIFT IN GLYCEROL CYCLIC ACETALS

BY HAROLD HIBBERT, MURIEL E. PLATT[1] AND NEAL M. CARTER

RECEIVED JULY 27, 1929 PUBLISHED DECEMBER 11, 1929

In the methylation of sugars and their derivatives two methods have been employed: (1) the use of silver oxide and methyl iodide, as first originated by Purdie and developed with so much success by Irvine,[2] and (2) the use of dimethyl sulfate and sodium hydroxide, developed by Denham and Woodhouse[3] in the methylation of cellulose, and later applied by Haworth[4] in the methylation of sugars.

The silver oxide method has had a very wide application, the reaction being carried out in neutral solvents. Thus methylated aldosides, obtained by treating glucosides dissolved in methyl alcohol, with methyl iodide and dry silver oxide yielded on hydrolysis the methyl ethers of the respective aldoses.

It has been established that under these mild experimental conditions profound changes, such as racemization, the Walden Inversion or the interconversion of glucosides (α- and β-forms) do not occur. On the other hand, conclusive evidence, to some extent, is lacking as to the total absence of (a) the migration of a methyl group and (b) ring scission and ring migration.

The employment of the expensive alkyl iodides and silver oxide, as well as the necessity for finding a suitable solvent for the carbohydrate in the initial stages of the reaction, prevented a wide and general application of

[1] Constructed from the thesis of Muriel E. Platt as presented to the Graduate School of McGill University in June, 1929, in candidacy for the degree of Master of Science.

[2] Purdie and Irvine, *J. Chem. Soc.*, **83**, 1021 (1903).

[3] Denham and Woodhouse, *ibid.*, **103**, 1735 (1913).

[4] Haworth, *ibid.*, **107**, 8 (1915).

the process, and restricted the further study of the alkylated disaccharides. Haworth, therefore, applied the dimethyl sulfate method, which Denham and Woodhouse had used with cellulose, to the sugars with satisfactory results. Inasmuch as Haworth states,[5] "There are eight available hydroxyl groups in a dihexose. These may be protected by simple methylation with methyl sulfate and dilute alkali, but the conditions must be so chosen that when the disaccharide is sensitive to acids, as is sucrose, the alkali should always be present in excess. On the other hand, since other disaccharides are adversely affected by alkali, it is necessary to ensure, particularly during the earlier stages of the methylation process, that alkalinity does not develop. These conditions can be controlled by maintaining an excess of methyl sulfate during the addition of dilute alkali solution," . . . it is evident that he assumes no ring scission or ring shift (for example, a furanose into a pyranose derivative) in the presence of an acid medium. The various researches carried out by Hibbert and co-workers on cyclic acetal formation indicate clearly, however, the very labile character of such rings and the remarkable ease with which one is transformed into the other in the presence of a trace of acid. It is, therefore, of considerable interest to ascertain whether in the case of a cyclic acetal characterized by ease of ring scission and ring migration, such changes occur during the process of methylation by means of dimethyl sulfate under varying conditions of acidity and alkalinity.

It is now known that in the condensation of acetone with glucose in the presence of a small amount of hydrochloric acid, a ring shift actually occurs,[6] and, since benzylidene glycerol is very similar to an acetone sugar with regard to its ease of hydrolysis in acid media, series of methylation experiments on crystalline 1,3-benzylidene glycerol, using dimethyl sulfate and alkali as the methylating agent, were undertaken with a view of determining: (a) the yield of crystalline 1,3-benzylidene-glycerol-2-methyl ether and (b) the possibility of ring shift with consequent formation of the *liquid*, isomeric 1,2-benzylidene-glycerol-3-methyl ether.

The structure of both of these ethers has been definitely determined.[7] The methylation of the 1,3-derivative was carried out under two sets of conditions: (a) in a reaction mixture containing at the start an excess of dimethyl sulfate, that is, in an acid medium, and (b) in a reaction mixture which was kept distinctly alkaline at all stages.

Reaction in Acid Medium.—The only product obtained when an excess of dimethyl sulfate was used was a small amount of benzaldehyde formed by hydrolysis of the 1,3-benzylidene glycerol by the dimethyl sulfate.

Reaction in Alkaline Medium.—Under these conditions 1,3-benzylidene-

[5] Haworth, "Constitution of Sugars," London, **1929**, p. 55.

[6] Anderson, Charlton and Haworth, *J. Chem. Soc.*, 1329 (1929).

[7] Hibbert and Carter, THIS JOURNAL, **50**, 3376 (1928).

glycerol-2-methyl ether and unchanged original product were obtained when the methylation was carried out in the presence of alkali at 30°, but no 1,2-benzylidene-3-methyl ether could be detected.

At lower temperatures small amounts of unchanged original product only were recovered.

A distinct odor of benzaldehyde was noticed in all the reaction mixtures, indicating that the sensitive acetal ring undergoes hydrolysis even under these conditions; this is probably the reason for the low yields of total recoverable crystalline products. Some of the benzaldehyde may also have been oxidized to benzoic acid, which would have been retained as the sodium salt, although none of the acid was obtained on neutralization and extraction of the aqueous reaction mixture. An attempt to isolate the *liquid* 1,2-benzylidene glycerol isomer (formed by ring shift of the 1,3-isomer) from the mother liquor, obtained after removal of the crystalline 6-membered form, through the formation of its *p*-nitrobenzoate,[8] was unsuccessful, no evidence being obtained of its formation in the methylation process.

The results of these experiments would seem to indicate that, with an alkali-insoluble acetal such as 1,3-benzylidene glycerol, methylation does not take place readily, but that no ring shift occurs under alkaline conditions. However, extensive hydrolysis to glycerol and benzaldehyde readily occurs in both acid and alkaline media.

Experimental

Preparation of 1,3-Benzylidene Glycerol.—Benzylidene glycerol was prepared from benzaldehyde and glycerol by the method previously described.[7] One hundred thirty-eight grams of benzaldehyde, 131 g. of glycerol and six drops of concentrated hydrochloric acid yielded 145 g. of a mixture of isomeric benzylidene glycerols. The 1,3-isomer isolated had a melting point of 80°.

Methylation of 1,3-Benzylidene Glycerol with Dimethyl Sulfate Solution.—To 14 g. of freshly recrystallized 1,3-benzylidene glycerol, dissolved in 62.5 g. (five times the theoretical amount) of dimethyl sulfate at 0°, 90 cc. of a 40% sodium hydroxide solution (five times the theoretical amount) was added slowly through a buret. After five hours of constant stirring at 0°, two layers separated, after which the mixture was stirred for two hours at room temperature. The aqueous layer which separated out was strongly alkaline. The mixture was extracted with ether, the ether extract separated from the aqueous layer and the latter then extracted several times. The combined ether extracts were dried over fused potassium carbonate and the ether distilled off. The residue on fractionation yielded 3 cc. of benzaldehyde. No crystals could be obtained from the residue when it was taken up in benzene–petroleum ether (2:1), this being the method usually employed for the separation of these isomers.

Methylation of 1,3-Benzylidene Glycerol with Dimethyl Sulfate in Alkaline Solution. Methylation at 0°.—To 13.9 g. of the freshly recrystallized 6-membered acetal dissolved in 20 cc. of methyl alcohol and cooled to 0°, 90 cc. of a 40% sodium hydroxide solution (a little more than five times the theoretical amount) and 62.5 g. of dimethyl

[8] Hibbert and Carter, THIS JOURNAL, **50**, 3120 (1928).

sulfate (five times the theoretical amount) were added slowly from different burets, using phenolphthalein as an indicator, in order to be certain that the mixture remained slightly alkaline. A precipitate which was present from the start proved to be sodium sulfate, which was insoluble in the aqueous alcoholic solution. After stirring for four hours at 0°, the product was filtered, the filtrate extracted with ether and the extract dried over potassium carbonate. On evaporation of the solution to about 15 cc. and cooling, crystals separated out. The product was taken up in benzene–petroleum ether (2:1) and cooled. Two grams of crystals (14.5% of original) was separated with a melting point of 80°, that is, the melting point of the original acetal.

Methylation at 30°.—The above experiment was repeated at 30° using 49 g. of the 1,3-acetal, 160 g. of sodium hydroxide (in 40% solution) and 175 g. of dimethyl sulfate. After stirring for four hours, a stream of carbon dioxide was bubbled through the mixture for two hours in order to change any sodium derivative of the unchanged acetal which might have been formed during the reaction back to the ether-soluble free acetal. The product was then extracted with ether and the ether removed under reduced pressure. The residue was taken up in a mixture of benzene and petroleum ether in the proportion of 2:1 and the following crops of crystals were obtained as the result of an exhaustive fractional crystallization of the solution: (1) unchanged 1,3-benzylidene glycerol (m. p. 83°), yield 2 g.; (2) unchanged 1,3-benzylidene glycerol (m. p. 80°), yield 2 g.; (3) 1,3-benzylidene-glycerol-2-methyl ether,[7] (m. p. 51°), yield 9 g.; (4) unchanged 1,3-benzylidene glycerol (m. p. 78°), yield 0.5 g.; (5) a residual oil, weight 4.5 g. The residual oil was investigated for the presence of the isomeric 1,2-benzylidene glycerol and of its methyl ether, but with negative results. The original 1,3-benzylidene glycerol apparently undergoes extensive hydrolysis to glycerol and benzaldehyde under these conditions.

***p*-Nitrobenzoylation of the Oil Obtained in the Previous Experiment.**—Four and one-half grams of Fraction V (the above residual oil) was added with shaking to 4.5 g. of *p*-nitrobenzoyl chloride dissolved in 19.8 g. of pyridine. After standing overnight at 20°, the mixture was poured into 400 cc. of water, the precipitate which formed filtered off and dissolved in benzene–petroleum ether (2:1). The crystals which separated on cooling were recrystallized from ethyl acetate and then had a melting point of 153–154° (melting point of 1,3-benzylidene glycerol-2-*p*-nitrobenzoate, 156°).[7] Four successive crops of crystals were obtained from the mother liquor, all having a melting point of 153–154°. Ligroin (30–50°) was then added to the mother liquor until the solution became murky. On cooling a last crop of crystals was obtained with a melting point of 152°. 1,2-Benzylidene-glycerol-3-*p*-nitrobenzoate, which would have been present had ring shift occurred during methylation, melts at 91°.[7] There was thus no evidence of any ring change.[9]

[9] The evidence submitted in this and the preceding paper renders it highly improbable that any "ring shift" or "wandering of a methyl group" occurs during the methylation of glucosides, anhydro sugars and polysaccharides, except in the isolated cases where the product in question undergoes ready hydrolysis by water, thus involving ring scission.

On the other hand, abnormal results are to be expected in the methylation of the free sugars in alkaline solution, since in these cases (that is, where a free carbonyl group is present) there is the possibility of a "Lobry de Bruyn–van Ekenstein transformation" involving conversion of the sugar into an equilibrium mixture of different carbohydrates or polyoses.

That other deep-seated changes are involved is indicated by the decrease in the rotation of a 0.25 *M* glucose solution to practically zero, in twelve hours, under the influence of 0.85 *N* potassium hydroxide [J. Groot, *Biochem. Z.*, **146**, 72 (1924)].

The low yield of β-methyl glucoside when prepared by the action of dimethyl

Summary

1. Methylation of 1,3-benzylidene glycerol, using dimethyl sulfate and sodium hydroxide under acid and alkaline conditions, has been described.

2. Attention has been drawn to the difficulty of methylating the 1,3-benzylidene glycerol under non-alkaline conditions. In the presence of an excess of dimethyl sulfate (that is, in an acid medium), 1,3-benzylidene glycerol undergoes ring scission into benzaldehyde and glycerol. It was not found possible to isolate any monomethyl ether of either the five- or the six-membered ring isomers.

3. Under alkaline conditions methylation takes place more readily, with formation of the corresponding methyl ether. The methylation is not accompanied by ring migration, as is evidenced by the absence of any 1,2-benzylidene-glycerol-3-methyl ether, although extensive hydrolysis occurs.

4. The necessity for great care in drawing conclusions from methylation experiments carried out on cyclic acetals, carbohydrates and polysaccharides in acid media is pointed out.

MONTREAL, CANADA

sulfate and sodium hydroxide on glucose [Maquenne, *Bull. soc. chim.*, [3] **33**, 260, 469 (1925); Schlubach and Maurer, *Ber.*, **57**, 1686 (1924)] would also seem to indicate the existence of other reactions in an alkaline medium.

For these reasons there would seem to be some doubt as to the presence of a new "active or gamma-sugar" formed under the conditions indicated in the recent paper of Whitnah [THIS JOURNAL, **51**, 3490 (1929)].

It is, however, to be expected that the nature of the glucoside formed in *neutral* and *very slightly* acid solutions of carbohydrates such as glucose, will vary markedly both with regard to the number and type of ring isomers formed, in accordance with the P_H value of the medium used. This has been pointed out repeatedly by the senior author in the last few years and is now found to be the case experimentally. The results are to be published in the near future and the reservation of this field (glucoside formation in neutral and faintly acid media) in view of long years of previous preparation is courteously requested for a short period. [H. H.]