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Partial Esterification of Methyl 4,6-*O*-Benzylidene-α-D-glucopyranoside in Pyridine Solution[1]

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Partial esterification of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside in pyridine solution with chlorides of carboxylic and sulfonic acids gave the monoester in position 2 in preponderant yield. When anhydrides were used for partial esterification, the carboxylic anhydrides gave the monoester in position 3 in preponderant yield, whereas the sulfonic anhydrides gave the monoester in position 2.

In order to study the influence of neighboring groups on the solvolysis of sulfonyl esters of glucose,[2] it has been necessary to prepare the various acetyl, benzoyl, methylsulfonyl and *p*-tolylsulfonyl derivatives of methyl 4,6-*O*-benzylidene-α-D-glucoside (I) reported in Fig. 1.

While this work was being completed, the preparation of some of the derivatives described here was reported either by different methods, or with quite different yields. Bourne, *et al.*,[3,4] have described the preparation of the partially substituted acetates III and IV and benzoates VI and VII using trifluoroacetyl intermediates. Since the preparation of the intermediates makes this method quite lengthy, the reagent is expensive and the yields starting from I are not excellent (III, 41%; IV, 38%; VI, 26%; VII, 41%), it seemed of interest to investigate the direct partial acetylation and benzoylation of I.

Monobenzoylation and mono-*p*-toluenesulfonylation of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (I) using the acid chlorides in pyridine solution have been described previously. Although Ohle and Spencker[5] reported that the hydroxyls in position 2 and 3 reacted at the same speed, and that they could not obtain a monoderivative, Robertson and Griffith[6] obtained the 2-*O*-*p*-tolylsulfonyl derivative, isolated as derivative XIX, in a 20% yield. Bolliger and Prins,[7] using a chromatographic separation, were able to increase the yield of XVII to 60 to 70%. Robertson and Griffith[6] reported that monobenzoylation was difficult to control and gave poor and not reproducible yields. The 2-*O*-benzoyl derivative VI was obtained in a 9% yield, after isolation as 2-*O*-benzoyl-3-*O*-*p*-tolylsulfonyl derivative XXI. In both esterifications the reaction in position 2 was preponderant. After completion of the work described here, the preparation of the 2-*O*-methylsulfonyl derivative XI from I using two intermediate steps was reported.[8]

Repetition of Robertson and Griffith's procedure,[6] consisting of a partial benzoylation of I followed by a *p*-toluenesulfonylation, gave a mixture of products quite complex, as the known methyl 2,3-di-*O*-benzoyl-4,6-*O*-benzylidene-α-D-glucoside (V) and methyl 2,3-di-*O*-*p*-tolylsulfonyl-4,6-*O*-benzylidene-α-D-glucoside (XVI) were isolated in addition to the 2-*O*-benzoyl-3-*O*-*p*-tolylsulfonyl derivative XXI already described by Robertson and Griffith. Consequently it was thought of interest to study separately each step of the reaction. The results of the monoesterification of I by various reagents under various conditions of temperature are reported in Table I.

When methyl 4,6-*O*-benzylidene-α-D-glucoside (I) was treated with acetic anhydride, most of the substitution took place in position 3 intead of position 2, as expected. From the 3-*O*-acetyl derivative IV, almost quantitative yields of the 2-*O*-methylsulfonyl XII and 2-*O*-*p*-tolylsulfonyl XVIII derivatives were obtained.

The preferential reaction of the carboxylic anhydride with position 3 as observed with acetic anhydride, was confirmed using benzoic anhydride, and from the 3-*O*-benzoyl derivative VII the 2-*O*-acetyl derivative VIII was obtained. However, all attempts at obtaining a 3-*O*-*p*-tolylsulfonyl derivative, using *p*-toluenesulfonic anhydride alone or in presence of bases like dimethylamine, were unsuccessful. Likewise, only the 2-*O*-methylsulfonyl derivative XI could be isolated, besides the dimesyl derivative X from the reaction of I with methanesulfonyl anhydride. In the latter case, the yields in crystalline material were much lower than when using methanesulfonyl chloride and in this case substitution of the anhydride for the chloride had not the advantage found by Linstead, Owen and Webb.[9]

Esterification with acid chlorides took place in position 2, as reported previously. However, acetylation with acetyl chloride did not afford a good yield in crystalline material and the best yield of 2-*O*-acetyl derivative III was obtained when the reaction was carried out at room temperature with acetic anhydride in presence of pyridinium chloride. From III, the 3-*O*-benzoyl VIII, the 3-*O*-methylsulfonyl XIV and 3-*O*-*p*-tolysulfonyl XX derivatives were obtained.

The best yield in 2-*O*-benzoyl derivative VI was

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(2) R. W. Jeanloz and D. A. Jeanloz, manuscript in preparation.

(3) E. J. Bourne, M. Stacey, C. E. M. Tatlow and J. C. Tatlow, *J. Chem. Soc.*, 826 (1951).

(4) E. J. Bourne, A. J. Huggard and J. C. Tatlow, *ibid.*, 735 (1953).

(5) H. Ohle and K. Spencker, *Ber.*, **61**, 2387 (1928).

(6) G. J. Robertson and C. F. Griffith, *J. Chem. Soc.*, 1193 (1935).

(7) H. R. Bolliger and D. A. Prins, *Helv. Chim. Acta*, **28**, 465 (1945).

(8) J. Honeyman and J. W. W. Morgan, *J. Chem. Soc.*, 3660 (1955).

(9) R. P. Linstead, L. N. Owen and R. F. Webb, *ibid.*, 1225 (1953).

TABLE I

ESTERIFICATION OF METHYL 4,6-*O*-BENZYLIDENE-α-D-GLUCOPYRANOSIDE IN PYRIDINE SOLUTION

Reagent	Amount of reagent, moles	Temp., °C. Initial	Final	Crystalline derivatives isolated in % 2,3-Diester	2-Ester	3-Ester	Starting material
$(CH_3CO)_2O$	1.25	20–30	20–30	26	3[b]	42	7
$(C_6H_5CO)_2O$	1.10	20–30	20–30	9	13	25	23
	1.10[a]	50	50	22	12	22	15
$(CH_3SO_2)O$	1.1	0	0	6	40		3
		0	20–30	8	34		4
		−20	0	5	36		22
$(CH_3C_6H_4SO_2)O$	1.1	20–30	20–30	15[b]	80–85[b]		
$(CH_3CO_2)O + C_5H_5N\cdot HCl$	1.05	0	20–30	21	30	5	16
CH_3COCl	1.25	0	0	23	16		3
C_6H_5COCl	1.25[a]	0	0	35	24	6	12
CH_3SO_2Cl	1.1	0	20–30	16	68		

Reaction time one day, except for experiments marked [a] five days. [b] Crude material.

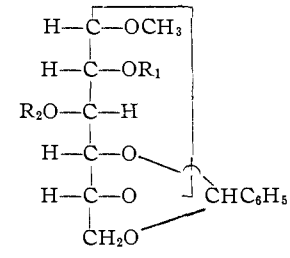
obtained when the reaction was started at −10°, carried out for some time at 0°, and finally at room temperature. Starting from VI, the 3-*O*-acetyl IX, 3-*O*-methylsulfonyl XV and 3-*O*-*p*-tolysulfonyl XXXI derivatives were prepared in an almost quantitative yield.

Methanesulfonylation was carried out with methanesulfonyl chloride added at 0° and the reaction left to proceed at room temperature. The results were very similar to the ones obtained by Bolliger and Prins[7] in the *p*-toluenesulfonylation procedure. Starting from the 2-*O*-methylsulfonyl derivatives XI, the 3-*O*-acetyl XIII and 3-*O*-benzoyl XIII derivatives were prepared in almost theoretical yield.

Bourne and co-workers[3,4] concluded that the 3-*O*-acetyl, 3-*O*-benzoyl and 3-*O*-trifluoroacetyl derivatives of I were stable, though the 2-*O*-*p*-tolylsulfonyl ester is formed preferentially. However, this finding was based on a reaction carried out in strongly alkaline aqueous solution. In dry or wet pyridine, the 2-benzoyl derivative was stable.

The experiments described here show that the relative reactivity of the positions 2 and 3 of I greatly depends on the number of protons present in the reaction medium, either by external addition, or by release during the reaction. When formed, the esters are stable under the conditions of the reaction, as no migrations of the 2-benzoyl under the action of pyridine,[4] or of the 3-acetyl under the action of pyridinium chloride are observed. However, displacement of the less stable ester by a competing grouping was observed in the isolation of some methyl 2-*O*-*p*-tolylsulfonyl-3-*O*-acetyl-4,6-*O*-benzylidene-α-D-glucoside (XX) after reaction of methyl 2-*O*-acetyl-4,6-*O*-benzylidene-α-D-glucoside (III), with *p*-toluenesulfonyl chloride. This result does not support Bourne's suggestion that acetic anhydride in presence of pyridine causes migration of ester whereas *p*-toluenesulfonyl chloride in the same medium is without effect. While displacement was observed with the latter reagent, as described above, no migration was ever seen during acetylation of the 2-*O*-benzoyl VI and 3-*O*-benzoyl VII derivatives.

While the influence of the other groupings (methyl and benzylidene) on the difference in reactivity of positions 2 and 3 cannot be estimated alone, conformation plays certainly a role. This is shown by the isolation in preponderant yield of the 3-*O*-*p*-tolylsulfonyl and 3-*O*-benzoyl esters after reaction of methyl 4,6-*O*-benzylidene-α-D-galactopyranoside with *p*-toluenesulfonyl chloride and benzoyl chloride respectively,[10] whereas benzoylation of methyl 4,6-*O*-benzylidene-α-D-altropyranoside with benzoic anhydride[2] gave only the 2-*O*-benzoyl derivative.



	R_1	R_2
I	H	H
II	CH_3CO	CH_3CO
III	CH_3CO	H
IV	H	CH_3CO
V	C_6H_5CO	C_6H_5CO
VI	C_6H_5CO	H
VII	H	C_6H_5CO
VIII	CH_3CO	C_6H_5CO
IX	C_6H_5CO	CH_3CO
X	CH_3SO_2	CH_3SO_2
XI	CH_3SO_2	H
XII	CH_3SO_2	CH_3CO
XIII	CH_3SO_2	C_6H_5CO
XIV	CH_3CO	CH_3SO_2
XV	C_6H_5CO	CH_3SO_2
XVI	$CH_3C_6H_4SO_2$	$CH_3C_6H_4SO_2$
XVII	$CH_3C_6H_4SO_2$	H
XVIII	$CH_3C_6H_4SO_2$	CH_3CO
XIX	$CH_3C_6H_4SO_2$	C_6H_5CO
XX	CH_3CO	$CH_3C_6H_4SO_2$
XXI	C_6H_5CO	$CH_3C_6H_4SO_2$

FIG. 1.

These results are not in agreement with the generalization that 2-hydroxyl groups of carbohydrates are more reactive than other secondary hydroxyl groups, especially in alkaline media.[11]

(10) E. Sorkin and T. Reichstein, *Helv. Chim. Acta*, **28**, 1 (1945); M. Gyr and T. Reichstein, *ibid.*, **28**, 226 (1945).

(11) J. M. Sugihara, *Advances in Carbohydrate Chem.*, **8**, 1 (1953).

Studies on a number of different carbohydrates besides glucose, using a variety of conditions, should be undertaken before general concepts are evolved.

Experimental[12]

Acetylation of Methyl 4,6-*O*-Benzylidene-α-D-glucopyranoside (I) with Acetic Anhydride.—To a solution of 10.0 g. of I in 20 ml. of anhydrous pyridine was added 4.2 ml. (1.25 moles) of acetic anhydride. After standing at room temperature for 24 hours, ice was added and the mixture extracted with chloroform. The organic phase was washed five times with ice-cold 2 *N* sulfuric acid, three times with saturated sodium bicarbonate and then water, and dried over sodium sulfate. After evaporation *in vacuo*, the resulting partially crystalline sirup (12.2 g.) was dissolved in benzene, an equal volume of hexane added, and chromatographed on 250 g. of silicic acid. A mixture of benzene and ether 19:1 eluted methyl 2,3-di-*O*-acetyl-4,6-*O*-benzylidene-α-D-glucopyranoside (II). After recrystallization, it melted at 109–110°, showing a rotation of $[\alpha]^{24}D$ +72 ± 1° (in chloroform, *c* 1.04)[13] and weighed 3.36 g. (26%).

A mixture of benzene and ether 9:1 eluted 0.30 g. (3%) of a crystalline mixture in which methyl 2-*O*-acetyl-4,6-*O*-benzylidene-α-D-glucopyranoside (III) (see below) was predominant. Mixtures of benzene and ether 4:1, 2:1, 1:1 and pure ether, eluted **methyl 3-*O*-acetyl-4,6-*O*-benzylidene-α-D-glucopyranoside** (IV). Crystallization from a mixture of acetone, ether and pentane gave 4.78 g. (42%) of silk-like needles, m.p. 176–177°, $[\alpha]^{23}D$ +114 ± 1° (in chloroform, *c* 0.57).[15] *Anal.* Calcd. for $C_{16}H_{20}O_7$: C, 59.25; H, 6.22. Found: C, 58.95; H, 5.94.

Mixtures of methanol and ether eluted the starting material. After recrystallization, 0.71 g. (7%) was obtained, m.p. 163–165°, showing no depression in admixture with authentic material.

Acetylation of I with Acetyl Chloride.—To a solution of 2.0 g. of I in 5 ml. of anhydrous pyridine was added at 0° 0.63 ml. (1.25 moles) of acetyl chloride. After standing overnight at 0°, the mixture was extracted and purified as described above. After chromatography and crystallization, 0.73 g. (23%) of diacetyl derivative II was obtained and 0.06 g. (3%) of starting material. Elution with mixtures of ether and benzene 4:1 and 2:1 gave crystalline fractions of **methyl 2-*O*-acetyl-4,6-*O*-benzylidene-α-D-glucopyranoside** (III). After crystallization from a mixture of ether and pentane, 0.37 g. (16%) of prismatic needles were obtained, m.p. 133–134°, $[\alpha]^{26}D$ +106 ± 2° (in chloroform, *c* 1.27).[16] *Anal.* Calcd. for $C_{16}H_{20}O_7$: C, 59.25; H, 6.22. Found: C, 59.17; H, 6.22.

Acetylation of I with Acetic Anhydride in Presence of Pyridinium Chloride.—To a solution of 1 ml. of anhydrous pyridine in 20 ml. of dry ether was added dry hydrochloric acid to saturation. After removal of the ether and excess hydrochloric acid, 20 ml. of anhydrous pyridine and 2.0 g. of I were added. After dissolution and cooling at 0°, 0.70 ml. (1.05 moles) of acetic anhydride was added and the solution left at room temperature overnight. After addition of ice, the reaction was worked as described above. The recrystallized 2,3-diacetyl II, 2-acetyl III, 3-acetyl IV derivatives and starting material I were recovered in 21, 30, 5 and 16% yields, respectively.

Benzoylation of I with Benzoyl Chloride.—To a solution of 5.0 g. of I in 5 ml. of anhydrous pyridine cooled at 0° was added slowly 2.0 ml. (1.25 moles) of cooled benzoyl chloride. The solution was left at 0° overnight, and, after addition of ice, was extracted as described above. The residual sirup (7.0 g.) was dissolved in benzene, four volumes of hexane were added, and the solution chromatographed on 200 g. of alumina. Pure benzene and mixtures of benzene and ether, 99:1, 49:1, 19:1 and 9:1, eluted crystalline fractions, which gave after crystallization from a mixture of acetone, ether and pentane 3.00 g. (35%) of methyl 2,3-di-*O*-benzoyl-4,6-*O*-benzylidene-α-D-glucopyranoside (V), m.p. 154°, $[\alpha]^{26}D$ +94 ± 2° (in chloroform, *c* 1.51),[17] and showing no depression in admixture with authentic material.

Mixtures of benzene and ether 4:1, 2:1, 1:1 and pure ether eluted crystalline fractions; crystallization from a mixture of acetone, ether and pentane gave 1.63 g. (24%) of prismatic needles of **methyl 2-*O*-benzoyl-4,6-*O*-benzylidene-α-D-glucopyranoside** (VI), m.p. 169–170° (moistening at 165°), $[\alpha]^{26}D$ +111 ± 2° (in chloroform, *c* 1.64).[18] *Anal.* Calcd. for $C_{21}H_{22}O_7$: C, 65.28; H, 5.74. Found: C, 65.22; H, 5.79. Pure ether, mixtures of ether and ethyl acetate and pure ethyl acetate eluted 3-*O*-benzoyl derivative VII. After crystallization from a mixture of acetone, ether and pentane, 0.42 g. (6%) was isolated, melting at 218–219° and showing no depression with the product isolated below.

Mixtures of ethyl acetate and methanol eluted 0.60 g. (12%) of crude crystalline starting material.

The same reaction was carried out in mixing a solution of 10.0 g. of I in 10 ml. of anhydrous pyridine with a solution of 4.1 ml. of benzoyl chloride (1.0 moles) in 10 ml. of anhydrous pyridine, both previously cooled to −10°. After a few hours at 0°, and overnight at room temperature, the mixture was worked out as described above: 2.15 g. (12%) of crystalline V, 5.90 g. (43%) of crystalline VI, 1.70 g. (8%) of crystalline VII and 2.20 g. (22%) of crystalline starting material was obtained.

Benzoylation of I with Benzoic Anhydride.—A solution of 2.0 g. of I and 1.80 g. (1.1 moles) of benzoic anhydride in 10 ml. of anhydrous pyridine was heated at 50° for 24 hours under moisture protection. After cooling, the mixture was purified by extraction and chromatography, as previously described. After elution of 0.76 g. (22%) of crystallized dibenzoate V and 0.34 g. (12%) of crystallized 2-*O*-benzoyl derivative VI, crystalline fractions were eluted and gave, after crystallization from a mixture of acetone, ether and pentane, 0.61 g. (22%) of **methyl 3-*O*-benzoyl-4,6-*O*-benzylidene-α-D-glucopyranoside** (VII) as long needles, m.p. 219–220°, $[\alpha]^{26}D$ + 34 ± 1° (in chloroform, *c* 1.10).[19] *Anal.* Calcd. for $C_{21}H_{22}O_7$: C, 65.28; H, 5.74. Found: C, 65.13; H, 5.60. In addition, 0.30 g. (15%) of crude starting material was recovered.

When the reaction was carried out at 70°, the yields obtained were approximately the same, whereas at room temperature (25–30°), 9% of V, 13% of VI, 25% of VII and 23% of I were obtained after crystallization.

Methanesulfonylation of I with Methanesulfonyl Chloride.—To a solution of 5.0 g. of I in 15 ml. of anhydrous pyridine, was added a solution of 1.75 ml. (1.3 moles) of methanesulfonyl chloride in 15 ml. of anhydrous pyridine. Both solutions had been previously cooled at 0°. After standing at room temperature for 24 hours, a small amount of ice was added and after 2 hours the solution was extracted with chloroform as described above. The residual sirup (7.15 g.) gave, after crystallization from a mixture of acetone, ether and pentane, 1.75 g. of **methyl 4,6-*O*-benzylidene-2-*O*-methylsulfonyl-α-D-glucopyranoside** (XI), as prismatic needles, m.p. 135–136°, $[\alpha]^{24}D$ +73 ± 1° (in chloroform, *c* 2.22).[20] *Anal.* Calcd. for $C_{15}H_{20}O_8S$: C, 49.99; H, 5.59; S, 8.90. Found: C, 49.91; H, 5.67; S, 8.92.

The mother liquors dissolved in a 1:1 mixture of hexane and benzene were chromatographed on silicic acid. A 1:1 mixture of benzene and ether eluted 1.50 g. of sirupy methyl **4,6-*O*-benzylidene-2,3-di-*O*-methylsulfonyl-α-D-glucopy-**

(12) R. W. Jeanloz, THIS JOURNAL, **76**, 555 (1954). "Silica Gel Davison" grade 923; 100–200 mesh was replaced by the less expensive grade 950; 60–200 mesh, without noticeable change in adsorption. In order to obtain good separations, a fully activated silicic acid was found necessary. When deactivation by contact with moist air occurred, reactivation was obtained by heating to 170–200° (Manufacturer's instructions). The proportion of weight of substance to be adsorbed to weight of adsorbent was 1 to 20–30 for alumina, and 1 to 50–100 for silicic acid. The proportion of weight of substance in g. to volume of fraction of eluent in ml. was 1 to 100. The ratio of diameter to length of the column was 1 to 5 for alumina and 1 to 20 for silicic acid.

(13) Mathers and Robertson[14] reported m.p. 108–109°, $[\alpha]D$ +75.5° (in chloroform).

(14) D. S. Mathers and G. J. Robertson, *J. Chem. Soc.*, 696 (1933).

(15) Bourne, *et al.*,[3] reported m.p. 174°, $[\alpha]^{14}D$ +110° (in chloroform).

(16) Bourne, *et al.*,[3] reported m.p. 133–134°, $[\alpha]^{19}D$ +112° (in chloroform, *c*, 0.86).

(17) Bourne, *et al.*,[4] reported m.p. 151–152°; Ohle and Spencker[5] m.p. 148°, $[\alpha]^{19}D$ +96.81° (in chloroform, *c*, 2.828).

(18) Bourne, *et al.*,[4] reported m.p. 165–166°, $[\alpha]^{21}D$ +109.5° (in chloroform, *c* 2.09).

(19) Bourne, *et al.*,[4] reported m.p. 217–218°, $[\alpha]^{19}D$ +33.5° (in chloroform, *c* 2.55).

(20) Honeyman and Morgan[8] reported m.p. 132–133°, $[\alpha]^{25}D$ +72° (in chloroform, *c* 1.2).

ranoside (X), which crystallized after a few days. Crystallization from a mixture of acetone, ether and pentane gave 1.22 g. (16%) of stout prisms, m.p. 188–190°, $[\alpha]^{26}D$ +49 ± 1° (in chloroform, *c* 1.46).[21] *Anal.* Calcd. for $C_{16}H_{22}O_{10}S_2$: C, 43.83; H, 5.02; S, 14.63. Found: C, 43.97; H, 5.18; S, 14.54.

Elution with a mixture of benzene and ether gave, after recrystallization, an additional crop of methyl 4,6-*O*-benzylidene-2-*O*-methylsulfonyl-α-D-glucopyranoside, 2.63 g., total yield 4.38 g. (68%).

Methanesulfonylation of I with Methanesulfonyl Anhydride.—To a solution of 500 mg. of I in 15 ml. of anhydrous dichloroethane was added 340 mg. (1.1 moles) of methanesulfonyl anhydride.[22] After cooling at 0°, 3 ml. of anhydrous pyridine was added and the mixture was left standing at 0° overnight. Ice was added and the solution was extracted with chloroform and purified by chromatography on silicic acid as previously described. Elution with 9:1 mixtures of benzene and ether gave methyl 4,6-*O*-benzylidene-2,3-di-*O*-methylsulfonyl-α-D-glucopyranoside (X), which after recrystallization from a mixture of acetone, ether and pentane weighed 45 mg. (6%), m.p. 186–188°, $[\alpha]^{24}D$ +51 ± 2° (in chloroform, *c* 1.33), and showed no depression in admixture with the product described above. Elution with mixtures of benzene and ether 4:1 gave 280 mg. of methyl 4,6-*O*-Benzylidene-2-*O*-methylsulfonyl-α-D-glucopyranoside (XI). After recrystallization from a mixture of acetone, ether and pentane, 255 mg. (40%) was obtained, m.p. 133–134°, $[\alpha]^{26}D$ +73 ± 2° (in chloroform, *c* 1.38). It showed no depression with the product described above. Elution with a mixture of ether and methanol 19:1 gave the starting material (15 mg., 3%, after recrystallization).

When mixing took place at 0°, and the reaction carried out at room temperature for 5 days, the yields were 8% for X, 34% for XI and 4% for the starting material. When the reaction was carried out in an excess of pyridine as solvent, extensive decomposition occurred at room temperature; when the mixture was made at −20° and the reaction carried out at 0° for 4 days, only slight decomposition occurred and the yields were 36% for X, 5% for XI and 22% for the starting material.

***p*-Toluenesulfonylation of I with *p*-Toluenesulfonic Anhydride.**—To a solution of 200 mg. of I in 2 ml. of anhydrous pyridine was added 280 mg. of *p*-toluenesulfonic anhydride (1.1 moles).[23] After standing at room temperature overnight and after addition of ice, the mixture was handled as previously described. Besides the 2,3-ditosyl derivative XVI isolated in a 15% crude yield, only methyl 4,6-*O*-benzylidene-2-*O*-*p*-tolylsulfonyl-α-D-glucopyranoside (XVII) (crude yield 80–85%) could be obtained after recrystallization, melting at 151–153°[24] and not showing a depression in admixture with authentic material.

Attempts at *p*-toluenesulfonylation with *p*-toluenesulfonic anhydride in the presence of ethylamine, in pyridine or dichloroethane solution, were unsuccessful.

Methyl 2-*O*-Acetyl-3-*O*-benzoyl-4,6-*O*-benzylidene-α-D-glucopyranoside (VIII) from III.—To a solution of 105 mg. of III in 2 ml. of anhydrous pyridine cooled at −20° was added 0.055 ml. (1.5 moles) of benzoyl chloride. After standing overnight at 0° and 2 hours at room temperature, ice was added and the mixture handled as previously described. The crystalline residue was crystallized from a mixture of ether and pentane to give 133 mg. (95%) of typical rectangular or hexagonal prisms, m.p. 154–155°, $[\alpha]^{25}D$ +24 ± 2° (in chloroform, *c* 1.39). *Anal.* Calcd. for $C_{29}H_{28}O_8$: C, 64.48; H, 5.65. Found: C, 64.33; H, 5.79.

From VII.—To a solution of 100 mg. of VII in 1 ml. of pyridine was added 0.5 ml. of acetic anhydride. After standing overnight at room temperature, the mixture was worked up as usual and gave 106 mg. (95%) of prisms, m.p. 153–154°, showing no depression with the compound described above.

Methyl 3-*O*-Acetyl-2-*O*-benzoyl-4,6-*O*-benzylidene-α-D-glucopyranoside (IX).—A solution of 100 mg. of VI in 1 ml. of anhydrous pyridine was treated with 0.05 ml. of acetic anhydride overnight at room temperature. After the usual work-up, crystallization from a mixture of ether and pentane gave 106 mg. (95%) of needles, m.p. 110–112°, $[\alpha]^{25}D$ +118 ± 2° (in chloroform, *c* 0.69). *Anal.* Calcd. for $C_{23}H_{24}O_8$: C, 64.48; H, 5.65. Found: C, 64.44; H, 5.71.

Methyl 3-*O*-Acetyl-4,6-*O*-benzylidene-2-*O*-methylsulfonyl-α-D-glucopyranoside (XII) from XI.—A solution of 0.75 g. of XI in 2.5 ml. of anhydrous pyridine was treated for one day at room temperature with 1.0 ml. of acetic anhydride. After the usual work-up, crystallization from a mixture of ether and pentane gave 0.79 g. (94%) of prismatic needles, m.p. 125–126°, $[\alpha]^{21}D$ +59 ± 1° (in chloroform, *c* 3.32). *Anal.* Calcd. for $C_{17}H_{22}O_9S$: C, 50.74; H, 5.51. Found: C, 50.29; H, 5.81.

From IV.—To a solution of 1.5 g. of IV in 5 ml. of anhydrous pyridine was added a solution of 0.5 ml. (1.4 moles) of methanesulfonyl chloride in 5 ml. of pyridine, both solutions previously having been cooled at 0°. After standing at room temperature overnight, the mixture was handled as previously described. Crystallization from a mixture of ether and pentane gave 1.82 g. (98%) of needles, m.p. 125–126°, showing no depression in admixture with the material described above.

Methyl 3-*O*-Benzoyl-4,6-*O*-benzylidene-2-*O*-methylsulfonyl-α-D-glucopyranoside (XIII).—To a solution of 0.94 g. of XI in 3 ml. of anhydrous pyridine cooled at 0° was added 0.45 ml. (1.5 moles) of benzoyl chloride. After standing for one day at 0°, the mixture treated as usual, gave after crystallization from a mixture of acetone, ether and pentane, 1.14 g. (94%) of prismatic needles, m.p. 174–175°, $[\alpha]^{23}D$ +39 ± 2° (in chloroform, *c* 2.13). *Anal.* Calcd. for $C_{22}H_{24}O_9S$: C, 56.89; H, 5.21. Found: C, 56.75; H, 5.09.

Methyl 2-*O*-Acetyl-4,6-*O*-benzylidene-3-*O*-methylsulfonyl-α-D-glucopyranoside (XIV).—To a solution of 0.50 g. of III in 5 ml. of anhydrous pyridine cooled at 0° was added 0.2 ml. (1.4 moles) of methanesulfonyl chloride. After standing at room temperature for a day, the mixture was treated as usual. Crystallization from a mixture of ether and pentane gave 0.59 g. (95%) of elongated prisms, m.p. 150–151°, $[\alpha]^{24}D$ +71 ± 2° (in chloroform, *c* 1.15). *Anal.* Calcd. for $C_{17}H_{22}O_9S$: C, 50.74; H, 5.51; S, 7.97. Found: C, 50.90; H, 5.67; S, 7.80.

Methyl 2-*O*-Benzoyl-4,6-*O*-benzylidene-3-*O*-methylsulfonyl-α-D-glucopyranoside (XV).—To a solution of 825 mg. of VI in 3 ml. of anhydrous pyridine previously cooled to 0° was added 0.23 ml. (1.4 moles) of methanesulfonyl chloride. After standing overnight at room temperature, the mixture was worked up as usual. Crystallization from a mixture of acetone, ether and pentane gave 930 mg. (94%) of prismatic needles, m.p. 169–171°, $[\alpha]^{26}D$ +123 ± 2° (in chloroform, *c* 1.06). *Anal.* Calcd. for $C_{22}H_{24}O_9S$: C, 56.89; H, 5.21; S, 6.90. Found: C, 56.93; H, 5.35; S, 6.97.

Methyl 3-*O*-Acetyl-4,6-*O*-benzylidene-2-*O*-*p*-tolylsulfonyl-α-D-glucopyranoside (XVIII) from XVII.—A solution of 1.0 g. of XVII in 2.5 ml. of anhydrous pyridine was treated overnight at room temperature with 1.0 ml. of acetic anhydride. After addition of ice and extraction with chloroform, as previously described, crystallization from a mixture of acetone, ether and pentane gave 1.03 g. (95%) of shiny platelets, m.p. 161–162° (moistening at 158°), $[\alpha]^{26}D$ +50 ± 1° (in chloroform, *c* 2.20).[25]

From IV.—To a solution of 1.5 g. of IV in 5 ml. of anhydrous pyridine was added a solution of 1.25 g. of *p*-toluenesulfonyl chloride in 5 ml. of pyridine, both solutions having previously been cooled to 0°. After standing one day at room temperature, ice was added and the product isolated as previously described. Crystallization from a mixture of acetone, ether and pentane gave 2.17 g. (97%) of shiny platelets, m.p. 160–161°, and not showing a depression in admixture with the product described above.

***p*-Toluenesulfonylation of Methyl 2-*O*-Acetyl-4,6-*O*-benzylidene-α-D-glucopyranoside (III).**—To a solution of 500 mg. of III in 5 ml. of anhydrous pyridine previously cooled at 0° was added 400 mg. (1.3 moles) of *p*-toluenesulfonyl chloride. After standing at room temperature for one week, the mixture was worked up as usual. The residual sirup was dissolved in benzene, an equal volume of hexane was added, and the solution was chromatographed on 20 g. of

(21) Honeyman and Morgan[8] reported m.p. 188–189°, $[\alpha]^{20}D$ +49° (in chloroform, *c* 1.4).

(22) L. Field and P. H. Settlage, THIS JOURNAL, **76**, 1222 (1954).

(23) L. Field, *ibid.*, **74**, 394 (1952).

(24) Ohle and Spencker[5] reported m.p. 149°, Robertson and Griffith[6] reported m.p. 153–154°.

(25) Bourne, *et al.*,[3] reported for an almost identical procedure 69% yield, m.p. 160–162°, $[\alpha]^{18}D$ +51.2° (in chloroform, *c* 0.76).

alumina. Mixtures of benzene and ether 19:1 and 9:1 eluted crystalline fractions. Crystallization from a mixture of acetone, ether and pentane gave 485 mg. (66%) of **methyl 2-O-acetyl-4,6-O-benzylidene-3-O-p-tolylsulfonyl-α-D-glucopyranoside (XX)**, as stout prisms, m.p. 124–125°, $[\alpha]^{24}D$ +26 ± 2° (in chloroform, *c* 0.51).[26] *Anal.* Calcd. for $C_{23}H_{26}O_9S$: C, 57.73; H, 5.48; S, 6.70. Found: C, 57.93; H, 5.58; S, 6.53. From the mother liquors, 8 mg. (1%) of shiny platelets, m.p. 157–159°, were obtained. In admixture with methyl 3-O-acetyl-4,6-O-benzylidene-2-O-p-tolylsulfonyl-α-D-glucopyranoside (XVIII) described above no depression of the m.p. was observed.

Elution with 4:1, 2:1 and 1:1 mixtures of ether and benzene gave crystalline fractions. After crystallization from a mixture of acetone, ether and pentane, 125 mg. (25%) was obtained, melting at 133–134° and showing no depression in admixture with the starting material.

Action of Pyridinium Chloride on Methyl 3-O-Acetyl-4,6-O-benzylidene-α-D-glucopyranoside (IV).—A solution of 0.1 ml. of anhydrous pyridine in 5 ml. of dry ether was saturated with dry hydrogen chloride. After removal of the ether and excess hydrogen chloride, 5 ml. of anhydrous pyridine and 200 mg. of IV were added. After one day at room temperature, ice was added and the product was isolated as described above. Recrystallization from a mixture of ether and pentane gave 190 mg. (95%) of starting material, m.p. 176–177°.

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(26) Bourne, *et al.*,[3] reported a yield of 49%, m.p. 120–121°, $\alpha^{25}D$ +23.1° (in chloroform, *c* 0.78).

[CONTRIBUTION FROM THE ROBERT W. LOVETT MEMORIAL LABORATORIES FOR THE STUDY OF CRIPPLING DISEASES, MASSACHUSETTS GENERAL HOSPITAL, AND THE DEPARTMENT OF BIOLOGICAL CHEMISTRY, HARVARD MEDICAL SCHOOL]

4-O-Methyl-D-glucosamine Hydrochloride (2-Amino-2-deoxy-4-O-methyl-D-glucose Hydrochloride)[1]

BY ROGER W. JEANLOZ AND CHARLES GANSSER[2]

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The synthesis of 4-O-methyl-D-glucosamine hydrochloride (2-amino-2-deoxy-4-O-methyl-D-glucose hydrochloride), a reference substance for structural studies of glucosamine-containing substances, is described. It was obtained in a sirupy state, starting from methyl 2-acetamido-2-deoxy-6-O-triphenylmethyl-α-D-glucopyranoside and from methyl 2-acetamido-3-O-tolylsulfonyl-α-D-glucopyranoside. It was transformed into the crystalline *N*-acetyl and *N*-(2'-hydroxynaphthylidene) derivatives.

In a previous paper[3] describing the methylation of methyl 2-acetamido-2-deoxy-6-O-triphenylmethyl-α-D-glucopyranoside (IV), a crystalline compound was isolated in addition to the known methyl 2-acetamido-2-deoxy-3-O-methyl-6-O-triphenylmethyl-α-D-glucopyranoside and methyl 2-acetamido-2-deoxy-3,4-di-O-methyl-6-O-triphenylmethyl-α-D-glucopyranoside. The structure of a methyl 2-acetamido-2-deoxy-4-O-methyl-6-O-triphenylmethyl-α-D-glucopyranoside (III) was ascribed to this product on the basis of its elementary analysis, of its mode of preparation, and because it was possible to prepare a monoacetyl derivative. It was of interest to ascertain this structure by an independent synthesis and at the same time synthesize the still unknown 4-O-methyl-D-glucosamine hydrochloride (VII), to complete the series of the known monomethyl derivatives of 2-amino-2-deoxy-D-glucopyranose.

The first attempt to obtain a 4-O-methyl-derivative, using as starting material a compound in which positions 3 and 6 were protected during methylation by methylsulfonyl groups, was unsuccessful, because such groupings could not be removed subsequently by reductive splitting.[4]

Another experiment in which the methylation of the methyl 2-acetamido-2-deoxy-3-O-p-tolylsulfonyl-6-O-triphenylmethyl derivative was attempted did not give conclusive results (see Experimental part).

Finally, the following route as shown in the accompanying diagram was successful: Controlled p-toluenesulfonylation of methyl 2-acetamido-2-deoxy-3-O-p-tolylsulfonyl-α-D-glucopyranoside (I)[5] gave, in excellent yield, the sirupy 3,6-di-O-p-tolylsulfonyl derivative II, characterized by a crystalline 4-O-acetyl derivative. Methylation with methyl iodide and silver oxide produced the sirupy 4-O-methyl derivative V. It was purified from the starting material by acetylation followed by chromatography. Although this product could not be obtained in crystalline form, and showed a rotation slightly different from the rotation of the product prepared by p-toluenesulfonylation of methyl 2-acetamido-2-deoxy-4-O-methyl-α-D-glucopyranoside (VI), it analyzed correctly and was used as such. Splitting of the p-tolylsulfonyl groups was accomplished by reduction and afforded in a 73% yield a crystalline methyl 2-acetamido-2-deoxy-4-O-methyl-α-D-glucopyranoside (VI) identical in all respects with the crystalline product obtained by weak acid hydrolysis of methyl 2-acetamido-2-deoxy-4-O-methyl-6-O-triphenylmethyl-α-D-glucopyranoside (III). Additional evidence for the identity of both compounds was obtained

(1) Studies on hyaluronic acid and related substances, XIV. This is publication No. 205 of the Robert W. Lovett Memorial Laboratories for the Study of Crippling Diseases, Department of Medicine, Harvard Medical School, Boston, and the Massachusetts General Hospital. This investigation has been supported by research grants from the National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Public Health Service (Grant A-148-C2), and from Eli Lilly and Co. It was presented before the Division of Carbohydrate Chemistry at the 129th Meeting of the American Chemical Society, Dallas, Texas, April, 1956.

(2) Fellow of the Swiss Foundation "Stiftung für Stipendien auf dem Gebiete der Chemie."

(3) R. W. Jeanloz, THIS JOURNAL, **74**, 4597 (1952).

(4) R. W. Jeanloz and C. T. Bothner-By, unpublished.

(5) R. W. Jeanloz, THIS JOURNAL, **76**, 555 (1954).