in all respects (mixture melting point, ir, specific rotation) with the product of method A.

Anal. Calcd for $C_{32}H_{44}O_{16}S$ (716.74): C, 53.61; H, 6.19. Found: C, 53.93; H, 6.26.

1D-1,2:5,6-Di-*O*-isopropylidene-3-*O*-methyl-4-*O*-(2,3,4-tri-*O*-acetyl-6-azido-6-deoxy-β-D-glucopyranosyl)-*chiro*-inositol (5).—Sodium azide (2.5 g, 38 mmol) was stirred with **4** (4.0 g, 5.6 mmol) in 50 ml of dimethylformamide for 1 hr at 100–105°. The mixture was then concentrated under reduced pressure, the residue was dissolved in hot methanol–water, and crystallization was induced by adding more water, dropwise, to the hot solution. The pure **5** thus obtained weighed 2.8 g (85%), melted at 140–140.5°, and had $[\alpha]^{24}D$ −13.5° (*c* 7, DMF), and nmr ($CDCl_3$), τ 6.46 (s, 3, OCH_3), 7.96 (s, 3, acetyl CH_3), 7.98 (s, 6, acetyl CH_3), 8.48 (s, 6, isopropylidene CH_3), 8.66 ppm (s, 6, isopropylidene CH_3); ir (KBr), 2950 (C–H), 2090 (N_3), 1740 cm^{-1} (C=O).

Anal. Calcd for $C_{25}H_{37}O_{13}N_3$ (587.37): C, 51.10; H, 6.35. Found: C, 51.03; H, 6.27.

1D-4-*O*-(6-Amino-6-deoxy-β-D-glucopyranosyl)-3-*O*-methyl-*chiro*-inositol (6). A. From 1D-1,2:5,6-Di-*O*-isopropylidene-3-*O*-methyl-4-*O*-(2,3,4-tri-*O*-acetyl-6-*O*-*p*-tolylsulfonyl-β-D-glucopyranosyl)-*chiro*-inositol (4) by Ammonolysis.—A solution of **4** (4.0 g, 5.6 mmol) in 60 ml of methanol saturated with ammonia at 0° was sealed in a glass-lined steel bomb and heated at 110° for 12 hr. The pale yellow reaction mixture was decolorized with Darco G-60 and concentrated to a syrup under reduced pressure.

For deacetonation the syrup was dissolved in 10 ml of acetic acid–water (1:1, v/v) and heated 8 hr in an oil bath at 100–105°. The resulting brown solution was chromatographed on a column of Bio-Rad AG 1-X2 anion-exchange resin (OH^- form, 200–400 mesh, 65 × 2.5 cm), by development with distilled water at 0.5 ml/min. Peaks were again detected by the sulfuric acid char method.[13] The components were identified on thin layer plates of cellulose (without binder). These were developed with pyridine–ethyl acetate–acetic acid–water (5:5:1:3 by volume), and spots were visualized with silver nitrate–alkali.[14]

The first product to be eluted was pinitol, 0.16 g; the eluate volume was 430–470 ml.[15] The following peak, eluate volume 700–2000 ml, was basic and contained the desired pinitol 6-aminoglucoside **6**. The product (1.45 g, 73%) was obtained as a colorless glass by removal of the solvent: $[\alpha]^{18}D$ +27° (*c* 1, H_2O); nmr (D_2O), τ 6.40 (s, 3, OCH_3), 5.24 ppm (d, 1, J = 8 Hz, anomeric H); ir (KBr), 3320 cm^{-1} (O—H), no band for ester C=O.

Anal. Calcd for $C_{13}H_{25}O_{10}N$ (355.34): C, 43.93; H, 7.09; N, 3.94. Found: C, 43.55; H, 7.15; N, 3.89.

The 8-Hz spacing of the doublet for the anomeric proton in the nmr spectrum indicates a β configuration for the glucoside bond, as previously deduced for compound **1** on other grounds.[5] Compound **6** did not reduce Fehling's solution, but treating it with 8 *N* hydrochloric acid for 15 min at 100°, followed by removal of the chloride ion with Dowex-1 (OH^-) resin, gave a hydrolysate with reducing properties. When the hydrolysate was chromatographed on cellulose thin layer plates, it gave reduced silver spots at R_f 0.24 (w), 0.34 (w), and 0.56 (s). Control spots showed R_f 0.24 for the unhydrolyzed glycoside and R_f 0.56 for authentic pinitol. Approximately 1 molar equiv of nitrogen was evolved when **6** reacted with nitrous acid in a Van Slyke apparatus.

B. From 1D-1,2:5,6-Di-*O*-isopropylidene-3-*O*-methyl-4-*O*-(2,3,4-tri-*O*-acetyl-6-azido-6-deoxy-β-D-glucopyranosyl)-*chiro*-inositol (5).—The azidoglucoside **5** (4.0 g, 6.8 mmol) was deacetylated,[8] and the deacetylated product was concentrated to a syrup. This was dissolved in *ca.* 100 ml of ethanol and added to a suspension of palladium-on-carbon catalyst (0.7 g, 5% Pd) in *ca.* 50 ml of ethanol. The mixture was stirred magnetically for 3 hr under hydrogen at 1 atm of pressure with frequent exchange of the gas for fresh hydrogen. The catalyst was then filtered off and the filtrate was concentrated to a glassy solid. The infrared spectrum of the solid showed no absorption in the ester carbonyl or azide regions.

The solid was deacetonated and chromatographed as described under A. The product was in eluate volume of 1050–2050 ml from the resin column. Concentration of this gave 2.0 g of colorless glass, thus a yield of 82% based on **5**, or 70% over-all from compound **4**. This product was identical in all respects with **6** prepared by method A.

Registry No.—**4**, 16802-83-8; **5**, 16802-81-6; **6**, 16802-82-7.

Acknowledgment.—This investigation was supported in part by the Graduate School of the University of Wisconsin from funds supplied by the Wisconsin Alumni Research Foundation. The authors are grateful to the Department of Chemistry for the use of their nmr spectrometer, purchased with funds granted by the National Science Foundation.

(14) L. Hough and J. K. N. Jones, *Methods Carbohyd. Chem.*, **1**, 28 (1962).

(15) The appearance of free pinitol in the eluate was probably due to the hydrolysis of pinitol 3,6-anhydroglucoside, an expected side product of the ammonolysis reaction. The 3,6-anhydroglucoside would be very acid labile, whereas the glucoside bond of **4** is stable to the deacetonation conditions.

Selective Reactions of Sulfonic Esters of Carbohydrates on Alumina[1]

FREDERICK W. PARRISH, RONALD C. CHALK, AND LOUIS LONG, JR.

Pioneering Research Laboratory, U. S. Army Natick Laboratories, Natick, Massachusetts 01760

Received March 19, 1968

Selective hydrolysis of primary sulfonic ester groups of carbohydrates occurs on basic or neutral alumina. In the presence of aliphatic alcohols, hydrolysis is accompanied by selective alcoholysis of a sulfonic ester group at a primary position.

Hydrolysis of carboxylic[2,3] and sulfonic[4] esters of steroids on basic alumina has long been known, and more recently selective hydrolysis of a primary acetate group in the presence of a secondary acetate group has been demonstrated[5] with several steroidal esters.

In carbohydrate chemistry, acetylation is frequently employed to protect hydroxyl functions but migration[6] of acetate groups can be a source of difficulty during a definitive synthetic procedure. Few examples have been reported[7,8] of migration of sulfonic ester groups of carbohydrates, and the usefulness of these esters in synthetic work is well documented.[9] Our studies on the hydrolysis of sulfonic esters of carbohydrates stemmed from our observations on deacetylation of sugar acetates on basic alumina. The sulfonic ester derivatives examined in detail in this study are readily

(1) This work was supported in part by the Army Research Office, Durham, N. C.

(2) A. Butenandt and L. Poschmann, *Chem. Ber.*, **77**, 392 (1944).

(3) R. H. Levin, A. V. McIntosh, Jr., G. B. Spero, D. E. Rayman, and E. M. Meinzer, *J. Amer. Chem. Soc.*, **70**, 511 (1948).

(4) R. J. W. Cremlyn and C. W. Shoppee, *J. Chem. Soc.*, 3515 (1954).

(5) W. F. Johns and D. M. Jerina, *J. Org. Chem.*, **28**, 2922 (1963).

(6) W. A. Bonner, *J. Amer. Chem. Soc.*, **80**, 3697 (1958).

(7) A. C. Cope and T. Y. Shen, *ibid.*, **78**, 5912 (1956).

(8) J. S. Brimacombe and L. C. N. Tucker, *Chem. Commun.*, 903 (1966).

(9) R. S. Tipson, *Advan. Carbohyd. Chem.*, **8**, 107 (1953).

available by partial methanesulfonylation[10] of the corresponding methyl D-aldohexopyranoside followed by methylation of unesterified hydroxyl groups.

When a slurry of methyl 3,4-di-*O*-methyl-2,6-di-*O*(methylsulfonyl)-α-D-glucopyranoside[11] (**1**) with basic alumina of Brockmann activity I in benzene is kept at 50°, then eluted with ether–methanol (19:1), a product (**2**) is obtained in 66% yield accompanied by unchanged **1** (33%). The mixture can be resolved by silica gel chromatography, and nuclear magnetic resonance and infrared spectral data for **2** indicate the presence of hydroxyl and methylsulfonyl groups. This indication was confirmed by formation of a crystalline triphenylmethyl(trityl) ether derivative (**3**) having an elemental analysis consistent with its being a mono-*O*-(methylsulfonyl)mono-*O*-trityl derivative. Formation of trityl ether derivatives is often employed[12] with primary alcohol groups, but trityl ethers of secondary alcohol groups have also been obtained;[13] consequently, formation of a trityl ether does not establish unequivocally which hydroxyl group is unsubstituted in **2**.

Thin layer chromatographic examination of the course of hydrolysis of **1**, methyl 3,4,6-tri-*O*-methyl-2-*O*-(methylsulfonyl)-α-D-glucopyranoside[11] (**4**), or methyl 2,3,4-tri-*O*-methyl-6-*O*-(methylsulfonyl)-α-D-glucopyranoside (0.03 *M* solution in 1.25 *M* aqueous sodium hydroxide) revealed no difference in the ease of hydrolysis of the primary *vs.* the secondary *O*-(methylsulfonyl) group under these conditions. However, methylation[14] of **2** afforded a crystalline derivative indistinguishable from **4**, and this establishes that selective hydrolysis of the primary sulfonic ester group of **1** had occurred on basic alumina.

Hydrolysis of **1** was extremely slow on activity I basic alumina at room temperature (27°); at 50° little hydrolysis occurred on activity III alumina, and none occurred on activity V alumina.

We then examined the reaction on basic alumina at 50° of methyl 4-*O*-methyl-2,3,6-tri-*O*-(methylsulfonyl)-α-D-mannopyranoside[10] (**5**) which in the favored *C1* (D) conformation possesses an axial methylsulfonyl group at C-2. A single crystalline product (**6**) was obtained in 98% yield which, from elemental analysis and spectral data, was shown to be a monohydroxy compound derived from **5** by hydrolysis of a single *O*-methylsulfonyl group. By analogy with the formation of **2** from **1**, we expected **6** to possess an unsubstituted hydroxyl group at C-6, and this was confirmed by comparison of the trityl ether of **6** with that prepared by the following unequivocal synthetic route. Methanesulfonylation of methyl 4,6-*O*-ethylidene-α-D-mannopyranoside[15] followed by deacetalation afforded crystalline methyl 2,3-di-*O*-(methylsulfonyl)-α-D-mannopyranoside in 40% over-all yield. The latter compound on tritylation was converted into a single, crystalline product (60% yield) which was methylated[14] to give methyl 4-*O*-methyl-2-3-di-*O*-(methylsulfonyl)-6-*O*-trityl-α-D-mannopyranoside (**7**) identical with the trityl ether derivative of **6**.

Methanesulfonic ester groups at C-4 in some methyl D-aldohexopyranosides exhibited similar reactivity to corresponding groups situated at C-6.[16] For this reason we investigated the reaction on basic alumina at 50° of methyl 2,3-di-*O*-methyl-4,6-di-*O*-(methylsulfonyl)-β-D-glucopyranoside (**8**), and obtained a single product (**9**) in 63% yield, derived from **8** by hydrolysis of a methylsulfonyl group. Compound **9** was shown to be methyl 2,3-di-*O*-methyl-4-*O*-(methylsulfonyl)-β-D-glucopyranoside which was synthesized by the following route. Methyl β-D-glucopyranoside was treated with 2,2-dimethoxypropane to give crystalline methyl 4,6-*O*-isopropylidene-β-D-glucopyranoside, which has not previously been described, in 51% yield. Methylation of the latter compound, in 87% yield, followed by deacetalation, gave the known crystalline methyl 2,3-di-*O*-methyl-β-D-glucopyranoside in 86% yield. This compound, when treated with trityl chloride, afforded a single derivative in 33% yield which from elemental analysis and nmr data was shown to be a mono-*O*-trityl ether; as tritylation would be expected to occur at the primary hydroxyl group of C-6 in preference to the secondary hydroxyl group at C-4,[12] we consider that the product is methyl 2,3-di-*O*-methyl-6-*O*-trityl-β-D-glucopyranoside (**10**). Support for this structural assignment was obtained by a comparison of the nmr spectra of **10** and of the product (**11**) obtained from **10** in 74% yield by methanesulfonylation. Esterification of a hydroxyl group causes the adjacent ring hydrogen to resonate at a lower field. The nmr spectrum of **11** showed this downfield shift to the region of the anomeric proton (τ 5.5) for one proton only. If methanesulfonylation had occurred at the primary position, the shift of two protons would have been observed. Detritylation of **11** afforded a crystalline product in 66% yield identical with **9**.

Little or no reaction occurred in benzene on basic alumina at 50° during 24 hr with 1,2-*O*-isopropylidene-3-*O*-(methylsulfonyl)-D-threose, methyl 2,3-di-*O*-benzyl-6-deoxy-4-*O*-(methylsulfonyl)-α-D-glucopyranoside, methyl 2,3-di-*O*-benzyl-6-deoxy-4-*O*-(methylsulfonyl)-α-D-galactopyranoside, 4,6-*O*-ethylidene-1,2-*O*-isopropylidene-3-*O*-*p*-tolylsulfonyl-D-galactose, 1,6-anhydro-3,4-*O*-isopropylidene-2-*O*-(methylsulfonyl)-D-galactose, or **4**. Under the same conditions, hydrolysis of 1,2:3,4-di-*O*-isopropylidene-6-*O*-*p*-tolylsulfonyl-D-galactose to 1,2:3,4-di-*O*-isopropylidene-D-galactose was slow requiring 100 hr for complete reaction.

When chloroform was used in place of benzene in the reaction of **1** with basic alumina, elution of the alumina with chloroform, after 15 hr of reaction at 50°, gave a syrupy product, in 21% yield, identical with that obtained by ethylation of **2**. The ethyl ether group in the above product from the reaction on alumina is derived from the 0.75% of ethanol used as a preservative in chloroform. Further elution of the alumina with chloroform afforded a mixture of **1** (1%) and **2** (67%) which was resolved by silica gel column chromatography.

(10) R. C. Chalk, D. H. Ball, and L. Long, Jr., *J. Org. Chem.*, **31**, 1509 (1966).
(11) A. K. Mitra, D. H. Ball, and L. Long, Jr., *ibid.*, **27**, 160 (1962).
(12) G. R. Baker, "Methods in Carbohydrate Chemistry," Vol. II, Academic Press Inc., New York, N. Y., 1963, p 168.
(13) R. C. Hockett and C. S. Hudson, *J. Amer. Chem. Soc.*, **53**, 4456 (1931).
(14) R. Kuhn, H. Trischmann, and I. Löw, *Angew. Chem.*, **67**, 32 (1955).
(15) G. O. Aspinall and G. Zweifel, *J. Chem. Soc.*, 2271 (1957).
(16) J. Hill, L. Hough, and A. C. Richardson, *Proc. Chem. Soc.*, 346 (1963).

Subsequently, we performed reactions of **1** on basic alumina in mixtures of benzene or ethanol-free chloroform with up to 3% methanol, and obtained **4** in 38% yield together with **2** (58%) and unchanged **1** (4%). Similarly, compound **5** gave methyl 4,6-di-*O*-methyl-2,3-di-*O*-(methylsulfonyl)-α-D-mannopyranoside (**12**) in 38% yield, identical with the methylation product from **6**, together with **6** (59%) and unchanged **5** (3%). The use of solvent mixtures containing more than 3% methanol caused inactivation of the alumina, and starting material was recovered quantitatively.

In attempts to increase the yields of 6-*O*-methyl derivatives, by generation of methanol *in situ*, we performed reactions of **1** or **5** on basic alumina at 50° in mixtures of benzene or ethanol-free chloroform with up to 3% methyl acetate. However, yields of **4** or **12** were not improved over those obtained with solvent mixtures containing methanol.

Similarly, reaction of **1** on basic alumina in benzene containing 2% benzyl alcohol or 2% benzaldehyde[17] afforded unchanged **1** (45%), **2** (44%), and methyl 6-*O*-benzyl-3,4-di-*O*-methyl-2-*O*-(methylsufolnyl)-α-D-glucopyranoside (11%).

Identical hydrolysis and alcoholysis reactions of methanesulfonic esters of aldohexopyranosides occur on neutral alumina of Brockmann activity I. For example, reaction of **5** at 50° for 20 hr on neutral alumina in chloroform containing 2% methanol gave **12** in 36% yield together with **6** (50% yield) and unchanged **5** (6% yield).

Experimental Section[18]

Methyl 3,4-Di-*O*-methyl-2-*O*-(methylsulfonyl)-α-D-glucopyranoside (2).—A slurry of methyl 3,4-di-*O*-methyl-2,6-di-*O*-(methylsulfonyl)-α-D-glucopyranoside (**1**) (1 g) and Woelm basic alumina (50 g) in benzene was placed in a jacketed column and heated at 50° for 41 hr. After being cooled to room temperature the column was eluted with ether–methanol (19:1), and the solvent was removed by evaporation. The residue was chromatographed on silica gel (120 g) with ethyl acetate as eluent to give 332 mg (33%) of **1**, 47 mg of a mixture of two unidentified materials, and 521 mg (66%) of syrupy **2** having $[\alpha]^{22}D$ +119° (*c* 2.8, chloroform).

Anal. Calcd for $C_{10}H_{20}O_8S$: C, 40.00; H, 6.71; S, 10.68. Found: C, 40.04; H, 6.73; S, 10.72.

Methyl 3,4-Di-*O*-methyl-2-*O*-(methylsulfonyl)-6-*O*-trityl-α-D-glucopyranoside (3).—A mixture of **2** (475 mg), trityl chloride (2.4 g), and dry pyridine (20 ml) was kept 16 hr at 25° and then 4 hr at 70°. Water (3 ml) was added, and the solution was evaporated. The residue was treated with chloroform (4 ml), filtered to remove some triphenylmethanol, and chromatographed on silica gel (150 g) with chloroform (containing 0.5% triethylamine to minimize hydrolysis) as eluent to give **3** (896 mg, 74%) with mp 63–64° and $[\alpha]^{22}D$ +84° (*c* 0.5, chloroform) after recrystallization from hexane.

Anal. Calcd for $C_{29}H_{34}O_8S$: C, 64.19; H, 6.32; S, 5.91. Found: C, 64.30; H, 6.38; S, 6.04.

Methyl 3,4,6-Tri-*O*-methyl-2-*O*-(methylsulfonyl)-α-D-glucopyranoside (4). A. From 2.—Compound **2** (100 mg) was dissolved in anhydrous *N*,*N*-dimethylformamide (5 ml) and methyl iodide (5 ml). Silver oxide (1 g) was added, and the mixture was shaken in the dark for 24 hr. Solids were removed by filtration and washed with *N*,*N*-dimethylformamide, then with chloroform. The filtrate and washings were combined and concentrated to a syrup which was redissolved in chloroform. Residual silver salts were removed by filtration, and the chloroform solution was concentrated to a syrup which crystallized. After recrystallization from ethanol, **4** (58 mg, 56%) was obtained having a melting point and mixture melting point with authentic material of 86° and $[\alpha]^{22}D$ +116° (*c* 1.0, chloroform).

B. From 1.—A slurry of **1** (1 g) and Woelm basic alumina (80 g) in benzene containing 2% methanol was kept 18 hr at 50°. After being cooled to room temperature, elution with ether (1 l.) gave **4** (404 mg) containing small amounts of **1** and **2** (mixture A); elution with ether–methanol (19:1) then gave **2** (463 mg, 58%). Fractionation of mixture A on silica gel (60 g) with ether as eluent gave **1** (40 mg, 4%), **2** (3 mg), and **4** (314 mg, 38%); the latter compound when crystallized from ethanol had mp 86° and $[\alpha]^{22}D$ +116° (*c* 1.0, chloroform).

Anal. Calcd for $C_{11}H_{22}O_8S$: C, 42.03; H, 7.05; S, 10.20. Found: C, 42.09; H, 7.13; S, 10.35.

Methyl 4-*O*-Methyl-2,3-di-*O*-(methylsulfonyl)-α-D-mannopyranoside (6).—Methyl 4-*O*-methyl-2,3,6-tri-*O*-(methylsulfonyl)-α-D-mannopyranoside (**5**) (1.04 g) and Woelm basic alumina (50 g) in benzene were kept 41 hr at 50°. After being cooled to room temperature, elution with ether–methanol (19:1) gave **6** (835 mg, 98%) which crystallized on removing solvent. Recrystallization from ether gave **6** having mp 131–132° and $[\alpha]^{22}D$ +19° (*c* 1.0, chloroform).

Anal. Calcd for $C_{10}H_{20}O_{10}S_2$: C, 32.96; H, 5.53; S, 17.60. Found: C, 33.01; H, 5.55; S, 17.84.

Methyl 4-*O*-Methyl-2,3-di-*O*-(methylsulfonyl)-6-*O*-trityl-α-D-mannopyranoside (7). A. From Methyl 4,6-*O*-Ethylidene-α-D-mannopyranoside.[15]—Methyl 4,6-*O*-ethylidene-α-D-mannopyranoside (1.1 g) in anhydrous pyridine (10 ml) at −30° was treated dropwise with stirring with methanesulfonyl chloride (1 ml). The reaction mixture was kept at −20° for 24 hr and at 25° for 24 hr. The syrup obtained on concentrating the pyridine solution was dissolved in water, and the aqueous solution was extracted with chloroform to give syrupy methyl 4,6-*O*-ethylidene-2,3-di-*O*-(methylsulfonyl)-α-D-mannopyranoside (1.5 g), homogeneous by tlc in ether or ethyl acetate.

The syrup was dissolved in hot methanol (100 ml), Dowex 50 W (H^+) resin (30 g) was added, and the mixture was stirred 12 hr at 50°. The resin was removed by filtration, and washed with warm methanol. On removing solvent and crystallizing from chloroform–heptane, methyl 2,3-di-*O*-(methylsulfonyl)-α-D-mannopyranoside (0.57 g, 40% yield) was obtained having mp 113–114.5° and $[\alpha]^{20}D$ +22° (*c* 1.3, acetone).

Anal. Calcd for $C_9H_{18}O_{10}S_2$: C, 30.85; H, 5.14; S, 18.28. Found: C, 30.80; H, 4.97; S, 17.98.

Methyl 2,3-di-*O*-(methylsulfonyl)-α-D-mannopyranoside (0.30 g) in anhydrous pyridine (8 ml) was treated with trityl chloride (0.26 g) at 25° for 24 hr then at 60° for 5 hr, when tlc in ether indicated reaction was complete. After removing pyridine, the product was chromatographed on silica gel with ether as eluent. Methyl 2,3-di-*O*-(methylsulfonyl)-6-*O*-trityl-α-D-mannopyranoside (0.30 g, 60% yield) was obtained on crystallization from ethanol and had mp 119–120° and $[\alpha]^{20}D$ +7.7° (*c* 1.0, chloroform).

Anal. Calcd for $C_{28}H_{32}O_{10}S_2$: C, 56.75; H, 5.40; S, 10.80. Found: C, 56.40; H, 5.57; S, 10.48.

Methyl 2,3-di-*O*-(methylsulfonyl)-6-*O*-trityl-α-D-mannopyranoside (0.09 g) in anhydrous N,N-dimethylformamide (2 ml) and methyl iodide (0.2 ml) at 0° was stirred with silver oxide (0.2 g) for 5.5 hr. After this time, methyl iodide (0.2 ml) and silver oxide (0.2 g) were added, and the reaction mixture was stirred for an additional 5.5 hr. The reaction mixture was worked up as previously described for the preparation of **4** to give **7** (0.05 g, 53% yield), on crystallization from ethanol, having mp 212.5–214° and $[\alpha]^{22}D$ +27° (*c* 1.0, chloroform).

Anal. Calcd for $C_{29}H_{34}O_{10}S_2$: C, 57.41; H, 5.65; S, 10.57. Found: C, 57.27; H, 5.41; S, 10.84.

B. From 6.—A mixture of **6** (400 mg), dry pyridine (8.5 ml), and trityl chloride (1.2 g) was kept 4 hr at 70°. Water (3 ml) was added, and the solution was evaporated. The residue was treated with chloroform (4 ml), filtered to remove some triphenylmethanol, and chromatographed on silica gel (100 g) with chloroform containing 0.5% triethylamine as eluent to give **7** (665 mg,

(17) V. J. Hruby, *Proc. N. Dakota Acad. Sci.*, **16**, 12 (1962).

(18) Solutions were concentrated under reduced pressure. Melting points were determined with a Thomas–Hoover capillary melting point apparatus and optical rotations were measured using an ETL-NPL automatic polarimeter. Infrared spectra were recorded on a Perkin-Elmer Infracord spectrophotometer and nmr spectra were recorded on a Varian Model A-60 spectrometer. Ascending thin layer chromatography (tlc) was performed on 0.25-mm layers of silica gel G (distributed by Brinkmann Instruments, Inc., Great Neck, Long Island, N. Y.). For the detection of spots, the plates were sprayed successively with a 1% solution of α-naphthol in ethanol and with 10% sulfuric acid and were then heated. Column chromatography was performed on 0.05–0.20-mm silica gel (distributed by Brinkmann Instruments, Inc.). The microanalyses were performed by C. DiPietro and nmr spectra were obtained by F. H. Bissett.

83%) having mp 213° on crystallization from hexane, $[\alpha]^{22}D$ +27° (*c* 1.0, chloroform).

This product was identical with that obtained on tritylation of **6** by mixture melting point determination and comparison of infrared and nmr spectra.

Anal. Calcd for $C_{29}H_{34}O_{10}S_2$: C, 57.41; H, 5.65; S, 10.57. Found: C, 57.60; H, 5.67; S, 10.80.

Methyl 4,6-Di-*O*-methyl-2,3-di-*O*-(methylsulfonyl)-α-D-mannopyranoside (12). A. From 6.—A mixture of **6** (105 mg), anhydrous *N*,*N*-dimethylformamide (2 ml), silver oxide (0.6 g), and methyl iodide (0.6 ml) was stirred for 6 hr at room temperature. The mixture was filtered, and the filtrate was concentrated to dryness. The residue was dissolved in chloroform, filtered to remove some silver salts, and concentrated to give **12** (96 mg, 88%) which on crystallization from ethanol had mp 128° and $[\alpha]^{22}D$ +30.5° (*c* 2.5, chloroform).

Anal. Calcd for $C_{11}H_{22}O_{10}S_2$: C, 34.91; H, 5.86; S, 16.94. Found: C, 35.19; H, 5.89; S, 16.83.

B. From 5.—A slurry of **5** (1.04 g) and Woelm basic alumina (80 g) in a mixture of benzene or ethanol-free chloroform containing 2% methanol was kept 18 hr at 50°, cooled to room temperature, then eluted with ether (1 l.) followed by ether–methanol (19:1, 250 ml). Evaporation of the ether eluate afforded a mixture which was fractionated on silica gel with ether as eluent to give unchanged **5** (31 mg, 3%) and **12** (350 mg, 38%): mp 128°; $[\alpha]^{22}D$ +30.5° (*c* 2.4, chloroform).

Anal. Calcd for $C_{11}H_{22}O_{10}S_2$: C, 34.91; H, 5.86; S, 16.94. Found: C, 35.08; H, 5.87; S, 16.85.

Concentration of the ether–methanol (19:1) eluate gave **6** (500 mg, 59%) having mp 132° (ether) and $[\alpha]^{22}D$ +19.5° (*c* 1.0, chloroform).

Anal. Calcd for $C_{10}H_{20}O_{10}S_2$: C, 32.96; H, 5.53; S, 17.60. Found: C, 33.05; H, 5.56; S, 17.80.

Methyl 2,3-Di-*O*-methyl-4-*O*-(methylsulfonyl)-β-D-glucopyranoside (9).—A slurry of methyl 2,3-di-*O*-methyl-4,6-di-*O*-(methylsulfonyl)-β-D-glucopyranoside (**8**, 300 mg) with Woelm basic alumina (30 g) in benzene was kept 24 hr at 50°, cooled to room temperature, and eluted with ether to give unchanged **8** (84 mg, 28%) then with ether–methanol (19:1) to give **9** (150 mg, 63%): mp 86°; ‡(ether); $[\alpha]^{22}D$ −29° (*c* 1.0, chloroform).

Anal. Calcd for $C_{10}H_{20}O_8S$: C, 40.00; H, 6.71; S, 10.68. Found: C, 40.08; H, 6.74; S, 10.75.

Synthesis of Methyl 2,3-Di-*O*-methyl-4-*O*-(methylsulfonyl)-β-D-glucopyranoside (9). A. Methyl 4,6-*O*-Isopropylidene-β-D-glucopyranoside.—Methyl β-D-glucopyranoside (6 g) was treated with 2,2-dimethoxypropane (7 g) in *N*,*N*-dimethylformamide (35 ml) using *p*-toluenesulfonic acid (0.05 g) as catalyst according to the method of Evans, Parrish, and Long.[19] The product, methyl 4,6-*O*-isopropylidene-β-D-glucopyranoside, crystallized and was recrystallized twice from 1-propanol: yield 2.6 g; mp 128–128.5°; $[\alpha]^{25}D$ −72° (*c* 1.4, water). A second crop of crystals (1.1 g) obtained from the mother liquors had mp 123–125°. The nmr spectrum of this compound was consistent with the proposed structure.

Anal. Calcd for $C_{10}H_{18}O_6$: C, 51.28; H, 7.69. Found: C, 51.45; H, 7.70.

B. Methyl 4,6-*O*-Isopropylidene-2,3-di-*O*-methyl-β-D-glucopyranoside.—Methyl 4,6-*O*-isopropylidene-β-D-glucopyranoside (1.0 g) in *N*,*N*-dimethylformamide was treated with methyl iodide (3 ml) and silver oxide (3 g) for 20 hr. Tlc (ethyl acetate) showed mainly one product. The product was purified on a silica gel column using ethyl acetate containing 1% triethylamine as solvent. The yield of syrupy product was 0.97 g, $[\alpha]^{28}D$ −43° (*c* 1.0, chloroform). The nmr spectrum was consistent with the proposed structure.

Anal. Calcd for $C_{12}H_{22}O_6$: C, 52.80; H, 8.80. Found: C, 52.45; H, 8.63.

C. Methyl 2,3-Di-*O*-methyl-β-D-glucopyranoside.—Methyl 4,6-*O*-isopropylidene-2,3-di-*O*-methyl-β-D-glucopyranoside (0.97 g) was stirred and heated at 50° in 95% methanol (45 ml) with Dowex 50 W (H^+) ion-exchange resin (10 g) for 5 hr. The resin was removed by filtration and the filtrate was concentrated to a syrup which crystallized. Recrystallization of the product from benzene gave 0.72 g of methyl 2,3-di-*O*-methyl-β-D-glucopyranoside: mp 61.5–63.5°; $[\alpha]^{21}D$ −45° (c 1.5, chloroform). Oldham[20] quotes mp 62–64° and $[\alpha]D$ −47.8° (*c* 4.4, chloroform) for this compound.

(19) M. E. Evans, F. W. Parrish, and L. Long, Jr., *Carbohyd. Res.*, **3**, 453 (1967).

(20) J. W. H. Oldham, *J. Amer. Chem. Soc.*, **56**, 1360 (1934).

D. Methyl 2,3-Di-*O*-methyl-6-*O*-trityl-β-D-glucopyranoside (10).—Methyl 2,3-di-*O*-methyl-β-D-glucopyranoside (0.32 g) and trityl chloride (0.26 g) were dissolved in pyridine (8 ml). The solution was left at room temperature for 20 hr and heated under reflux at 75° for 2 hr. Tlc (ether and isopropyl ether) indicated complete reaction. The mixture was concentrated to a syrup and the product was purified using silica gel chromatography with isopropyl ether containing 1% triethylamine as eluent. The product was obtained as a syrup in a yield of 0.228 g, $[\alpha]^{25}D$ −35° (*c* 2.0, chloroform). The nmr spectrum was consistent with the proposed structure.

E. Methyl 2,3-Di-*O*-methyl-4-*O*-(methylsulfonyl)-6-*O*-trityl-β-D-glucopyranoside (11).—Methyl 2,3-di-*O*-methyl-6-*O*-trityl-β-D-glucopyranoside (0.152 g) was dissolved in pyridine (8 ml) and cooled to −40°. Methanesulfonyl chloride (0.3 ml) was added and the mixture left at −20° for 16 hr and at room temperature for 24 hr. The pyridine was removed on the evaporator and the resultant syrup was dissolved in water and extracted into chloroform. The chloroform extracts were combined and dried (anhydrous magnesium sulfate); the solids were removed by filtration; and the filtrate was concentrated to a syrup. The 4-*O*-mesyl derivative moved slightly slower than the starting material on tlc in ether, isopropyl ether, or chloroform–ethyl acetate (1:1). The product was obtained as a syrup by purification on a silica gel column using hexane–ether (1:2) as solvent: yield 0.119 g; $[\alpha]^{25}D$ −12° (*c* 1.5, chloroform).

Anal. Calcd for $C_{29}H_{34}O_8S$: C, 64.2; H, 6.3; S, 5.9. Found: C, 64.5; H, 6.5; S, 6.0.

F. Methyl 2,3-Di-*O*-methyl-4-*O*-(methylsulfonyl)-β-D-glucopyranoside (9).—Methyl 2,3-di-*O*-methyl-4-*O*-(methylsulfonyl)-6-*O*-trityl-β-D-glucopyranoside (0.8 g) was dissolved in 80% aqueous acetic acid (20 ml) and heated at 50° for 45 min. Tlc in ether indicated complete removal of the trityl group. The product was purified by passage down a silica gel column using ether as solvent. The product crystallized and was recrystallized from ether: yield 0.292 g; mp 85.5–86.5°; $[\alpha]^{22}D$ −28° (*c* 0.9, chloroform).

Anal. Calcd for $C_{10}H_{20}O_8S$: C, 40.00; H, 6.67; S, 10.67. Found: C, 40.07; H, 6.39; S, 10.4.

Methyl 6-*O*-Benzyl-3,4-di-*O*-methyl-2-*O*-(methylsulfonyl)-α-D-glucopyranoside (13).—A slurry of **1** (1 g) and Woelm basic alumina in benzene containing 2% benzyl alcohol was kept 24 hr at 50°, cooled to room temperature, and eluted with ether–methanol (19:1). The concentrated eluate was fractionated on silica gel (100 g) with ethyl acetate to give unchanged **1** (450 mg, 45%), **2** (345 mg, 44%), and a syrupy product (113 mg, 11%) having $[\alpha]^{22}D$ +102° (*c* 2.4, chloroform) designated as **13** by analogy with the other products from **1** described above. The structure proposed as **13** was supported by spectral data and elemental analysis.

Anal. Calcd for $C_{17}H_{26}O_8S$: C, 52.29; H, 6.71; S, 8.21. Found: C, 52.50; H, 6.68; S, 8.00.

Similarly, **1** (300 mg) and Woelm basic alumina (30 g) in benzene containing 2% benzaldehyde[17] afforded unchanged **1** (120 mg, 40%), **2** (99 mg, 42%), and **13** (55 mg, 17%) having $[\alpha]^{22}D$ +100° (*c* 2.4, chloroform).

Methyl 2,3,4-Tri-*O*-methyl-6-*O*-(methylsulfonyl)-α-D-glucopyranoside.—Methyl 6-*O*-(methylsulfonyl)-α-D-glucopyranoside[10] (3 g) in anhydrous *N*,*N*-dimethylformamide (50 ml) was treated with methyl iodide (10 ml) and silver oxide (10 g) according to the procedure of Kuhn, *et al.*[14] The product was shown by tlc in hexane–methyl ethyl ketone (6:4) to consist of two components which were separated with this solvent by silica gel chromatography. The faster moving compound was shown by comparison of infrared and nmr spectra to be methyl 2,3,4,6-tetra-*O*-methyl-α-D-glucopyranoside.

The second component, obtained as a syrup (0.73 g), had $[\alpha]^{23}D$ +106° (*c* 1.0, chloroform).

Anal. Calcd for $C_{11}H_{22}O_8S$: C, 42.05; H, 7.01; S, 10.21. Found: C, 42.05; H, 7.05; S, 10.18.

Hydrolysis of 1, 4, and Methyl 2,3,4-Tri-*O*-methyl-6-*O*-(methylsulfonyl)-α-D-glucopyranoside.—A solution of methyl 2,3,4-tri-*O*-methyl-6-*O*-(methylsulfonyl)-α-D-glucopyranoside, **1**, or **4** (0.3 mmol) in boiling 1.25 *M* sodium hydroxide (10 ml) was examined at 15-min intervals by tlc on silica gel with ether as solvent. All three compounds were completely hydrolyzed after 90 min with no apparent differences in rate.

Methyl 6-*O*-Ethyl-3,4-di-*O*-methyl-2-*O*-(methylsulfonyl)-α-D-glucopyranoside. A. From 1.—A slurry of **1** (7.0 g) and Woelm basic alumina (500 g) in chloroform (containing 0.75% ethanol

as preservative) was kept 15 hr at 50°. After cooling to room temperature, elution with chloroform afforded methyl 6-*O*-ethyl-3,4-di-*O*-methyl-2-*O*-(methylsulfonyl)-α-D-glucopyranoside (1.266 g, 21% yield) having $[\alpha]^{26}D$ +120° (*c* 2.0, chloroform).

Anal. Calcd for $C_{12}H_{24}O_8S$: C, 43.89; H, 7.37; S, 9.76. Found: C, 44.09; H, 7.30; S, 9.52.

Further elution with chloroform afforded a mixture of **1** (99 mg, 1%) and **2** (4.71 g, 67%) which was resolved by silica gel column chromatography.

B. From 2.—Compound **2** (0.104 g) in N,N-dimethylformamide (2 ml) with ethyl iodide (0.5 ml) and silver oxide (0.5 g) was stirred 3.5 hr when reaction was complete as judged by tlc using ether as solvent. The reaction mixture was worked up as described above for methylation reactions to give methyl 6-*O*-ethyl-3,4-di-*O*-methyl-2-*O*-(methylsulfonyl)-α-D-glucopyranoside (0.094 g, 83%) having $[\alpha]^{26}D$ +119° (*c* 2.4, chloroform). The infrared and nmr spectra were identical with those of the product from **1** described in A.

Anal. Calcd for $C_{12}H_{24}O_8S$: C, 43.89; H, 7.37; S, 9.76. Found: C, 43.87; H, 7.48; S, 9.62.

Registry No.—**2**, 16802-84-9; **3**, 16802-85-0; **4**, 7045-36-5; **6**, 16802-87-2; **7**, 16853-03-5; methyl 2,3-di-*O*-(methylsulfonyl)-α-D-mannopyranoside, 16802-88-3; methyl 2,3-di-*O*-(methylsulfonyl)-6-*O*-trityl-α-D-mannopyranoside, 16802-89-4; **9**, 16802-90-7; methyl 4,6-*O*-isopropylidene-β-D-glucopyranoside, 16802-97-4; methyl 4,6-*O*-isopropylidene-2,3-di-*O*-methyl-β-D-glucopyranoside, 16802-91-8; **11**, 16802-92-9; **12**, 16802-93-0; **13**, 16802-94-1; methyl 2,3,4-tri-*O*-methyl-6-*O*-(methylsulfonyl)-α-D-glucopyranoside 16802-95-2; methyl 6-*O*-ethyl-3,4-di-*O*-methyl-2-*O*-(methylsulfonyl)-α-D-glucopyranoside, 16802-96-3.

Stereochemistry of the Anomers of Methyl 2-Deoxy-D-ribofuranoside. Synthesis of Methyl 5-(6-Aminopurin-9-yl)-2,5-dideoxy-α-D-ribofuranoside, a "Reversed" Nucleoside[1]

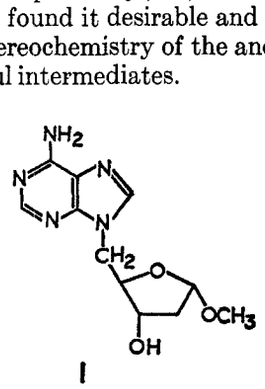
NELSON J. LEONARD, FRANK C. SCIAVOLINO, AND VASUDEWAN NAIR

Department of Chemistry and Chemical Engineering, University of Illinois, Urbana, Illinois 61801

Received February 6, 1968

Methyl 2-deoxy-5-*O*-triphenylmethyl-α-D-ribofuranoside (**2**) and methyl 2-deoxy-5-*O*-triphenylmethyl-β-D-ribofuranoside (**3**) were synthesized and the stereochemistry of their anomeric centers was established unambiguously by chemical means and by complete analysis of their nmr spectra. The results are in agreement with those predicted by the Hudson isorotation rules. The syntheses of related ribofuranosides and of methyl 5-(6-aminopurin-9-yl)-2,5-dideoxy-α-D-ribofuranoside (**1**) are also described.

A route to the synthesis of ribose derivatives of adenine bonded at C-5 of the sugar moiety ("reversed" nucleosides) has been described[2] as part of a cooperative program with Professor Skoog at the University of Wisconsin[3] to determine the cytokinin activity[4,5] and chemical properties of compounds closely related to kinetin.[6,7] In providing a synthetic route to 2-deoxyribose derivatives of "reversed" nucleoside type, as exemplified by methyl 5′-(6-aminopurin-9-yl)-2′,5′-dideoxy-α-D-ribofuranoside (**1**), we found it desirable and also necessary to establish the stereochemistry of the anomeric centers for a series of useful intermediates.



1

A mixture of the α and β forms of methyl 2-deoxy-D-ribofuranosides[8] was treated with 1 equiv of triphenylmethyl chloride. Chromatography on silica gel afforded a separation of methyl 2-deoxy-5-*O*-triphenylmethyl-α-D-ribofuranoside (**2**) (28%), $[\alpha]^{26}D$ 64.4° (*c* 1.2, $CHCl_3$), and methyl 2-deoxy-5-*O*-triphenylmethyl-β-D-ribofuranoside (**3**) (24%), $[\alpha]D^{26}$ −43.8° (*c* 1.3, $CHCl_3$). The stereochemistry of the anomeric centers was temporarily assigned on the basis of Hudson's rules of isorotation[9] which correlate optical rotation and anomeric configuration. However, it has recently been discovered that several pyrimidine[10-12] and purine[13] 2-deoxy-D-ribonucleosides constitute exceptions to Hudson's rules. Although there is consistency among the rotations of a wide variety of 2-deoxy-D-ribofuranose esters and glycosides and there is no evidence currently available that Hudson's rules are not applicable to such substances,[14] it was desirable to confirm the assignments by further physical and chemical means. Accordingly, the configuraton of the anomeric center in **2** and **3** was rigorously established by an unambiguous chemical synthesis and by a complete analysis of their nmr spectra.

(1) The support of this work by a research grant (USPHS-GM-05829) from the National Institutes of Health, U. S. Public Health Service, is gratefully acknowledged.

(2) N. J. Leonard and K. L. Carraway, *J. Heterocycl. Chem.*, **3**, 485 (1966); see also J. Hildesheim, J. Cléophax, S. D. Géro, and R. D. Guthrie, *Tetrahedron Lett.*, 5013 (1967).

(3) F. Skoog, H. Q. Hamzi, A. M. Szweykowska, N. J. Leonard, K. L. Carraway, T. Fujii, J. P. Helgeson, and R. N. Loeppky, *Phytochemistry*, **6**, 1169 (1967).

(4) F. Skoog, F. M. Strong, and C. O. Miller, *Science*, **148**, 532 (1965).

(5) J. van Overbeek, *ibid.*, **152**, 721 (1966).

(6) F. M. Strong, "Topics in Microbial Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1958, p 98.

(7) C. O. Miller, *Ann. Rev. Plant Physiol.*, **12**, 395 (1961).

(8) R. E. Deriaz, W. G. Overend, M. Stacey, and L. F. Wiggins, *J. Chem. Soc.*, 2836 (1949).

(9) C. S. Hudson, *J. Amer. Chem. Soc.*, **31**, 66 (1909); C. S. Hudson, *Advan. Carbohyd. Chem.*, **3**, 1 (1948).

(10) M. Hoffer, R. Duschinsky, J. J. Fox, and N. Yung, *J. Amer. Chem. Soc.*, **81**, 4112 (1959).

(11) R. U. Lemieux and M. Hoffer, *Can. J. Chem.*, **39**, 110 (1961).

(12) T. R. Emerson and T. L. V. Ulbricht, *Chem. Ind.* (London), 2129 (1964).

(13) R. H. Iwamoto, E. M. Acton, and L. Goodman, *J. Med. Chem.*, **6**, 684 (1963).

(14) D. L. MacDonald and H. G. Fletcher, Jr., *J. Amer. Chem. Soc.*, **84**, 1262 (1962).