heated in quinoline (2.5 moles) at 100° for six hours and the solution was then cooled in ice and benzoyl chloride (2.2 mols) was added. After standing for four hours at 0°, followed by twenty-four hours at 25°, the reaction product yielded by customary procedure 0.4 g. (4.4%) of 1,6-dibenzoyl-2,3,4,5-diacetone dulcitol and 6.5 g. (72.5%) of 1,4-dibenzoyl-2,3,5,6-diacetone-D,L-galactitol. The rearrangement in this test is so slight that the cause of the extensive rearrangement which occurs when the benzoylation reaction is carried out at 100°, cannot be attributed to an action of the quinoline alone, particularly if the result of the next experiment be considered. It was carried out with the same quantities of materials but some anhydrous quinoline hydrochloride (1.2 mols) was present during the period of heating at 100°; it yielded 3.8 g. (42.4%) of 1,6-dibenzoyl-2,3,4,5-diacetone dulcitol and 3.5 g. (39%) of 1,4-dibenzoyl-2,3,5,6-diacetone-D,L-galactitol. It appears therefore that the rearrangement is catalyzed by such substances as quinoline hydrochloride and (in less degree) pyridine hydrochloride.

Summary

It is shown that the properties of the α- and β-diacetone dulcitols, as well as those of several new derivatives of these substances, exclude the possibility that they can be enantiomorphous substances and prove that they are structural isomers. Evidence has been obtained from periodate and lead tetraacetate oxidations that neither α- nor β-diacetone dulcitol contains a glycol grouping. The results of a study of the ditosyl, diiodo and ditrityl derivatives of β-diacetone dulcitol indicate that it contains two free primary hydroxyl groups, and a study of the oxidation of the diacyl dulcitols, derivable from it, proves that its structure is that of 2,3,4,5-diacetone dulcitol, a meso form. The results of a study of the ditosyl, monotosyl-mono-iodo, and monotrityl-monoacetyl derivatives of α-diacetone dulcitol indicate that it contains one free primary hydroxyl group and one free secondary hydroxyl group, and a study of the oxidation of the dibenzoyl dulcitol derived from it proves that it is 2,3,5,6-diacetone-D,L-galactitol, a racemic form. An acyl migration by which 1,4-dibenzoyl-D,L-galactitol (a racemic form) passes to 1,6-dibenzoyl dulcitol (a meso form) has been demonstrated. A cyclic acetal shift has been shown to be the cause of the interesting and unusual changes which Fischer and Bergmann noticed upon acylation of α-diacetone dulcitol. The shift occurs as a stage in the benzoylation of α-diacetone dulcitol with benzoyl chloride and quinoline or pyridine at elevated temperatures and it is catalyzed by quinoline hydrochloride or pyridine hydrochloride. In structural terms it is represented as the passage of 2,3,5,6-diacetone-D,L-galactitol to 1,6-dibenzoyl-2,3,4,5-diacetone dulcitol. Reasons have been given for preferring the name galactitol to dulcitol in designating non-meso structures of derivatives of dulcitol which carry in their names a numbering of its carbon atoms.

Procedure for Preparation of Fully Methylated Carbohydrates and their Derivatives

BY EUGENE PACSU AND S. M. TRISTER[1]

For investigation of certain structural problems in carbohydrate chemistry, it is often necessary to methylate all free hydroxyl groups in the molecule. Methylation usually is carried out either with methyl iodide and silver oxide,[2] dimethyl sulfate and alkali solution,[3] alkali metals in liquid ammonia and methyl iodide,[4] or with the thallium salts of the carbohydrates and methyl iodide.[5]

However, none of these methods, if used alone, gives entirely satisfactory results for various reasons. For complete methylation usually a combination of two of these methods is necessary. In most instances first the dimethyl sulfate-alkali procedure is employed and the products obtained are then repeatedly treated with silver oxide and methyl iodide.

In this Laboratory excellent results were obtained from combination of Haworth's dimethyl sulfate–alkali procedure with a slightly modified process of Freudenberg and Hixon.[6] These

(1) Research Assistant on Special Funds from the Rockefeller Foundation.

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

(3) (a) Haworth, ibid., **107**, 8 (1915); (b) Haworth and Leitch. ibid., **113**, 188 (1918); (c) West and Holden, THIS JOURNAL, **56**, 930 (1934).

(4) (a) Muskat, ibid., **56**, 693, 2449 (1934); (b) Hendricks and Rundle, ibid., **60**, 2563 (1938).

(5) (a) Fear and Menzies, J. Chem. Soc., 937 (1926); (b) Purves and Hudson, THIS JOURNAL, **59**, 49, 1170 (1937); (c) Hirst and Jones,

J. Chem. Soc., 496 (1938); (d) Barker, Hirst and Jones, ibid., 169 (1938).

(6) Freudenberg and Hixon, Ber., **56**, 2119 (1923).

authors' simple but apparently seldom used method is based on the reaction between methyl iodide and the sodium alcoholates of the carbohydrates prepared in ether solution. In many instances we have observed that the incomplete methylation in the dimethyl sulfate–alkali procedure is mainly due to the resistance of the primary hydroxyl group toward the alkylating agent. Since this also holds true but in still higher degree for Purdie's reagent, it seemed to us impractical to attempt the completion of methylation of partially methylated sugars, or to start the methylation of sugar derivatives containing primary hydroxyl groups, by means of methyl iodide and silver oxide. We adopted, therefore, the Freudenberg procedure and found that metallic sodium reacted readily with such products giving sodium alcoholates soluble in ether, toluene and other inert solvents. These sodium alcoholates which can be analyzed easily for sodium, if necessary, would suffer partial decomposition in the presence of moisture, in which case the subsequent treatment with methyl iodide would result in products of low methoxyl content. We have found that this can be avoided if a little methyl iodide is added to the solution of the alcoholate before concentration under diminished pressure. The residue is then shaken vigorously with methyl iodide and the reaction mixture is allowed to stand for several hours. We have successfully applied this comparatively simple and inexpensive procedure to several carbohydrates and their derivatives always obtaining products with correct methoxyl content. Since many of these methyl derivatives represent new compounds to be described in forthcoming publications, in the experimental part of the present article only the methylation of sucrose is given for illustration of the details of the procedure.

Experimental

Preparation of Octamethylsucrose.—Purdie and Irvine[7] methylated sucrose with silver oxide and methyl iodide and after four such methylations isolated a product with a methoxyl content of 50.93% instead of the theoretical value of 54.63%. Haworth[3a] methylated sucrose with dimethyl sulfate and sodium hydroxide and found that after one methylation the isolated product had a methoxyl content of 50.5% which could not be increased after further treatment with the same methylating agent. However, by two subsequent methylations with Purdie's reagent the compound isolated had a methoxyl content of 54.12%. In a later paper[8] he claimed that by modify-

ing the conditions somewhat a fully methylated sucrose was obtained after three operations using dimethyl sulfate and alkali as the only alkylating agent. It is interesting to note, however, that Irvine and Stiller,[9] repeating Haworth's procedure, claimed that the methylation yielded a complex mixture of partially methylated compounds boiling at approximately constant temperature.

In our experiment sucrose was methylated with dimethyl sulfate and potassium hydroxide and worked up in the usual manner. The sirup was non-reducing to Fehling's solution and had a methoxyl content of 45.36%. This upon a single methylation with sodium and methyl iodide gave pure octamethylsucrose with the correct methoxyl content of 54.48%. The methylation was carried out in the following way. A 5-g. sample of the partially methylated product (OCH_3, 45.36%) was dissolved in 50 cc. of absolute ether in a flask fitted with a calcium chloride tube and to the solution 1 g. of clean sodium wire was added. The mixture was gently shaken on an apparatus for several hours and allowed to stand overnight at room temperature. Then the solution was decanted rapidly into a distilling flask containing 10 cc. of methyl iodide. The mixture was evaporated under reduced pressure to a paste, to which 25 cc. of methyl iodide was added. The cloudy solution was shaken vigorously for several hours, then kept standing at room temperature for twelve hours. Throughout the above operation precautions were taken to exclude all atmospheric moisture from the reaction vessel. An equal volume of absolute ether was then added to the reaction mixture and the sodium iodide precipitate was filtered off with activated carbon and washed with absolute ether. The combined filtrate and washings were evaporated *in vacuo* at 30–40° to a sirup which was twice purified by filtration of its petroleum ether (b. p. 30–40°) solution with activated carbon. On evaporation under reduced pressure the clear filtrate gave 3.4 g. of a very pale yellow liquid, octamethylsucrose, with the correct methoxyl content (54.48%) and the following specific rotations for sodium light: 65.5° (chloroform solution; *c*, 1.634; *t*, 26°); 67.6° (methyl alcohol solution; *c*, 5.592; *t*, 25°); 65.6° (acetone solution; *c*, 6.007; *t*, 25°). Haworth[3a] reported 69.3° (methyl alcohol solution; *c*, 7.345) and 66.8° (acetone solution; *c*, 6.782).

In another experiment the partially methylated sample was dissolved in absolute toluene and to the solution sodium wire was added. After the reaction had subsided the mixture was heated on a water-bath at 80° for three hours, then cooled and worked up as described in the previous experiment. A pale yellow liquid with 54.37% methoxyl was isolated.

All the methoxyl estimations were carried out by the method of Viebock and Schwappach[10] as modified by Clark.[11]

Summary

1. Combination of the Haworth methylation process with a slightly modified method of Freudenberg and Hixon is recommended for prepa-

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(7) Purdie and Irvine, *J. Chem. Soc.*, **87**, 1028 (1905).

(8) Haworth and Mitchell, *ibid.*, **123**, 309 (1923).

(9) Irvine and Stiller, THIS JOURNAL, **54**, 1486 (1932).

(10) Viebock and Schwappach, *Ber.*, **63**, 2818 (1930).

(11) Clark, *J. Assoc. Official Agr. Chem.*, **15**, 136 (1932).

ration of fully methylated carbohydrates or derivatives which contain primary hydroxyl groups.

2. Detailed description of the procedure is given for the exhaustive methylation of sucrose.

[CONTRIBUTION FROM THE FRICK CHEMICAL LABORATORY OF PRINCETON UNIVERSITY]

The Acetone Derivatives of the Mercaptals of Some Monosaccharides. IV.[1] The 4,5-Monoacetone Derivative of the Dibenzylmercaptal and of the Dimethylacetal of d-Galactose

BY EUGENE PACSU, S. M. TRISTER[2] AND JOHN W. GREEN

Fifteen years ago it was shown by Pacsu[1] that new isomers of partially methylated hexoses could be obtained by a series of reactions in which the sugar mercaptals should first be converted into their di- and monoacetone derivatives. Subsequent methylation of the free hydroxyl group or groups would yield compounds which on deacetonylation and removal of the mercaptan residues would give rise to the respective mono- and trimethyl sugars. The exact positions of the methyl groups once determined, the structure of the intermediate acetone derivatives would be known. On the other hand, the knowledge of the positions of the acetone residues would determine the structure of the methylated sugars. At that time it appeared that the elucidation of the structure of the methylated sugars rather than that of the intermediate acetone derivatives was more feasible since methods for removal of the mercaptan residues without simultaneous hydrolysis of the acetone groups were unknown. Direct determination of the positions of the methyl groups in partially methylated sugars fifteen years ago presented almost insurmountable difficulties mainly due to the lack of suitable experimental methods. It was customary, therefore, to assign the structure of newly discovered partially methylated sugars by taking recourse to the method of elimination and to other indirect procedures. However, conclusions based on such negative evidence are usually valid only as long as the accepted structural formulas of the eliminated compounds remain unchanged. In the special field of partially methylated sugars new interpretation of some old experimental results became necessary after Brigl and Schinle discovered[3] that the true

2-methyl glucose[4] was capable of osazone formation with the loss of the methyl group. This striking discovery cast doubt on the structure of those partially methylated sugars the formulas of which previously had been assigned on the assumption, till then unquestioned, that a 2-methyl aldose could not possibly form an osazone. Among those partially methylated sugars affected by this discovery were the assumed 4-methyl sugars and all their mercaptal and acetonylated mercaptal derivatives previously described.[1] As was pointed out by Pacsu,[5] the assignment of position 4 to the methyl group in the new monomethyl glucose was left as the only possibility at the time when the compound was discovered, because a 2-methyl glucose with entirely different properties had been described already both by Pictet[6] and by Irvine.[7] Since Levene and co-workers[8] noticed that this supposed 4-methyl glucose was identical with the true 2-methyl glucose of Brigl, it followed that all the previous conclusions based on an unquestioned existence of the 2-methyl glucose of Pictet and of Irvine became necessarily invalid. In the light of these facts, therefore, a reinvestigation of the entire problem was begun and in the present paper the results concerning the structure of one of the monoacetone galactose mercaptals are presented.

In a preliminary communication[9] it was reported that the formerly described[1c] crystalline "2,3-monoacetone galactose dibenzylmercaptal" with m. p. 102–103° and $[\alpha]^{18}D$ 8.8° in acetylene tetrachloride solution, in spite of its apparent uniformity, is not a chemical individual. By repeated fractional recrystallization from acetone

(1) (a) Part I, Pacsu, Ber., 57, 849 (1924); (b) Part II, Pacsu and von Kary, ibid., 62, 2811 (1929); (c) Part III, Pacsu and Löb, ibid., 62, 3104 (1929); cf. (d) Pacsu, ibid., 58, 1455 (1925).

(2) Research Assistant on Special Funds from the Rockefeller Foundation.

(3) Brigl and Schinle, Ber., 62, 1716 (1929).

(4) Brigl and Schinle, ibid., 63, 2884 (1930).

(5) Pacsu, ibid., 65, 51 (1932).

(6) Pictet and Castan, Helv. Chim. Acta, 3, 645 (1920).

(7) Irvine, J. Chem. Soc., 125, 1 (1924).

(8) Levene, Meyer and Raymond, J. Biol. Chem., 91, 497 (1931); cf. Science, 73, 291 (1931).

(9) Pacsu, THIS JOURNAL, 58, 2076 (1936).