(*c* 2.1, methanol), $n^{20}D$ 1.4568; lit.[25] $[\alpha]D$ +61.8° (methanol), nD 1.4581.

D. Methyl 2,3-Di-O-methyl-4-O-tosyl-D-xyloside.—The procedure is similar to that used for the preparation of the corresponding D-glucose derivative. The methyl 2,3-di-O-methyl-D-xyloside (21.5 *g.*) was allowed to react with 25.7 g. of tosyl chloride in 45 ml. of pyridine for 3 days. The yield was 36.0 g. (93%) of light brown syrup, $[\alpha]^{28}D$ 20.95° (*c* 6.2, chloroform). The infrared spectrum indicated no hydroxyl absorption.

E. 2,3-Di-O-methyl-4-O-tosyl-D-xylose.—The procedure is the same as that used for the preparation of the corresponding glucose derivative. The methyl 2,3-di-O-methyl-D-xyloside (35.3 g.) was hydrolyzed for 12 hr. in 900 ml. of a mixture of water–dioxane (1:1) containing 5 g. of hydrogen chloride per 100 ml. of solvent mixture. The yield was 19.1 g. (57%) of dark brown syrup, $[\alpha]^{28}D$ 25.1° (*c* 6.9, chloroform). The infrared spectrum indicated appreciable hydroxyl absorption.

F. 1,4-Anhydro-2,3-di-*O*-methyl-D-arabinose.—The procedure is the same as that used for the preparation of the corresponding D-galactose derivative. The 2,3-di-O-methyl-4-O-tosyl-D-xylose (18.8 g., 0.0565 mole) was dissolved in 940 ml. of anhydrous isopropyl alcohol and allowed to react with 0.0565 mole of sodium isopropoxide in 240 ml. of isopropyl alcohol. A simple vacuum distillation yielded 4.86 g. (54%) of a colorless oil, b.p. 61–63° (0.6 mm.). This material was found to be at least 95% pure in the two isomeric anhydro sugars by gas–liquid chromatography [3-ft. 10% poly(ethyleneglycol succinate), 190°]. Several crude fractions prepared as described above were combined and distilled on a 16-in. spinning-band column. The distillate (10.8 g., b.p. 49–50° at 0.22 mm.) was better than 99% pure in the two isomers as analyzed by gas–liquid chromatography (3-ft. 10% poly(ethyleneglycol succinate), 6-ft. 20% Carbowax 20M, and 6-ft. 20% silicone SE 52, all on firebrick, 180°). The last traces of impurities were removed by preparative gas–liquid chromatography (20-ft. 20% QF-1 on Chromosorb P, 180°). The product showed $[\alpha]^{29}D$ 128.5° *c* 3.5, chloroform), d^{25} 1.18.

Anal.[15] Calcd. for $C_7H_{12}O_4$: C, 52.49; H, 7.55. Found: C, 52.50; H, 7.57.

Paper Chromatography.—After hydrolysis of the anhydro sugars in 1% hydrochloric acid, the separation of the resulting sugars was done on Whatman No. 1 paper using a moving phase consisting of 1-butanol–water–ethanol (5:4:1) (upper layer) according to Hirst and Jones.[26] The pertinent R_G values have been compiled by Lederer.[27] 2,3-Di-O-methyl-D-xylose, 2,3,6-tri-O-methyl-D-glucose, and 2,3,4,6-tetra-O-methyl-D-glucose were used as reference compounds.

Acknowledgment.—This investigation has been supported by Research Grant GM-06168 from the Division of General Medical Sciences, National Institutes of Health.

(25) H. A. Hampton, W. N. Haworth, and E. L. Hirst, *J. Chem. Soc.*, 1739 (1929).

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Preparation of 2- and 4-Substituted D-Glucose Derivatives from 1,6-Anhydro-β-D-glucopyranose[1]

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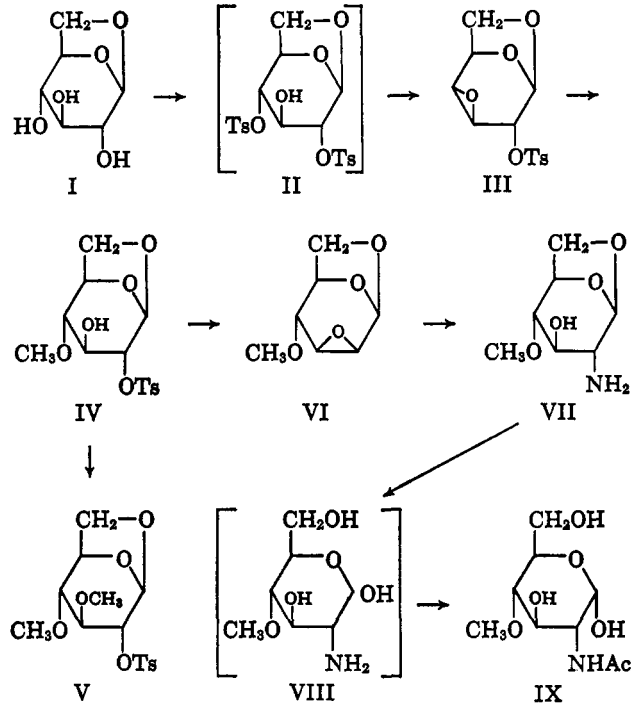
The partial esterification of 1,6-anhydro-β-D-glucopyranose (I) has been reported.[2,3] Substitution occurs predominantly at the 2- and 4-positions. Jeanloz, Rapin, and Hakomori[3] have pointed out that *p*-tolylsulfonate esters of 1,6-anhydro-β-D-glucopyranose should form epoxides useful for the preparation of derivatives of D-glucose. The molecule is made rigid by the 1,6-anhydro ring and places all hydroxyl groups in the axial position. This allows one to predict with confidence the results of opening the epoxide groups.[4-6] In addition the yields are better and the reaction products are less complicated by the selective opening. This will be the case, however, only if the 1,6-anhydro ring is preserved during the opening of the epoxide groups.

This paper reports on some 2,4-substituted compounds with the D-glucose configuration prepared *via* the diester and on the unusual action of sulfonic acid ion-exchange resins in opening the 3,4-epoxide group without splitting the 1,6-anhydro ring if the 2-position is occupied by the *p*-tolylsulfonyl group.

The diester II could possibly give two epoxides. Treatment with base has given only 1,6:3,4-dianhydro-2-*O*-*p*-tolylsulfonyl-β-D-galactopyranose (III).[2] This dianhydro compound is readily obtained from the crude ester mixture in about 50% yield from 1,6-anhydro-β-D-glucopyranose. It has also been obtained by Hann and Richtmyer from 1,6-anhydro-2,3,4-tri-*O*-*p*-tolylsulfonyl-β-D-glucopyranose.[7]



Attempts were made to open the 3,4-anhydro ring of III by methanol using both acidic and basic conditions. Reaction with sodium methoxide in methanol gave a complex mixture of products that was not investigated further. Černý, Buben, and Pacák[8] have shown that several compounds are formed when III is

(1) Presented at the 20th Northwest Regional Meeting of the American Chemical Society, Corvallis, Ore., June 1965.

(2) M. Černý, V. Gut, and J. Pacák, *Collection Czech. Chem. Commun.*, **26**, 2542 (1961).

(3) R. W. Jeanloz, A. M. C. Rapin, and S. Hakomori, *J. Org. Chem.*, **26**, 3939 (1961).

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(6) S. J. Angyal, *ibid.*, 1230 (1954).

(7) R. W. Jeanloz and A. M. C. Rapin, *J. Org. Chem.*, **28**, 2978 (1963), footnote 5.

(8) M. Černý, I. Buben, and J. Pacák, *Collection Czech. Chem. Commun.*, **28**, 1569 (1963).

treated with sodium hydroxide in aqueous ethanol. Hydrogen chloride in methanol also gave a mixture of products probably caused by cleavage of the 1,6-anhydro ring which destroyed the rigidity and made the opening of the epoxide ring undirected.

A method was discovered for opening the epoxy ring of III under acidic conditions which did not destroy the 1,6-anhydro bond. This involved refluxing in anhydrous methanol in the presence of an ion-exchange resin. A sulfonic acid resin such as Dowex 50 in the hydrogen form was found suitable. The dianhydro compound (III) gave, under these conditions, 1,6-anhydro-4-*O*-methyl-2-*O*-*p*-tolylsulfonyl-β-D-glucopyranose (IV) in excellent yield. This was an unexpected result in view of the fact that the same conditions with 1,6-anhydro-β-D-glucopyranose gave a quantitative yield of methyl glucoside. The presence of the tosyl group in the 2-position evidently prevents the opening of the 1,6-anhydro ring under these conditions. Similar ion-exchange resins have been used as catalysts to open the 1,6-anhydro group in compounds substituted in the 2-position with a methyl group.[8] Methylation of IV gave a compound with the same physical properties as reported for 1,6-anhydro-3,4-di-*O*-methyl-2-*O*-*p*-tolylsulfonyl-β-D-glucopyranose (V).[3]

The opening of the epoxy ring in III liberated a hydroxyl group in the 3-position. This is in position, with respect to the remaining tosyl group, to form a 2,3-epoxy ring. Treatment of IV with sodium methoxide in methanol gave 1,6:2,3-dianhydro-4-*O*-methyl-β-D-mannopyranose (VI).

The epoxy group of VI was opened by reaction with aqueous ammonia to give 2-amino-1,6-anhydro-2-deoxy-4-*O*-methyl-β-D-glucopyranose (VII). This compound was difficult to hydrolyze. The course of hydrolysis with refluxing 10% hydrochloric acid was followed by thin layer chromatography. This indicated a mixture of products forming but one predominant spot. After *N*-acetylation of the hydrolysate, a compound was crystallized which had physical constants which compared well with 2-acetamido-2-deoxy-4-*O*-methyl-α-D-glucopyranose (IX) described previously[9] and the infrared spectra were identical.[10] Separation of the mother liquor from the crystallization of IX by column chromatography yielded more IX and gave a small amount of crystalline material with same melting point and mixture melting point as authentic 2-acetamido-2-deoxy-D-glucopyranose.

Experimental Section

Melting points were taken on a Fischer melting point apparatus and correspond to "corrected melting point." Column chromatograms were by the elution method on Mallinckrodt silicic acid (Mallinckrodt Chemical Works, St. Louis, Mo.). The sequence of eluents was benzene, ether, ethyl acetate, acetone, and methanol, alone or in binary mixture. The ratio of weight of substance adsorbed to weight of adsorbent was about 1 to 100. The ratio of diameter to length of column was 1 to 23. Thin layer chromatography was performed by ascending method on silica gel G[11] (E. Merck, Darmstadt, Germany) or on Avirin microcrystalline cellulose[12] (American Viscose Division, FMC Corporation, Marcus Hook, Pa.). Spots were located on silica gel plates by spraying with anisaldehyde–sulfuric acid[11] and on cellulose plates by silver nitrate–sodium hydroxide.[13] Microanalyses were conducted by Drs. G. Weiler and F. B. Strauss, Oxford, England, and Galbraith Laboratories, Knoxville, Tenn.

Partial Esterification and Preparation of 1,6:3,4-Dianhydro-2-*O*-*p*-tolylsulfonyl-β-D-galactopyranose (III).—A solution of 10.0 g. of I in 50 ml. of dry pyridine was cooled to 0°. *p*-Toluenesulfonyl chloride (24.4 g.) in 70 ml. of pyridine and 100 ml. of chloroform was added dropwise. The reaction mixture was stirred at room temperature for 2 days. Water (10 ml.) was then added and the mixture was stirred for 2 hr. The chloroform layer was separated and washed with water, several portions of 5% sulfuric acid, and water. The solution was dried over sodium sulfate and the solvent was evaporated at reduced pressure. The syrupy residue weighed 24.7 g. It was dissolved in 260 ml. of chloroform, and 4.7 g. of sodium in 94 ml. of anhydrous methanol was added. After standing overnight there was a fine precipitate which was dissolved by the addition of a small amount of water. The layers were separated and the aqueous layer was extracted with chloroform. The combined chloroform solution was dried (sodium sulfate) and evaporated under reduced pressure to give a residue weighing 12.7 g. This was recrystallized from methanol containing a small amount of chloroform. The yield of crystals was 8.8 g., m.p. 150–151°, $[\alpha]^{28}D$ −37° (*c* 1.5, chloroform).[14]

1,6-Anhydro-4-*O*-methyl-2-*O*-*p*-tolylsulfonyl-β-D-glucopyranose (IV).—Dowex 50 (Dow Chemical Co., Midland, Mich.) ion-exchange resin (H^+ form) was dried by washing repeatedly with anhydrous methanol and drying in a vacuum oven at 50°. A mixture of 50.0 g. of dry Dowex 50 and a solution of 7.0 g. of dianhydro compound III in 300 ml. of anhydrous methanol was refluxed for 16 hr. Thin layer chromatography of the reaction mixture indicated a complete reaction to a new compound. The reaction mixture was filtered, and the ion-exchange resin was washed with methanol. Evaporation of the combined methanol solution gave 6.39 g. of syrup which crystallized. It was recrystallized twice from ethanol–water: yield 3.8 g. (49%), m.p. 89–90°, $[\alpha]^{25}D$ −43.6° (*c* 1.1, chloroform).

Anal. Calcd. for $C_{14}H_{18}O_7S$: C, 51.0; H, 5.46; S, 9.7; OCH_3, 9.4. Found: C, 51.1; H, 5.48; S, 9.8; OCH_3, 9.1.

1,6-Anhydro-3,4-di-*O*-methyl-2-*O*-*p*-tolylsulfonyl-β-D-glucopyranose (V).—A mixture of 700 mg. of IV, 700 mg. of freshly prepared silver oxide, and 25 ml. of methyl iodide was refluxed with stirring for 24 hr. An additional 700 mg. of silver oxide was added and heating was continued for a total of 3 days. The reaction mixture was filtered and the residue was washed several times with hot acetone. Evaporation of the solvents left 820 mg. of syrup which was chromatographed on silicic acid. Mixtures of benzene and ether (9:1, 8:2, and 7:3) eluted 490 mg. which was recrystallized from acetone, ether, and petroleum ether (b.p. 30–60°) to give 250 mg. (34%), m.p. 105–107°, $[\alpha]^{25}D$ −34.3° (*c* 1.2, methanol).[15]

Anal. Calcd. for $C_{15}H_{20}O_7S$: C, 52.31; H, 5.85; S, 9.31; OCH_3, 18.02. Found: C, 52.15; H, 5.82; S, 9.04; OCH_3, 17.48.

1,6:2,3-Dianhydro-4-*O*-methyl-β-D-mannopyranose (VI).—A solution of 10.0 g. of methanolysis product IV in 200 ml. of anhydrous methanol containing 0.92 g. of sodium was stirred at room temperature for 18 hr. The reaction mixture was neutralized carefully with 5% sulfuric acid. The salt was filtered. The filtrate was evaporated at reduced pressure. The residue was dissolved in acetone, filtered to remove salt, and evaporated again. This was repeated three times. The final residue from evaporation of the solvent weighed 4.8 g. It was recrystallized from petroleum ether, ether, and methanol: yield 3.4 g. (71%), m.p. 52–58°, $[\alpha]^{20}D$ −40.2° (*c* 1.2, methanol).

Anal. Calcd. for $C_7H_{10}O_4$: C, 53.16; H, 6.33; OCH_3, 19.6. Found: C, 53.29; H, 6.73; OCH_3, 17.5.

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(13) W. F. Trevelyan, D. P. Proctor, and J. S. Harrison, *Nature*, **166**, 444 (1950).
(14) Černý, Gut, and Pacák[2] reported m.p. 148–150°, $[\alpha]D$ −40° (*c* 1.4, chloroform); Jeanloz and Rapin[15] reported m.p. 149–150°, $[\alpha]^{28}D$ −37° (*c* 0.56, chloroform); Hann and Richtmyer[7] observed m.p. 149–149.5°, $[\alpha]^{20}D$ −41.7° (*c* 1, chloroform).
(15) R. W. Jeanloz and A. M. C. Rapin, *J. Org. Chem.*, **28**, 2978 (1963).
(16) Jeanloz, Rapin, and Hakomori[3] reported m.p. 105–107°, $[\alpha]^{22}D$ −38 ± 10° (*c* 0.92, methanol).

2-Amino-1,6-anhydro-2-deoxy-4-*O*-methyl-β-D-glucopyranose (VII).—1,6:2,3-Dianhydro-4-*O*-methyl-β-D-mannopyranose (0.1 g.) was sealed in a glass tube with 5.0-ml. of concentrated ammonium hydroxide. The ampoule was heated in a steam bath for 30 hr. Evaporation of the aqueous ammonia at reduced pressure left a residue of 0.1 g. which crystallized. Recrystallization from isopropyl alcohol gave 0.076 g. (68%), m.p. 160–161°, $[\alpha]^{20}D$ −69.6° (*c* 1.2, methanol).

Anal. Calcd. for $C_7H_{13}NO_4$: C, 48.0; H, 7.43; N, 8.0. Found: C, 48.26; H, 7.46; N, 8.20.

2-Acetamido-2-deoxy-4-*O*-methyl-α-D-glucopyranose (IX).—2-Amino-1,6-anhydro-2-deoxy-4-*O*-methyl-β-D-glucopyranose (0.45 g.) was refluxed with 25 ml. of 10% hydrochloric acid for 48 hr. The reaction mixture was filtered through a layer of Celite and decolorizing carbon. The colorless filtrate was evaporated under reduced pressure to give 0.57 g. of residue. The residue was dissolved in 6 ml. of anhydrous methanol containing 0.06 g. of sodium. The salt that separated was removed by filtration. To the filtrate was added 0.31 g. of acetic anhydride (1.2 equiv.) with stirring. After standing at room temperature for 40 hr. the reaction mixture was evaporated at 50° at reduced pressure. The residue (0.7 g.) was dissolved in methanol. Ether was added to turbidity. About 0.2 g. of crystalline material separated on standing which had m.p. 209–212° dec. after a second recrystallization.

The mother liquor from the crystallization (0.5 g.) was chromatographed on a column of silicic acid. An additional 34 mg. of IX was separated which, after recrystallization from methanol–ether, had m.p. 218–219° dec. The compound showed mutarotation from $[\alpha]^{20}D$ +83° to $[\alpha]^{20}D$ +70° (after 16 min.) to $[\alpha]^{20}D$ +47° (after 24 hr. in water, *c* 0.85).[17]

Anal. Calcd. for $C_9H_{17}NO_6$: C, 45.95; H, 7.28; N, 5.95. Found: C, 45.81; H, 7.13; N, 6.05.

Also isolated from the column chromatography was 10 mg. of crystals which, after recrystallization from methanol–ether, had m.p. 207–209°. The mixture melting point with authentic 2-acetamido-2-deoxy-D-glucopyranose[18] was not lowered.

Acknowledgment.—The author thanks Dr. Roger W. Jeanloz for the infrared spectra of 2-acetamido-2-deoxy-4-*O*-methyl-α-D-glucopyranose.

(17) Jeanloz and Gansser[9] reported m.p. 211–215° dec. and mutarotation from $[\alpha]^{24}D$ +79° (after 16 min.) to $[\alpha]^{22}D$ +69° (after 24 hr.) (*c* 1.02, water).

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2-Deoxy Sugars. XI. Additional Pyrimidine Nucleosides Containing 2-Deoxy-D-*arabino*-hexopyranose and 2-Deoxy-D-*ribo*-hexopyranose[1]

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Received July 1, 1965

The discovery[3] that 1-(2-deoxy-β-D-*arabino*-hexopyranosyl)thymine ("2-deoxyglucosylthymine")[4] is a powerful and specific inhibitor of a pyrimidine nucleoside phosphorylase, obtained from Ehrlich's ascites tumor cells, prompted us to investigate the preparation of additional pyrimidine nucleosides containing 2-deoxyhexoses.

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(2) (a) Predoctoral research assistant. (b) Postdoctoral research associate, Georgetown University, 1963–1965.

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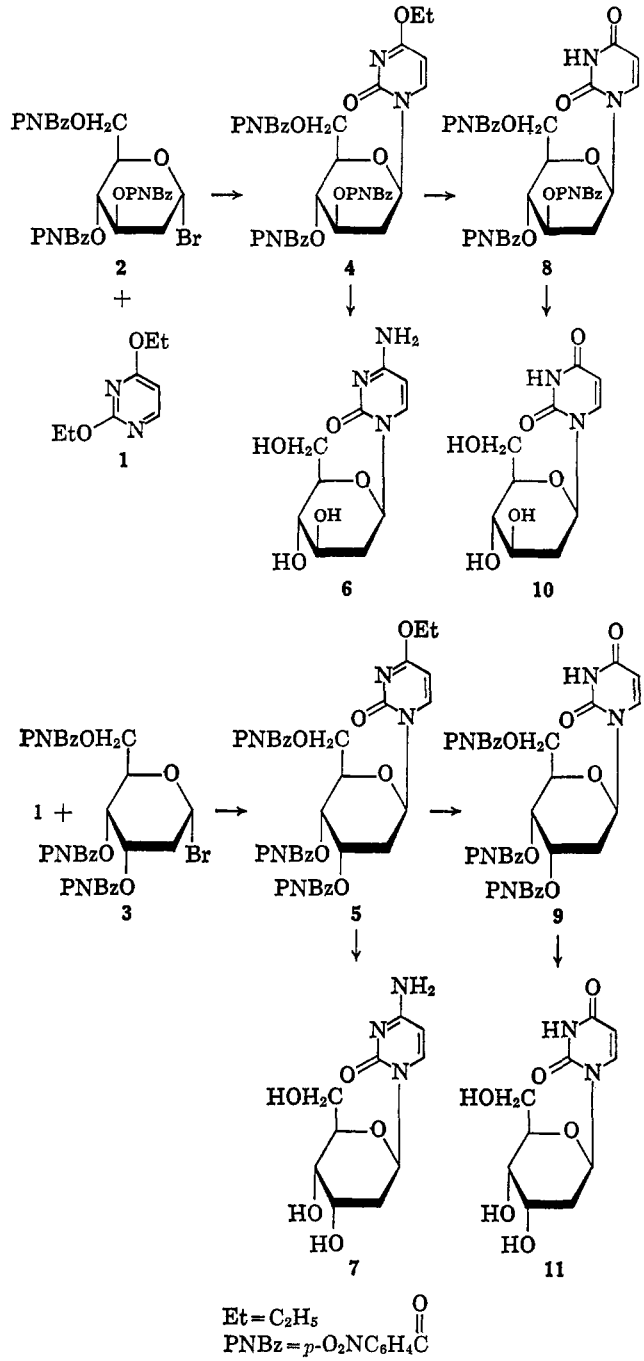
SCHEME I



The presently described study provides for a further extension of our work dealing with the direct synthesis of 2-deoxyglycosides employing stable, crystalline 2-deoxy-*O*-*p*-nitrobenzoylglycosyl halides. An added advantage of this methodology, adequately demonstrated in the present study, is that nitrobenzoylation has conferred crystalline character on *all* nucleoside intermediates[5] which could, therefore be characterized by elemental analysis.

The coupling (see Scheme I) of 2,4-diethoxypyrimidine (1) with 2-deoxy-3,4,6-tri-*O*-*p*-nitrobenzoyl-α-

(5) The use of nitrobenzoylated halides led to crystalline intermediates in the synthesis of (a) 1-(2-deoxy-β-D-*ribo*-hexopyranosyl)thymine [W. W. Zorbach and S. Saeki, *ibid.*, **29**, 2018 (1964)], and also (b) of 1-(2-deoxy β-D-*arabino*-hexopyranosyl)-5-fluorocytosine [G. J. Durr, *J. Med. Chem.*, **8**, 140 (1965)].