tylation of the swelling impregnant is an essential step: (1) The acetylation at 95° of cellulose impregnated with urea:ammonium sulfate follows the same course as the acetylation of urea in the presence of ammonium sulfate or sulfuric acid at about 100°; *i.e.*, there is an induction period of several minutes and then a sudden, vigorous reaction.[6] A sample of cellulose removed from the mixture after 14 minutes in the procedure for acetylation at 95° (near the end of the induction period, before the rapid change in appearance) was found to contain only 0.27 Ac/G.U., or 9% of the triacetate acetyl content. (2) Salts of tertiary amines, which cannot be acetylated, are inactive swelling impregnants.

The following points can be made for the thesis that acetylation of the swelling impregnant is not an essential step: (1) Diethylene glycol diethyl ether, which contains no free hydroxyl groups, is an active swelling impregnant. To see whether diethylene glycol diethyl ether would be degradatively acetylated under the conditions used in acetylation of cellulose, diethylene glycol diethyl ether, ammonium sulfate and excess acetic anhydride were heated together at 138° for five minutes. No ethyl acetate was isolated, and the amount of saponifiable material (not identified) distilling with unchanged ether at the boiling point of ethylene glycol diacetate corresponded to a 4% yield of this ester. (2) The apparent inactivity of carboxylic acid salts of tertiary amines and quaternary ammonium hydroxides as swelling impregnants may actually be due to the real inactivity of the corresponding sulfates as catalyst inpregnants. Thus, when the water in a solution containing 38% triethylamine acetate and only 2% ammonium sulfate is evaporated from cellulose, most of the sulfate may be left behind as triethylamine sulfate (an inactive catalyst impregnant). A corresponding metathesis might take place in a 38:2 benzyltrimethylammonium acetate:ammonium sulfate mixture.

Acknowledgment.—I am indebted to Dr. M. L. Ernsberger for many helpful discussions and suggestions in connection with this work.

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(6) R. C. Blume, private communication; see also E. A. Werner, *J. Chem. Soc.*, 1120 (1916).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE OHIO STATE UNIVERSITY]

Selective Hydroxyl Reactivity in Methyl α-D-Glucopyranoside[1]

BY M. L. WOLFROM AND M. A. EL-TARABOULSI[2]

RECEIVED JUNE 10, 1953

Following the general technique of Gaver, methyl monosodio-α-D-glucopyranoside was prepared. On methylation, this produced the 2-methyl ether, characterized as the crystalline triacetate. Benzylation gave a sirup in which the presence of an open glycol group was demonstrated by periodate cleavage. Xanthation of the monosodium derivative was not possible without the addition of small amounts of water but thereupon yielded the 2-(methyl xanthate), characterized as the crystalline triacetate. Although these reactions proceeded in low yield, it is believed that they are best interpreted as indicating that, in the main, the sodium formed a true alkoxide at position two of the glucoside which then reacted by replacement to yield derivatives substituted in this position.

The question of a possible selective reactivity of the hydroxyl groups of the D-glucopyranoside structure is of interest both from the synthetic and theoretical points of view. The enhanced reactivity of the 2-hydroxyl function as compared to that of other secondary hydroxyl groups, in carbohydrates, has been noted primarily in reactions requiring alkaline media. This effect is probably a result of the greater acidity of the hydrogen on the hydroxyl group adjacent to a carbonyl or to a potential carbonyl group. The preparation of 2-O-methyl-D-glucose diethyl thioacetal (mercaptal) by Lieser and Leckzyck[3] and of 2-O-methyl-starch by Gaver[4] constitute examples of the selective reactivity of the 2-hydroxyl in reactions requiring alkaline media.[5] Alkali and alkaline earth hydroxides appear to form "addition complexes" with sugars and polysaccharides.[6,7] These have been scrutinized by Percival and collaborators[8] to determine at what points the base was bound. They concluded that the various sugars behave rather differently but show a common feature in that positions 2 and 6 are especially capable of reaction. These addition compounds are unstable and while they are much utilized in the cellulose field, this instability is undesirable.[9] Gaver,[4] however, in his studies on the action of alkali on starch in non-aqueous media, was able to prepare a monosodium "starchate" which had a true alkoxide structure and in which the sodium had largely replaced the hydrogen of the 2-hydroxyl. Following Gaver's work, Sugihara and Wolfrom[10] prepared a monosodiocellulosate in which the sodium was mainly on the second position of each anhydro-D-glucose unit. The purpose of the present investigation was to extend Gaver's monoalkala-

(1) Presented before the XIIIth International Congress of Pure and Applied Chemistry, Stockholm, Sweden, August 1, 1953.

(2) Fellow of the Egyptian Government.

(3) T. Lieser and E. Leckzyck, *Ann.*, **511**, 137 (1934).

(4) K. M. Gaver, Dissertation, The Ohio State University, 1945; U. S. Patents 2,397,732 (1946), 2,518,135 (1950), 2,609,368 (1952); *Abstracts Papers XIIth Intern. Congr. Pure and Appl. Chem.*, 623 (1951); K. M. Gaver, Esther P. Lasure and D. V. Tieszen, U. S. Patent 2,572,923 (1951); K. M. Gaver, Esther P. Lasure and L. M. Thomas, U. S. Patents 2,602,084 and 2,609,367 (1952).

(5) For a review on the selective reactivities of the hydroxyl groups in carbohydrates, see J. M. Sugihara, *Advances in Carbohydrate Chem.*, **8**, in press.

(6) J. Groot, *Biochem. Z.*, **180**, 341 (1927).

(7) J. E. Mackenzie and P. J. Quin, *J. Chem. Soc.*, 951 (1929).

(8) W. J. Heddle and E. G. V. Percival, *ibid.*, 1690 (1938); E. G. V. Percival, *ibid.*, 1160 (1934); 648 (1935); E. G. V. Percival and G. G. Ritchie, *ibid.*, 1765 (1936).

(9) Z. H. Skraup and R. Kremann, *Monatsh.*, **22**, 1037 (1901).

(10) J. M. Sugihara and M. L. Wolfrom, THIS JOURNAL, **71**, 3509 (1949).

tion reaction to the α-D-glucopyranoside structure and, in particular, to the synthesis of methyl monosodio-α-D-glucopyranoside, to establish the point of attachment of the sodium and to investigate the potentialities of the new compound for synthetic purposes.

The reaction of one mole of methyl α-D-glucopyranoside with 1.25 moles of sodium hydroxide in anhydrous 1-butanol led to the introduction of nearly one equivalent of base for each mole of methyl α-D-glucopyranoside. The removal from the product of the small amount (8%) of unreacted methyl α-D-glucopyranoside and of any adsorbed sodium hydroxide was not experimentally feasible.

The reaction of methyl monosodio-α-D-glucopyranoside with methyl iodide led to the formation besides an unreacted or possibly hydrolyzed (by moisture) portion (15%) of the starting material, of methyl 2-O-methyl-α-D-glucopyranoside which was isolated as methyl 3,4,6-tri-O-acetyl-2-O-methyl-α-D-glucopyranoside by a chromatographic procedure. Although the yields were low, no other crystalline compounds were isolable.

The xanthation of methyl monosodio-α-D-glucopyranoside with carbon disulfide under anhydrous conditions was not possible. Water was required as a catalyst. This finding is in agreement with the work of Berl and Bitter,[11] Scherer and Gotsch[12] and others, who have shown that the reaction of dry polyhydric alkoxides with carbon disulfide either does not proceed at all or proceeds very slowly. The xanthation product was then investigated to locate the position of the xanthate group. The sodium xanthate derivative was converted,[13] through the silver salt, to its methyl ester which was definitely characterized as the known[13] methyl α-D-glucopyranoside 3,4,6-triacetate 2-(methyl xanthate). The over-all yield of the methyl tri-O-acetyl-α-D-glucopyranoside 2-(methyl xanthate), which was obtained in four steps, was very low (3%). This low yield was due to the hydrolysis of the methyl monosodio-α-D-glucopyranoside by the water in the xanthation reaction and to the losses due to the undesirable side reactions effected by the action of silver nitrate on the xanthate.[13]

Methyl monosodio-α-D-glucopyranoside, which is very simple to prepare, would appear to have definite potentialities for synthetic purposes, particularly in cases where the desired 2-substituted derivatives are difficult to obtain. A typical illustration is the synthesis, as a chromatographed sirup, of what is believed to be a new methyl 2-O-benzyl-α-D-glucopyranoside, obtained by treating methyl monosodio-α-D-glucopyranoside with benzyl chloride. Its chromatographed triacetate was likewise a sirup. The monobenzyl ether of the glucoside consumed one mole of periodate (per mole of glucoside derivative), thus limiting its structure to that of methyl 2- or 4-O-benzyl-α-D-glucopyranoside with the latter being considered highly improbable.

(11) E. Berl and J. Bitter, *Cellulosechem.*, **7**, 137 (1926).

(12) P. C. Scherer, Jr., and L. P. Gotsch, *Bull. Virginia Polytech. Inst., Eng. Expt. Sta. Series Bull.*, No. **39**, 3 (1939); *C. A.*, **34**, 259 (1940).

(13) T. Lieser and E. Leckzyck, *Ann.*, **519**, 279 (1935).

Experimental

Methyl Monosodio-α-D-glupyranoside.—A hot solution of 3.86 g. (1.25 molar ratio) of powdered anhydrous sodium hydroxide in 110 ml. of 1-butanol was added under mechanical stirring, to a warm solution of 15 g. of dry methyl α-D-glucopyranoside in 110 ml. of 1-butanol. An immediate exothermic reaction was initiated and distillation of the 1-butanol–water azeotrope was effected through a 12-cm. Vigreux column with a temperature at its top of 80–95°. Distillation was continued for 3.5 hr. with additional 75-ml. amounts of 1-butanol being added at 45-min. intervals. The precipitated reaction product was quickly removed by filtration through sintered glass, washed with 500 ml. of abs. ether and dried in a vacuum desiccator; yield 16 g. (96%).

Anal. Na, 0.92 equiv. per glycoside unit (by acidimetry).

Methylation of Methyl Monosodio-α-D-glucopyranoside.—An amount of 5 g. of finely ground methyl monosodio-α-D-glucopyranoside and 20 ml. of methyl iodide were heated in a sealed tube for 3 hr. at 95 ± 5°. The contents of the tube were dissolved in ethanol and treated in the warm with an excess of silver carbonate followed by filtration (carbon). Solvent removal, under reduced pressure, from the filtrate yielded a residue from which sodium carbonate was separated by adding 20 ml. of 100% ethanol followed by filtration. A colorless sirup was obtained on solvent removal under reduced pressure; yield 2.5 g. (47%). Trituration of the sirup with 100% ethanol followed by the addition of ethyl acetate, led to the crystallization of methyl α-D-glucopyranoside; yield 0.7 g. (14%, basis initial starting material), m.p. 164–166°, $[\alpha]^{24}D$ +158° (*c* 0.5, water).

An amount of 1.1 g. of the residual mother liquor sirup was acetylated for 20 hr. at 0° with pyridine (2.6 ml.) and acetic anhydride (2.5 ml.). The sirupy product that formed on pouring the reaction mixture onto ice and water, was extracted with chloroform and washed successively with aqueous solutions of cadmium chloride and sodium carbonate, and finally with water. A sirup was obtained on solvent removal under reduced pressure; yield 1.12 g. (63.5%). This sirup was dissolved in 50 ml. of benzene and added to the top of a 17.5 × 4.5 (diam.) cm.[14] of Magnesol[15]–Celite[16] (5:1 by wt.) and the chromatogram was developed with 400 ml. of benzene–(*t*-butyl alcohol) (200:1 by vol.). The permanganate indicator (1% potassium permanganate in 2.5 *N* sodium hydroxide) streak located a main zone, on the extruded column, 0–78 mm. from the top. Elution with acetone yielded a sirup (0.85 g., 76%) which partially crystallized; yield (of crystals) 140 mg. (12.5%), m.p. 120–121°, $[\alpha]^{22}D$ +149° (*c* 0.8, chloroform) in agreement with those (120° and 145°) cited[17] for methyl 3,4,6-tri-O-acetyl-2-O-methyl-α-D-glucopyranoside.

Anal. Calcd. for $C_{12}H_{16}O_7(OCH_3)_2$: OCH_3, 18.56. Found: OCH_3, 18.59.

Xanthation of Methyl Monosodio-α-D-glucopyranoside.—No apparent reaction took place when 6.7 g. of dry, finely ground methyl monosodio-α-D-glucopyranoside was mechanically shaken in 120 ml. of carbon disulfide for 24 hr. at room temperature. Reaction was effected by adding portionwise over 6 hr. a total amount of 0.8 ml. of water. After 3 hr. of further shaking, the excess solvent was decanted and the sticky, brownish-red xanthate was dissolved in 100 ml. of 1.5% barium hydroxide. A rapid stream of carbon dioxide gas was passed into this solution at 0° for 30 min. and the resultant reaction mixture was filtered. Slow addition, under stirring and at 0°, of 300 ml. of cold 0.05 *M* silver nitrate, precipitated the silver salt which was removed by centrifugation. Addition of a further amount, 130 ml., of cold of the silver nitrate solution to the centrifugate yielded more silver salt which was combined with the other, washed by centrifugation with cold water and shaken, while moist, for 6 hr. at room temperature with 2.6 ml. of methyl iodide. The filtered (carbon) xanthate solution was concentrated under reduced pressure to a sirup which was

(14) Adsorbent dimensions.

(15) A hydrated magnesium acid silicate produced by the Westvaco Chemical Division of the Food Machinery and Chemical Corp., South Charleston, W. Va.

(16) No. 535, a siliceous filter-aid produced by the Johns-Manville Co., New York, N. Y.

(17) W. N. Haworth, E. L. Hirst and Ethel G. Teece, *J. Chem. Soc.*, 2858 (1931).

treated with ethyl acetate–(petroleum ether) and filtered. Crystallization was effected on concentration in a stream of dry air; yield of crude methyl α-D-glucopyranoside 2-(methyl xanthate),[13] 750 mg. (9.2%).

An amount of 446 mg. of the above product was acetylated at 0° for 20 hr. with pyridine (1 ml.) and acetic anhydride (1 ml.). The sirupy product obtained on pouring the reaction mixture into an excess of ice and water was separated by decantation and crystallized from methanol–water; yield 255 mg. (30%) of beautiful needle crystals, m.p. 72–73° undepressed on admixture with an authentic specimen of methyl α-D-glucopyranoside 3,4,6-triacetate 2-(methyl xanthate) of like melting point, $[\alpha]^{27}D$ +126° (*c* 2.81, 95% ethanol). Lieser and Leckzyck[13] cite the m.p. 75–76° and record no rotation.

Benzylation of Methyl Monosodio-α-D-glucopyranoside.—An amount of 5 g. of dry methyl monosodio-α-D-glucopyranoside was shaken with 90 ml. of benzyl chloride for 24 hr. at 90 ± 5°. The excess benzyl chloride was removed by steam distillation and the residual sirup, separated by decantation, was treated with 50 ml. of ethanol and filtered. Solvent removal under reduced pressure gave a sirup; yield 3.6 g. (55%).

An amount of 0.56 g. of the above sirup was dissolved in 50 ml. of 100% ethanol and added to the top of a 17.5 × 4.5 (diam.) cm.[14] column of Florex XXX[18]–Celite[16] (5:1 by wt.) and the chromatogram was developed with 100 ml. of ethanol–water (100:3 by vol.). The extruded column was wrapped with aluminum foil to leave an exposed area 15 mm. wide along the length of the column and after 24 hr. the dried exposed area was streaked with the permanganate indicator. Solvent removal from an eluted (with acetone) second zone (from the column top) appearing near the middle of the column, gave a light brown sirup; yield 0.11 g. (20%).

Anal. Calcd. for $C_7H_{13}O_5(OCH_2C_6H_5)$: C, 58.74; H, 7.04. Found: C, 58.62; H, 7.06; periodate assay (moles per mole of reductant, 0.05 *M* $NaIO_4$ in 0.002 *M* reductant, 25 ± 2°, extrapolated value, few min. required for complete reaction): oxidant consumed, 1.0; formic acid, absent; formaldehyde, absent.

An amount of 1.0 g. of the above original (not chromatographed) sirup was acetylated with pyridine (3.5 ml.) and acetic anhydride (3.5 ml.) at 0° for 24 hr. The product (0.64 g., 44%) was chromatographed on a 17.5 × 4.5 (diam.) cm. column of Magnesol–Celite (5:1) and developed with 600 ml. of benzene–(*t*-butyl alcohol) (200:1). The acetone eluate material from the main upper zone was a sirup; yield 0.52 g. (81%).

Anal. Calcd. for $C_{20}H_{26}O_9$: C, 58.53; H, 6.34. Found: C, 58.30; H, 6.57.

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(18) A fullers earth type of clay produced by the Floridin Co., Warren, Pa.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND THE DEPARTMENT OF OBSTETRICS AND GYNECOLOGY, COLLEGE OF MEDICINE, NEW YORK UNIVERSITY]

The Synthesis of 17β-Estradiol-16-C^{14}

BY MORTIMER LEVITZ

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A method for the preparation of labeled dimethylmarrianolate methyl ether is described. Ring closure of this compound by the acyloin condensation and reduction of the C_{16}-carbonyl group gives 17β-estradiol-3-methyl ether-16-C^{14}. Demethylation with pyridine hydrochloride results in 17β-estradiol-16-C^{14}.

A study of the metabolism of an estrogen and its relation to cancer can be facilitated by the use of a compound labeled with radioactive carbon. Accordingly, the synthesis of labeled 17β-estradiol, the physiologically most potent estrogen,[1] was undertaken in this Laboratory.

To our knowledge, the only previous method available was that of Heard.[2] Briefly, ring D in estrone is oxidatively cleaved[3] to marrianolic acid. It is reconstituted essentially by the method of Litvan and Robinson,[4] involving the use of diazomethane-C^{14} in the Arndt–Eistert reaction to extend the side chain of marrianolic acid and results in estrone-16-C^{14}. Finally, reduction with lithium aluminum hydride[5] gives 17β-estradiol-16-C^{14} (I).

We wish to report a novel synthesis which affords I in good yield, avoids the use of diazomethane-C^{14} and allows the direct utilization of the readily available and relatively inexpensive $C^{14}O_2$.

With dimethylmarrianolate methyl ether (II)[2,3] serving as the starting material for the introduction of C^{14}, the method of Hudson and Hauser[6] for the alkylation of esters using triphenylmethylsodium and alkyl halides was extended to carboxylate, with $C^{14}O_2$, the α-position of the primary ester group. The sodium enolate of II did not undergo intermolecular condensation as is the case with low molecular weight monosubstituted esters. After carboxylation with carbon dioxide (3.43 millicuries/millimole[7]) and saponification the presumed tricarboxylic acid III was obtained. Thermal decarboxylation yielded a mixture consisting chiefly of marrianolic acid anhydride methyl ether, with carbon dioxide (87% of theory, 1.75 millicuries/millimole[8]) being evolved and precipitated as barium carbonate. Treatment with alkali and esterification with diazomethane produced labeled dimethylmarrianolate (IV) in 83% yield (based on barium carbonate). Admixture of II and IV

(1) L. F. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," Reinhold Publishing Corp., New York, N. Y., 1949, p. 329.

(2) R. D. H. Heard, J. Saffran and L. Thompson, private communication.

(3) J. Heer and K. Miescher, *Helv. Chim. Acta*, **28**, 156 (1945).

(4) F. Litvan and R. Robinson, *J. Chem. Soc.*, 1997 (1939).

(5) G. Papineau-Couture, E. M. Richardson and C. A. Grant, *Can. J. Research*, **27B**, 902 (1949).

(6) B. E. Hudson and C. R. Hauser, THIS JOURNAL, **62**, 2457 (1940).

(7) Assays for radioactivity were performed by Tracerlab, Inc., Boston, Mass.

(8) The two carboxyl groups of the malonic acid fragment of III are chemically indistinguishable. Consequently, except for isotope effects (P. E. Yankwich and M. Calvin, *J. Chem. Phys.*, **17**, 109 (1949); J. Bigeleisen, *ibid.*, **17**, 425 (1949)) the molar specific activities of C^{14} in the precipitated barium carbonate and either in IV or each succeeding compound should be identical. The values obtained 1.75 for barium carbonate and 1.66 for I are in good agreement. No statement can be made concerning the apparent reverse isotope effect because information on the homogeneity of III is unavailable.