Synthetic Nucleosides. LIV.[1,2] Facile Displacement Reactions in the D-Mannitol Series. I

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Received September 24, 1962

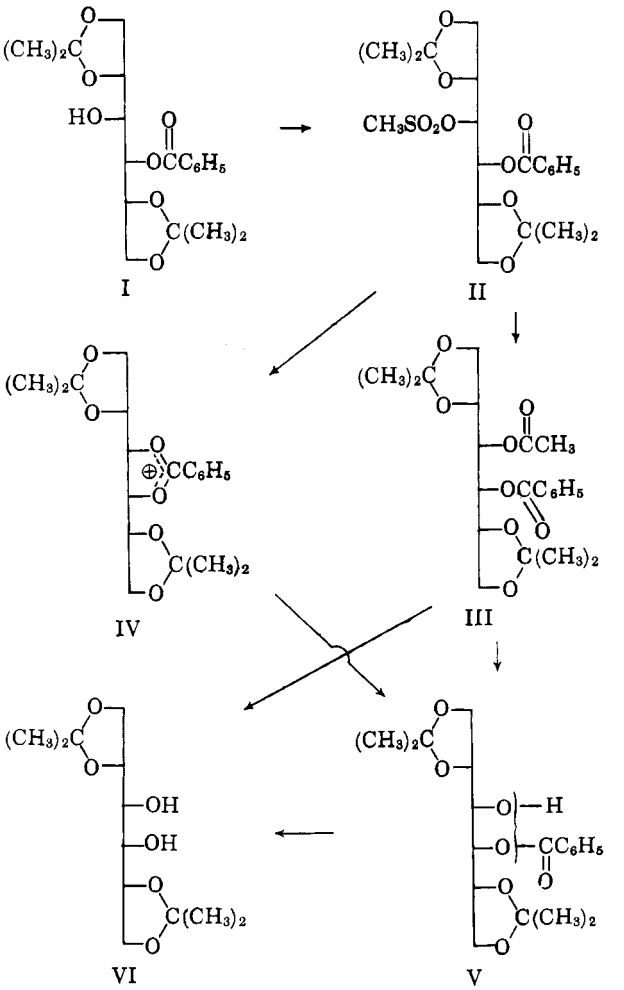
The mesyloxy group of 4-O-benzoyl-1,2:5,6-di-O-isopropylidene-3-O-mesyl-D-mannitol (II) could be displaced by nucleophilic groups, in contrast to most acetonated furanosides and pyranosides containing a ring sulfonate. The mesyloxy group of II could be displaced anchimerically by the adjacent benzoyloxy group, which on debenzoylation afforded the C-3 inversion product (VI) with the D-talitol configuration. The bimolecular reaction of II with acetate ion was shown to be weakly competitive with the anchimeric reaction; the more nucleophilic azide ion was strongly competitive with the anchimeric reaction and allowed introduction of the azido group into the hexitol chain. The anchimeric assistance with an adjacent 4-methoxyl group was negligible, as anticipated, and evidence for SN2 displacement of the mesyloxy group of IX by acetate was observed.

Displacement reactions of a secondary sulfonate on a carbohydrate derivative, useful for synthesis of rare sugars, has been limited primarily to sulfonates on a side chain carbon or to cases where neighboring group participation can occur. For example, reaction of methyl 6-deoxy-2,3-O-isopropylidene-5-O-tosyl-β,D-allofuranoside with sodium benzoate in boiling dimethylformamide readily forms methyl 5-O-benzoyl-6-deoxy-2,3-O-isopropylidene-α,L-talofuranoside with Walden inversion[3]: in contrast, 1,2:5,6-di-O-isopropylidene-3-O-tosyl-D-glucofuranose, a compound with a ring sulfonate, fails to react under these conditions.[4] Only in relatively rare instances of favorable conformation and reactivity can ring sulfonates be displaced by the sodium benzoate–dimethylformamide reagent, such as conversion of methyl 2,3-di-O-benzoyl-4,6-di-O-tosyl-α,D-galactopyranoside to methyl 2,3,4,6-tetra-O-benzoyl-α,D-glucopyranoside.[5]

Although neighboring participation by an acetamido group is a feasible reaction for inversion of carbohydrate configuration,[6] this type of inversion by the less reactive[7] neighboring acyloxy group has been uniformly unsuccessful[4, 8]; these results are attributed to the low reactivity of the system which results only in slow cleavage of the acyloxy group, rather than the desired C—O cleavage of the sulfonate ester.

The relative ease of oxidation of the open chain hydroxyl of 3-O-benzoyl-1,2:5,6-di-O-isopropylidene-D-mannitol (I) with chromium trioxide in pyridine to the corresponding ketone, 4-O-benzoyl-1,2:5,6-di-O-isopropylidene-D-*arabo*-3-hexulose, in 50% yield[9] contrasts drastically with the poor yields (0.3–5%) obtained by oxidation of a carbohydrate ring hydroxyl.[10] Since one of the important factors in oxidation of a carbinol to the ketone is the ability of the carbinol to break at the C—H bond,[11] it follows that the difficulty of displacement of the corresponding carbinyl sulfonate (II) with Walden inversion would be roughly parallel. That such is the case has now been demonstrated in the D-mannitol series.

Treatment of 3-O-benzoyl-1,2:5,6-di-O-isopropylidene-D-mannitol (I)[9] with methanesulfonyl chloride



in pyridine gave a 96% yield of sirupy 4-O-mesyl derivative (II), suitable for further transformations; this ultimately crystallized and had m.p. 73–75°. Treatment of II with sodium acetate in boiling dimethyl-

(1) A list of collected references on synthetic nucleosides by B. R. Baker and co-workers will be sent on request.

(2) This work was generously supported by the National Cancer Institute, grant no. CY-5845.

(3) E. J. Reist, L. Goodman, and B. R. Baker, *J. Am. Chem. Soc.*, **80**, 5775 (1958).

(4) Unpublished work by B. R. Baker and co-workers.

(5) E. J. Reist, R. R. Spencer, and B. R. Baker, *J. Org. Chem.*, **24**, 1618 (1959).

(6) (a) B. R. Baker and R. E. Schaub, *ibid.*, **19**, 646 (1954); (b) B. R. Baker, R. E. Schaub, and J. H. Williams, *J. Am. Chem. Soc.*, **77**, 7 (1955); (c) R. W. Jeanloz, *ibid.*, **79**, 2591 (1957).

(7) S. Winstein and R. Boschan, *ibid.*, **72**, 4669 (1950).

(8) S. Peat and L. F. Wiggins, *J. Chem. Soc.*, 1088 (1938); R. W. Jeanloz and D. A. Jeanloz, *J. Am. Chem. Soc.*, **80**, 5692 (1958).

(9) J. M. Sugihara and G. U. Yuen, *ibid.*, **79**, 5780 (1957).

(10) O. Theander, *et al.*, *Acta Chem. Scand.*, **15**, 437 (1961); **12**, 1507 (1958); **11**, 1557 (1957); E. Brimacombe, J. S. Brimacombe, and B. Lindberg, *ibid.*, **14**, 2236 (1960); B. R. Baker and E. J. Reist, unpublished data on chromium trioxide–pyridine oxidation of 1,2:5,6-di-O-isopropylidene-D-glucofuranose and 1,2-O-isopropylidene-5-carbomethoxy-D-xylofuranose.

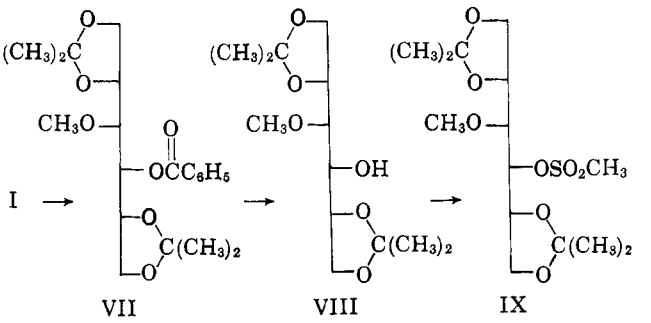
(11) F. H. Westheimer and N. Nicolaides, *J. Am. Chem. Soc.*, **71**, 25 (1949).

formamide containing 0.5% of water for twenty-two hours gave what appeared to be a mixture of monobenzoates (V). One of these two benzoates could be isolated crystalline, m.p. 124–125°. Debenzoylation of the crystalline benzoate with methanolic sodium methoxide gave 1,2:5,6-di-O-isopropylidene-D-talitol (VI), m.p. 62–64°, identical with an authentic sample.[9, 12] Debenzoylation of the mixed benzoates (V) gave crystalline VI in 44% over-all yield from I *via* II. This preparation of VI is stereospecific and is probably a superior preparative method to reduction of the ketone to two diastereoisomers which can be separated by column technics to give about 25% yield of VI from I.[9]

Since it is possible for V to arise either by direct SN2 displacement of the mesylate group of II by acetate *via* III or by participation of the neighboring benzoyloxy group *via* the ortho ester ion, IV, the reaction was investigated in greater detail to shed light on the possible mechanism. Chromatographic separation of the crude reaction product gave, in addition to the mixed hydroxy benzoates (V), about 10% yield of an oil having no hydroxyl absorption in the infrared, but showing characteristic acetate bands with carbonyl at 1725 cm.$^{-1}$ and greatly increased C—O—C at 1220 cm.$^{-1}$; the benzoate group showed C=O at 1720 cm.$^{-1}$ and C—O—C at 1265 cm.$^{-1}$. Deacylation of this acetate with methanolic sodium methoxide afforded the crystalline talitol derivative, VI, showing that the acetate must have structure III. Since O-acetates can be hydrolyzed under the conditions of this reaction,[6b] III could also serve as a source of the monobenzoates, V. Thus the SN2 mechanism can and does operate.

It was also of interest to see if fluoride ion was a sufficiently strong nucleophile to displace the mesylate of II, since the resultant fluorohexitol could feasibly be converted into a 2′-fluoro-2′-deoxynucleoside of potential use in chemotherapy. Not too surprising was the fact that fluorine was not introduced into the hexitol molecule when the mesylate (II) reacted with sodium fluoride in anhydrous dimethylformamide at the boiling point; in fact, the same crystalline benzoate (V) was obtained as in the sodium acetate experiment, which, in turn was debenzoylated to crystalline VI. The formation of V in the sodium fluoride experiment can only be interpreted to proceed *via* the ortho ester ion (IV). Without sodium fluoride, the mesylate group of II was still ejected in boiling dimethylformamide to give an oil with an infrared spectrum compatible with structure V; however, the crystalline talitol (VI) could not be isolated on debenzoylation indicating that some additional structure changes might have taken place. Thus, the fact that III could be isolated from the sodium acetate experiment and the fact that the sodium fluoride gave V *via* an ortho ester ion (IV) show that both the SN2 and the neighboring group participation reaction can operate in a molecule such as II. Therefore, it should be possible to influence the ratio of the SN2 route to the anchimeric route by using either more powerful nucleophiles or more or less powerful anchimeric groups.

In order to investigate the effects of two less effective anchimeric groups, the O-*p*-nitrobenzoyloxy and the methoxyl groups were investigated. Methylation of I with methyl iodide and silver oxide in dimethylformamide[13] gave VII as an oil, which could be debenzoylated with methanolic sodium methoxide to crystalline VIII[14] in 46% over-all yield from I. Treatment of VIII with mesyl chloride in pyridine afforded 75% of IX, m.p. 72–73°.



The effect of boiling a solution of IX in dimethylformamide with and without the presence of sodium acetate was investigated qualitatively. Without sodium acetate, the mesylate (IX) was recovered essentially unchanged after five hours, although some darkening occurred. In the presence of sodium acetate, the solution darkened less readily and could be refluxed for twenty-two hours; after this time an infrared spectrum of the product showed the loss of the mesylate bands at 1325 and 1175 cm.$^{-1}$ and the formation of an acetate band at 1740 cm.$^{-1}$. The latter experiment was repeated in the presence of 1% water; again the mesylate was ejected by SN2 attack of acetate and some of the resultant acetate was hydrolyzed to hydroxyl as shown by an additional band at 3500 cm.$^{-1}$. These experiments show qualitatively, as anticipated, that the methoxyl is a poor anchimeric group and that mesylate displacement occurs primarily by the SN2 mechanism.

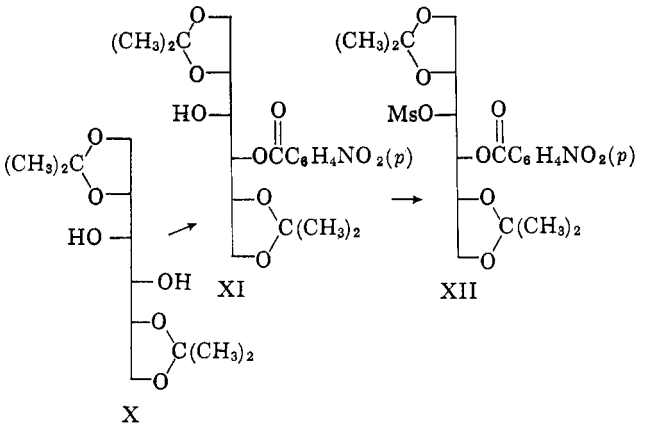
The *p*-nitrobenzoyloxy anchimeric group was also investigated, since it could be expected to be better than methoxyl but poorer than benzoyloxy. Treatment of 1,2:5,6-di-O-isopropylidene-D-mannitol[15] (X) with one mole-equivalent of *p*-nitrobenzoyl chloride in pyridine gave—as in the case of benzoyl chloride—a mixture of mono-*p*-nitrobenzoyl (XI) di-*p*-nitrobenzoyl, and unchanged X. Unfortunately, the mono derivative (XI) could not be crystallized, but could be obtained essentially pure by removal of the di derivative by crystallization from ethyl acetate–methanol and the unchanged X from ethyl acetate–petroleum ether. Mesylation of XI in pyridine gave a 55% yield of XII, m.p. 94–96°. In a qualitative experiment, the *p*-nitrobenzoyloxy group could act as an anchimeric group, since reflux of a solution in dry dimethylformamide in the absence of acetate gave a product that showed hydroxyl absorption at 3500 cm.$^{-1}$; in the presence of sodium acetate and 1% water, the product showed both hydroxyl and acetate absorption.

(12) We wish to thank Dr. Sugihara for sending us an authentic sample of this compound.

(13) R. Kuhn, H. Trischmann, and I. Löw, *Angew. Chem.*, **67**, 32 (1955)

(14) (a) P. Bladon and N. Owen [*J. Chem. Soc.*, 604 (1950)] have obtained VIII as an oil contaminated with 1,2:5,6-di-O-isopropylidene-3-O-methyl-D-iditol when 3,4-anhydro-1,2:5,6-di-O-isopropylidene-D-talitol reacted with methanolic sodium methoxide at 100°; (b) W. T. Haskins, R. M. Hann, and C. S. Hudson [*J. Am. Chem. Soc.*, **65**, 70 (1943)] obtained a 3-O-methyl-di-O-isopropylidene-D-mannitol of unassigned structure from 3-O-methyl-D-mannitol and acetone; the properties of their compound agree with that of VIII.

(15) E. Baer, *ibid.*, **67**, 338 (1945).



The more powerful nucleophile, azide ion, could give direct SN2 displacement of the mesylate of II with formation of an azido hexitol; reduction of the azide to give 3-amino-3-deoxy-1,2:5,6-di-O-isopropylidene-D-altritol and the structure proof of the latter compound is the subject of the following paper.[16]

In conclusion, the SN2 displacement of the secondary tosylate group of methyl 6-deoxy-2,3-O-isopropylidene-5-O-tosyl-β,D-allofuranoside[3] can be duplicated on a carbon further down the sugar chain, providing that carbon is not part of a ring. Although a hexitol derivative is cited as an example, open chain pentose or hexose derivatives—such as acetals or thioacetals—may possibly be used for displacement reactions. Finally, the chemistry of hexitols has been sufficiently established[17] to suggest the belief that the new hexitol formed in a displacement reaction could be converted further to a pentose or hexose. Thus, any laboratory desiring to run a difficult displacement reaction on a carbohydrate derivative should consider the increased reactivity afforded by the open chain forms.

Experimental[18]

3-O-Benzoyl-1,2:5,6-di-O-isopropylidene-4-O-mesyl-D-mannitol (II).—To a solution of 15 g. (41 mmoles) of 3-O-benzoyl-1,2:5,6-di-O-isopropylidene-D-mannitol (I)[9] in 30 ml. of reagent pyridine was added 7.1 g. (62 mmoles) of mesyl chloride. After 24 hr. at room temperature in a stoppered flask, the mixture was poured into 300 g. of ice–water which had been saturated with sodium bicarbonate. The mixture was extracted with chloroform (5 × 80 ml.) and the combined extracts were washed with excess sodium bicarbonate, then water. The dried (magnesium sulfate) organic solution was concentrated *in vacuo*, and the last traces of pyridine were removed by addition and evaporation of toluene *in vacuo*. A solution of the sirup in petroleum ether–benzene was treated with charcoal, then concentrated *in vacuo* to yield 17.4 g. (96%) of an analytically pure sirup which was suitable for further transformations. On storage at room temperature for several days, the material crystallized. The crystalline material was triturated with petroleum ether and recrystallized from petroleum ether–benzene, to give colorless needles, m.p. 73–75°, $[\alpha]^{24}D$ +13.9 ± 0.5; ν_{max}^{Nujol} 1725 (C=O); 1350, 1170 (—OSO_2—); 706 cm.$^{-1}$ (C—H of benzoate).

Anal. Calcd. for $C_{20}H_{28}O_9S$: C, 54.0; H, 6.36; S, 7.20. Found: C, 54.1; H, 6.15; S, 7.28.

1,2-5,6-Di-O-isopropylidene-D-talitol (VI).—A mixture of 4.4 g. (10 mmoles) of II, 2.5 g. (31 mmoles) of anhydrous sodium acetate, and 40 ml. of dimethylformamide, containing about 0.5% water, was refluxed for 22 hr. The cooled solution was filtered, and the solid was washed with chloroform. The filtrate was diluted with 150 ml. of chloroform and washed with 50 ml. of water. The aqueous layer was extracted with chloroform (2 × 30 ml.), and the combined chloroform extracts were extracted with 30 ml. of water. Concentration of the dried (magnesium sulfate) organic solution *in vacuo* yielded a dark-colored sirup which was treated with charcoal in petroleum ether–benzene. Reconcentration of the filtered solution yielded a clear sirup of V; ν_{max}^{film} 3500 (OH), 1725 cm.$^{-1}$ (C=O).

To a solution of this sirup in 30 ml. of methanol was added about 0.01 g. of sodium; after storage overnight at room temperature in a stoppered flask, 0.1 ml. of water was added and carbon dioxide passed through the solution for 10 min. The residue obtained on concentration of the solution *in vacuo* was extracted with petroleum ether containing 5% ethyl acetate. Concentration of the extract gave a sirup which was crystallized from petroleum ether to yield 1.0 g. (46%) of VI, m.p. 62–63°; a mixture with an authentic sample[9] had m.p. 63–64° and infrared spectra of the two samples were indistinguishable.

Benzoylation of VI overnight in pyridine with benzoyl chloride yielded 85% of 3,4-di-O-benzoyl derivative, m.p. 144–145°, $[\alpha]^{24}D$ +55.4 ± 0.3; ν_{max}^{Nujol} 1725 (C=O); 1260 and 1120 (benzoate C—O—C); 712 cm.$^{-1}$ (benzoate C—H).

Anal. Calcd. for $C_{26}H_{30}O_8$: C, 66.4; H, 6.44. Found: C, 66.1; H, 6.47.

Reaction of II with Sodium Acetate in Dimethylformamide Containing Water.—A mixture of 2.2 g. (5 mmoles) of II, 1.25 g. (15 mmoles) of anhydrous sodium acetate and 20 ml. of dimethylformamide, containing about 0.5% water, was heated under reflux for 22 hr., and the sirupy product isolated as described above for V. The dark-colored sirup was clarified by passing its ether solution through a short column of alumina.[19] The eluate was evaporated *in vacuo*, the residue (1.48 g.) dissolved in 10 ml. of benzene, and introduced onto a column of alumina (35 × 1.2 cm.). The column was eluted initially with 50% benzene–petroleum ether, and 50 ml. fractions were collected. Fractions 1 and 2 gave residues of 0.165 g. and 0.094 g. respectively, both of them having, in their infrared spectra, no absorption at 3600 (OH), broad absorption at 1725 (acetate C=O), and increased absorption at 1220 cm.$^{-1}$ (acetate C—O—C) in addition to absorption due to benzoate. These two fractions were combined; 0.113 g. of the resultant sirup was deacylated as described in the previous experiment for VI; yield 0.033 g. of VI, m.p. 59–62°.

Fraction 4 showed an absorption at 3600 (OH) and a narrow absorption band at 1710 cm.$^{-1}$ (C=O). The column was then eluted with 200 ml. of ether to give on concentration of the eluate 1.1 g. of a sirup of the mixed benzoates (V). A portion (0.74 g.) of this sirup was fractionally crystallized from petroleum ether–ethyl acetate to give 0.214 g. of a compound, m.p. 119–122°, whose infrared spectrum was identical to that of the mono-O-benzoyl-1,2,-5,6-di-O-isopropylidene-D-talitol, m.p. 124–125°, isolated from the reflux of a mixture of II and sodium fluoride in dimethylformamide solution (*vide infra*). The mother liquor from the fractional crystallization yielded an oil on concentration, which was de-O-benzoylated with usual manner to yield 0.03 g. of VI, m.p. 60–61°.

Reaction of II with Sodium Fluoride in Dimethylformamide.—A mixture of 0.61 g. of II, 0.6 g. of sodium fluoride, and 6 ml. of dry dimethylformamide (spectro grade) was heated under reflux for 8 hr., protected from moisture, and then poured into 100 ml. of 1% aqueous sodium hydrogen carbonate. The aqueous mixture was heated to 80° and then allowed to stand at room temperature for 24 hr., during which time 0.12 g. of crystals was deposited. The collected crystals were recrystallized from ethyl acetate–petroleum ether to yield a product (V), m.p. 124–125°; $[\alpha]^{24}D$ +15.3 ± 0.3; ν_{max}^{Nujol} 3650 (OH); 1720 (C=O); 1270 and 1120 (benzoate C—O—C); 708 cm.$^{-1}$ (benzoate C—H).

Anal. Calcd. for $C_{19}H_{26}O_6$: C, 62.3; H, 7.15. Found: C, 62.5; H, 6.95.

De-O-benzoylation of this compound gave VI, m.p. 62–64°, and mixed m.p. 63–64° with an authentic sample.[9,12] Their infrared spectra were also identical.

A similar reaction using sodium azide in place of sodium fluoride resulted in a product containing a C-azido band at 2110 cm.$^{-1}$.

(16) B. R. Baker and A. H. Haines, paper LV of this series, *J. Org. Chem.*, **28**, 442 (1963).

(17) S. A. Barker and E. J. Bourne, *Advan. Carbohydrate Chem.*, **7**, 137 (1952).

(18) Routine identifications were based on mixed melting points and infrared spectra. Melting points were determined in capillary tubes on a Mel-Temp heated block apparatus and are uncorrected. Optical rotations were determined in a 1-dm. microtube as a 1% chloroform solution. Petroleum ether refers to that fraction of b.p. 30–60°.

(19) The alumina used in the chromatographic experiments was Bio-Rad chromatographic aluminum oxide, neutral alumina AG-7, 100–200 mesh to which 6% water was added giving approximately Brockmann activity grade III.

The nature of this product is the subject of the accompanying paper.[16]

3-O-Benzoyl-1,2:5,6-di-O-isopropylidene-4-O-methyl-D-mannitol (VII).—To a solution of 9.8 g. of I[15] in 90 ml. of dimethylformamide and 10 ml. of methyl iodide was added, portionwise 10.5 g. of silver oxide; then the mixture was stirred at room temperature for 48 hr.[13] The solution was diluted with 150 ml. of chloroform, filtered, and concentrated *in vacuo* to give a sirup which was filtered through a charcoal pad to remove silver residues. After concentration *in vacuo*, the residue was redissolved in petroleum ether and again filtered through charcoal. Concentration *in vacuo* yielded 8.9 g. (88%) of VII as an oil; ν_{max}^{film} 1725 (benzoate C=O), 710 (benzoate C—H), and no OH near 3600 cm.$^{-1}$.

Anal. Calcd. for $C_{20}H_{18}O_7$: C, 63.1; H, 7.43. Found: C, 63.0; H, 7.50.

1,2:5,6-Di-O-isopropylidene-3-O-methyl-D-mannitol (VIII). To a solution of 8.26 g. (22 mmoles) of VII in 50 ml. of methanol was added 1 ml. of N-sodium methoxide; then the solution was refluxed for 2 hr. Water (0.1 ml.) was added followed by solid carbon dioxide, and the reaction mixture was concentrated *in vacuo*. The residue was extracted with 100 ml. of chloroform, and the organic extract washed with 25 ml. of water and dried over magnesium sulfate. Filtration and evaporation *in vacuo* yielded a sirup containing methyl benzoate; the latter was azeotropically removed by the addition and spin-evaporation of water (4 × 25 ml.) *in vacuo*. The sirup was dried by azeotropic removal of traces of water with benzene, then dissolved in petroleum ether and filtered. Concentration of the filtrate *in vacuo* yielded 4.3 g. (75%) of a sirup which crystallized on standing at room temperature. Recrystallization from petroleum ether in an ethanol–Dry Ice bath afforded 1.88 g. (31%) white crystals, m.p. 55–57°, and a second crop of 0.9 g. (15%), m.p. 50–55°. A further recrystallization from petroleum ether gave white crystals, m.p. 58–59°; $[\alpha]^{24}D$ −0.3 ± 0.2; ν_{max}^{Nujol} 3500 (OH), and no C=O absorption near 1725 cm.$^{-1}$.

Anal. Calcd. for $C_{13}H_{24}O_6$: C, 56.5; H, 8.77. Found: C, 56.7; H, 8.89.

1,2:5,6-Di-O-isopropylidene-3-O-mesyl-4-O-methyl-D-mannitol (IX).—To a solution of 0.92 g. (3.3 mmoles) of VIII (m.p. 55–57°) in 5 ml. of reagent pyridine was added 0.4 ml. of mesyl chloride, then the mixture was stored for 24 hr. at room temperature in a stoppered flask. The reaction mixture was poured into saturated aqueous sodium bicarbonate, and the suspension was extracted with chloroform (3 × 50 ml.). The combined extracts were washed with 25 ml. of water, dried over magnesium sulfate and concentrated to yield 1.2 g. of a sirup from which the last traces of pyridine were removed by the addition and evaporation of toluene *in vacuo*. The sirup was treated with charcoal in petroleum ether, then in methanol, and finally crystallized from ethyl acetate–petroleum ether to yield 0.88 g. (75%) of IX, m.p. 71–73°, $[\alpha]^{24}D$ + 9.0 ± 0.2; ν_{max}^{Nujol} 1325, 1175 cm.$^{-1}$ (—OSO_2—).

Anal. Calcd. for $C_{14}H_{26}O_8S$: C, 47.4; H, 7.41; S, 9.03. Found: C, 47.6; H, 7.50; S, 8.96.

Reaction of IX with Sodium Acetate in Dimethylformamide.—A mixture of 0.18 g. (0.51 mmole) of IX, 0.125 g. (1.52 mmoles) of anhydrous sodium acetate, and 2 ml. of dimethylformamide (spectro grade) was heated under reflux, protected from moisture for 22 hr.; isolation of the product as described above[20] afforded 0.080 g. of a sirup; ν_{max}^{film} 1740 cm.$^{-1}$ (C=O) and adsorption at 1175 cm.$^{-1}$ (—OSO_2 -) was absent, indicating no sulfonate group in the product. Neither this sirup nor its O-deacylated product could be crystallized.

In the absence of sodium acetate, IX was recovered unchanged after 5 hr.

(20) This method of isolation of the reaction product for reactions carried out in dimethylformamide was that described for preparation of VI.

Reaction of IX with Sodium Acetate in Dimethylformamide Containing 1% Water.—Reflux of a solution of 0.18 g. (0.51 mmole) of IX and 0.125 g. (1.52 mmoles) of sodium acetate in 2 ml. of dimethylformamide containing 1% water for 22 hr. and isolation of the product as described above[20] yielded 0.085 g. of a sirup; ν_{max}^{film} 3500 (OH); 1740 cm.$^{-1}$ (C=O). Absorption at 1175 cm.$^{-1}$ (—OSO_2—) was barely apparent, suggesting the presence of a small amount of unreacted IX.

1,2:5,6-Di-O-isopropylidene-3-O-*p*-nitrobenzoyl-D-mannitol (XI).—A solution of 3.1 g. (16.8 mmoles) of *p*-nitrobenzoyl chloride in 15 ml. of reagent pyridine (warmed to achieve solution) was added to a solution of 4.4 g. (16.8 mmoles) of 1,2:5,6-di-O-isopropylidene-D-mannitol (X)[15] in 6 ml. of reagent pyridine, and the mixture was stored overnight at room temperature protected from moisture. Water (0.5 ml.) was then added and after 10 min., the solution was poured into 500 ml. of ice–water saturated with sodium bicarbonate. The suspension was extracted with chloroform (5 × 100 ml.), then the combined extracts were washed with 100 ml. of water and dried over magnesium sulfate. Concentration of the solution gave a sirup from which pyridine was removed by the addition and evaporation of toluene *in vacuo*. The syrup was dissolved in hot methanol and cooled, when 0.96 g. of the di-O-*p*-nitrobenzoate derivative of X crystallized. An analytical sample obtained by recrystallization from methanol, m.p. 166–168°; $[\alpha]^{24}D$ + 37.6 ± 0.3; ν_{max}^{Nujol} 1725 (C=O); 1525 (NO_2); 720 cm.$^{-1}$ (C—H of benzoate).

Anal. Calcd. for $C_{26}H_{28}N_2O_{12}$: C, 55.7; H, 5.04; N, 5.00. Found: C, 55.5; H, 5.06; N, 5.02.

The mother liquor from the above crystallization was concentrated, and the residues dissolved in hot petroleum ether containing sufficient ethyl acetate to cause solution. Unchanged X crystallized on cooling; concentration of the mother liquor gave 2.35 g. (34%) of XI as an analytically pure sirup; ν_{max}^{film} 3500 (OH); 1710 (C=O); 1510 (NO_2); 720 cm.$^{-1}$ (C—H of benzoate).

Anal. Calcd. for $C_{19}H_{25}NO_9$: C, 55.5; H, 6.14; N, 3.41. Found: C, 55.6; H, 6.33; N, 3.23.

1,2:5,6-Di-O-isopropylidene-3-O-mesyl-4-O-*p*-nitrobenzoyl-D-mannitol (XII).—To a solution of 2.35 g. (5.7 mmoles) of XI in 15 ml. of reagent pyridine was added 0.9 ml. (11.8 mmoles) of mesyl chloride. After 24 hr. at room temperature, then processed as described for II, the residual sirup crystallized from methanol after treatment with charcoal, to yield 1.55 g. (55%) of XII, m.p. 94–96°,[21] ν_{max}^{Nujol} 1725 (benzoate C=O); 1510 (NO_2); 1175 (—OSO_2—), 720 cm.$^{-1}$ (benzoate CH).

Anal. Calcd. for $C_{20}H_{27}NO_{11}S$: C, 49.1; H, 5.57; N, 2.86; S, 6.53. Found: C, 49.0; H, 5.36; N, 2.99; S, 6.62.

A solution of 0.16 g. (0.39 mmole) of XII in 2 ml. of spectrograde dimethylformamide was heated under reflux for 5 hr., protected from moisture, and the product isolated as described above[20] to yield 0.12 g. of a sirup; ν_{max}^{film} 3500 (OH); 1725 (C=O); 1525 (NO_2); 720 cm.$^{-1}$ (C—H of benzoate). The absorption at 1175 cm.$^{-1}$ (—OSO_2—) was still present suggesting that the major part of XI was unchanged.

A mixture of 0.5 g. (1.21 mmoles) of XII, 0.25 g. (3.04 mmoles) of sodium acetate, and 5 ml. of dimethylformamide containing 1% water was heated under reflux for 24 hr.; and the product isolated as previously described,[20] to yield 0.16 g. of a dark sirup; ν_{max}^{film} 3500, 3400 (OH); 1725 (broad, C=O); 1525 cm.$^{-1}$ (NO_2).

Acknowledgment.—The authors wish to thank the Cancer Chemotherapy National Service Center and Starks Associates, Inc., for large scale preparation of certain intermediates, mediated by contract no. SA-43-ph-4346.

(21) The optical rotation of this compound could not be determined since the only sample available had decomposed in a few weeks.