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Synthesis of the Two 2-*O*-Nitro-3,5-di-*O*-*p*-nitrobenzoyl-D-arabinofuranosyl Chlorides, an Anomeric Pair of Crystalline Pentofuranosyl Halides Having a Nonparticipating Group at C-2

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Hydrolysis of 2,3,5-tri-*O*-*p*-nitrobenzoyl-α-D-arabinofuranosyl bromide is, in part, accompanied by migration of a *p*-nitrobenzoyl group from C-2 to C-1. The resulting 1,3,5-tri-*O*-*p*-nitrobenzoyl-β-D-arabinofuranose (IV) was characterized by several methods, *inter alia*, by conversion into its 2-*O*-methylsulfonyl derivative which, in turn, gave methyl β-D-ribopyranoside when treated with sodium methoxide. The 2-*O*-nitro derivative of IV gives crystalline 2-*O*-nitro-3,5-di-*O*-*p*-nitrobenzoyl-α-D-arabinofuranosyl bromide. Treatment of this halide with "active" silver chloride affords the two crystalline 2-*O*-nitro-3,5-di-*O*-*p*-nitrobenzoyl-D-arabinofuranosyl chlorides; apparently, this is the first pair of crystalline anomeric glycosyl halides having a nonparticipating group at C-2.

The broad utility of the fully acylated glycosyl halides in the synthesis of a wide variety of carbohydrate derivatives is to an extent circumscribed by the participation of neighboring acyl groups in the displacement of the halogen atom by nucleophilic species. As a result, these halides are best suited for the synthesis of those aldose derivatives in which the substituent at C-1 is *trans* to that at C-2. Although numerous special methods for the synthesis of the corresponding *cis* derivatives have been devised, they have not, on the whole, proved as satisfactory as those for the *trans* derivatives. One general approach to the synthesis of *cis* C-1–C-2 derivatives of the aldoses is through the use of glycosyl halides wherein the hydroxyl groups are completely masked with relatively nonparticipating substituents. 2,3,5-Tri-*O*-benzyl-D-arabinofuranosyl chloride, for instance, has been used for the synthesis of the "*cis* nucleoside," 9-β-D-arabinofuranosyladenine (spongoadenosine).[2] Another general approach involves the use of glycosyl halides having mixed masking groups, the hydroxyl group at C-2 being blocked with a nonparticipating substituent and the others by acyl groups. 3,4,6-Tri-*O*-acetyl-2-*O*-nitro-β-D-glucopyranosyl chloride[3,4] is such an intermediate and was initially used for the synthesis of isomaltose (6-*O*-α-D-glucopyranosyl-D-glucose).

Although fully benzylated glycosyl halides are readily accessible by a pathway which appears to have general applicability,[2,5,6] none has as yet been obtained in the crystalline state. On the other hand, a number of glycosyl halides with mixed masking groups, including a nonparticipating substituent at C-2, have been obtained in crystalline form.[4,7] Furthermore, since aldoses, acylated save at C-2, may be made through the hydrolysis (with acyl migration) of fully acylated glycosyl halides,[8-14] those halides with nonparticipating substituents at C-2 are comparatively accessible, and compounds of this class may be expected to play an increasingly important role in the syntheses of *cis* C-1–C-2 aldose derivatives.

Although the stereochemical features of the behavior of ordinary acylated glycosyl halides with nucleophilic reagents have been much investigated, comparatively little in this respect is known about those glycosyl halides lacking a participating group at C-2[15] and, indeed, no anomeric pair of crystalline halides of this class has hitherto been available for such a study.[16] We therefore turned our attention to the problem of the synthesis of such a pair of anomers and, owing to interest in the synthesis of nucleosides, we concerned ourselves with pentofuranosyl halides. Previous work in this laboratory had shown that anomeric pairs of 2,3,5-tri-*O*-benzoylarabinofuranosyl halides are readily

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(9) R. K. Ness and H. G. Fletcher, Jr., *ibid.*, **80**, 2007 (1958).

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(11) W. M. Corbett, J. Kidd, and A. M. Liddle, *J. Chem. Soc.*, 616 (1960).

(12) B. Helferich and J. Zirner, *Ber.*, **95**, 2604 (1962).

(13) B. Helferich and W. Ost, *ibid.*, **95**, 2616 (1962).

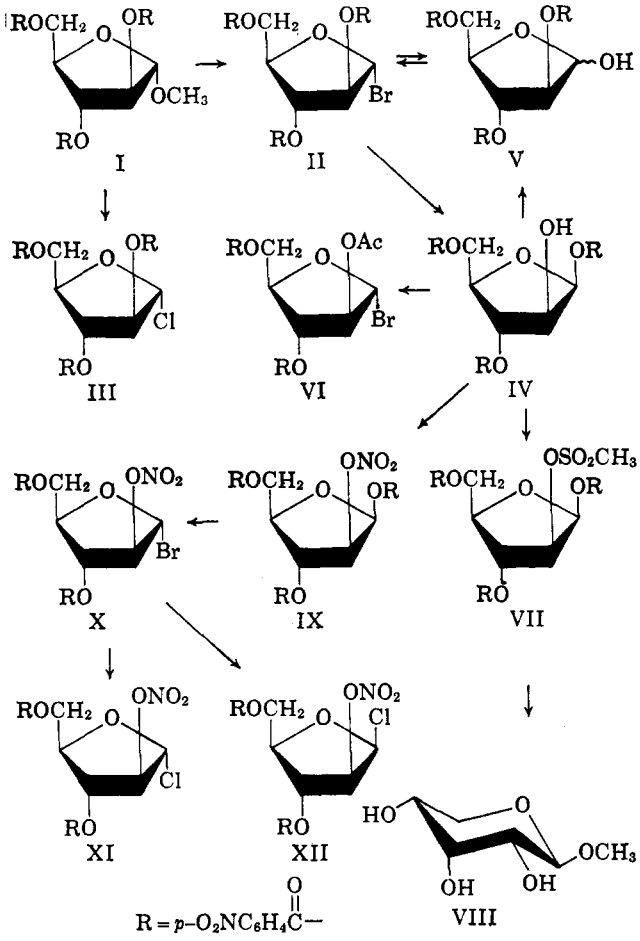
(14) B. Helferich and J. Zirner, *ibid.*, **96**, 385 (1963).

(15) As far as we are aware, the only systematic investigation in this area is that of A. J. Rhind-Tutt and C. A. Vernon [*J. Chem. Soc.*, 4637 (1960)] who used the amorphous 2,3,4,6-tetra-*O*-methyl-D-glucopyranosyl and 2,3,-4,6-tetra-*O*-methyl-D-mannopyranosyl chlorides.

(16) The β-anomer of 3,4,6-tri-*O*-acetyl-2-*O*-nitro-D-glucopyranosyl chloride is crystalline (ref. 3 and 4), but the α-anomer is known only as a sirup [M. L. Wolfrom, A. Thompson, and D. R. Lineback, *J. Org. Chem.*, **28**, 1930 (1963)].

preparable[9,17,18] and, for this reason, the D-arabinose series was chosen for the present work. The use of an *O*-nitro group at C-2 and *p*-nitrobenzoyl groups at C-3 and C-5 appeared attractive inasmuch as both of these groups tend to give crystalline derivatives and the electron-withdrawing character of the former tends to stabilize the C-1 halogen bond in a glycosyl halide.[19]

The readily accessible methyl 2,3,5-tri-*O*-benzoyl-α-D-arabinofuranoside[9,20] was debenzoylated and the parent glycoside was *p*-nitrobenzoylated to give crystalline methyl 2,3,5-tri-*O*-*p*-nitrobenzoyl-α-D-arabinofuranoside (I) in good yield. The methoxyl group was cleaved from I, through the action of hydrogen bromide, affording a 2,3,5-tri-*O*-*p*-nitrobenzoyl-D-arabinofuranosyl bromide which showed $[\alpha]^{20}D$ +42.5° (CH_2Cl_2); the corresponding chloride, made in an analogous fashion, showed $[\alpha]^{20}D$ +0.5° (CH_2Cl_2). The fact that the bromide is more dextrorotatory than the chloride clearly indicates that the bromide is the α-anomer (II)[17,21]; on the other hand, this evidence throws no light upon the anomeric configuration of the chloride (III), although, as mentioned later in this paper, III is probably an α-anomer also.



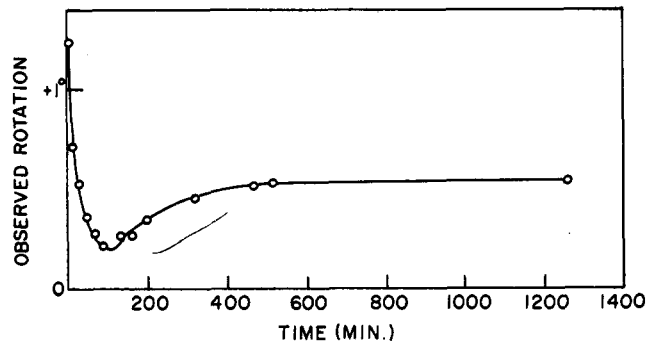


Fig. 1.—Reaction of X in benzene with suspended silver chloride.

Hydrolysis of II gave two tri-*O*-*p*-nitrobenzoyl-D-arabinofuranoses, one crystalline and one amorphous. The crystalline isomer afforded a methanesulfonate which was treated with sodium methoxide to yield methyl β-D-ribopyranoside (VIII); since an inversion at C-2 took place in the last step, the crystalline ester is 1,3,5-tri-*O*-*p*-nitrobenzoyl-β-D-arabinofuranose (IV) and arose through a C-2 → C-1 acyl migration which accompanied the hydrolysis of II.[22] The *p*-nitrobenzoyl group at C-1 in IV was readily displaced with acetyl bromide to give a 2-*O*-acetyl-3,5-di-*O*-*p*-nitrobenzoyl-D-arabinofuranosyl bromide which is assigned the α-configuration (VI) on the basis of its strong positive rotation ($[\alpha]^{20}D$ +105°), and its n.m.r. spectrum in which the signal for H-1 was a singlet.

The amorphous tri-*O*-*p*-nitrobenzoyl-D-arabinofuranose readily gave II when treated with acetyl bromide; furthermore, IV mutarotated in acetone solution to a value corresponding to that of the amorphous tri-*p*-nitrobenzoate, and treatment with acetyl bromide then gave II. It is apparent therefore that the amorphous ester is 2,3,5-tri-*O*-*p*-nitrobenzoyl-D-arabinofuranose (V).

Nitration of 1,3,5-tri-*O*-*p*-nitrobenzoyl-β-D-arabinofuranose (IV) at a low temperature with a mixture of fuming nitric acid and acetic anhydride[23] gave 2-*O*-nitro-1,3,5-tri-*O*-*p*-nitrobenzoyl-β-D-arabinofuranose (IX) which was converted, through the action of hydrogen bromide, into a 2-*O*-nitro-3,5-di-*O*-*p*-nitrobenzoyl-D-arabinofuranosyl bromide. The rotation of this bromide ($[\alpha]^{20}D$ +103.6° in CH_2Cl_2) suggests that it is the α-anomer X. Treatment of a solution of X in either benzene or dichloromethane with "active" silver chloride[24] caused its optical rotation to fall to a minimum and then turn upward (Fig. 1). When the reaction was halted near the point of minimum rotation, two crystalline 2-*O*-nitro-3,5-di-*O*-*p*-nitrobenzoyl-D-arabinofuranosyl chlorides could be separated; one of these was dextrorotatory ($[\alpha]^{20}D$ +68° in CH_2Cl_2) with a singlet at τ 3.60 and is, therefore, the α-anomer XI, whereas the other was levorotatory ($[\alpha]^{20}D$ −88.5° in CH_2Cl_2) and, hence, is designated as the β-anomer XII. Since X is more

(17) A. K. Bhattacharya, R. K. Ness, and H. G. Fletcher, Jr., *ibid.*, **28**, 428 (1963).

(18) Other than in the arabinose series, only one pair of anomeric pentofuranosyl halides has been made, the 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl fluorides [C. Pedersen and H. G. Fletcher, Jr., *J. Am. Chem. Soc.*, **82**, 941 (1960); note comment in ref. 17]. H. Zinner and L. Belau [*J. prakt. Chem.*, [4] **18**, 79 (1962)] reported a 2,3,5-tri-*O*-*p*-toluoyl-D-ribofuranosyl chloride; no crystalline tri-*O*-acylpentofuranosyl halides have been reported in the xylose or lyxose series as of this writing as far as we are aware.

(19) P. A. J. Gorin [*Can. J. Chem.*, **40**, 275 (1962)] studied 3,5-di-*O*-benzoyl-2-*O*-nitro-L-arabinofuranosyl and -D-ribofuranosyl bromides, but, owing to their lability, made no attempt to crystallize them.

(20) R. S. Wright and H. G. Khorana, *J. Am. Chem. Soc.*, **80**, 1994 (1958).

(21) C. S. Hudson, *ibid.*, **46**, 462 (1924).

(22) This acyl migration may be regarded as confirming the α-anomeric configuration assigned to II since the corresponding β-anomer, having the substituents at C-1 and C-2 in a *cis* relationship, would not be expected to undergo acyl migration on hydrolysis.

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

(24) H. H. Schlubach, *Ber.*, **59**, 840 (1926); H. H. Schlubach and R. Gilbert, *ibid.*, **63**, 2292 (1930).

dextrorotatory than either XI or XII, it follows that X must be the α-anomer. Prolonged treatment of X with silver chloride gave only XI. In earlier work,[9,17] treatment of arabinofuranose tetrabenzoates with hydrogen halides was found to lead predominantly to the formation of the 2,3,5-tri-*O*-benzoyl-α-arabinofuranosyl halides; it should be noted that VI and X are α-halides and that XI is more stable than XII in the presence of silver chloride. Although no direct evidence is available, it appears likely that the chloride III is also an α-anomer.

In conclusion, we wish to draw attention to the rearrangement of 1,3,5-tri-*O*-*p*-nitrobenzoyl-β-D-arabinofuranose (IV) to 2,3,5-tri-*O*-*p*-nitrobenzoyl-D-arabinofuranose (V). Inasmuch as 1,3,5-tri-*O*-benzoyl-β-D-arabinofuranose had been made through the hydrolysis of 2,3,5-tri-*O*-benzoyl-α-D-arabinofuranosyl bromide in aqueous acetone,[9] the rearrangement of IV to V in dry acetone was somewhat unexpected. We have now reinvestigated this matter and find that 1,3,5-tri-*O*-benzoyl-β-D-arabinofuranose also mutarotates in dry acetone, the first-order rate constant (min., decimal log) being 0.37×10^{-3} and the half-life of the reaction being 814 min. Comparable figures for the mutarotation of IV in dry acetone are $k = 11 \times 10^{-3}$ and $t_{1/2} = 27$ min. Thus the difference in the behavior of the two esters is quantitative only, the *p*-nitrophenyl group conferring on the ester carbonyl carbon a higher positive charge than the phenyl group and facilitating nucleophilic attack on this carbon by the adjacent hydroxyl group, the necessary first step in the $C_1 \rightarrow C_2$ acyl migration.

Experimental[25]

Methyl 2,3,5-Tri-*O*-*p*-nitrobenzoyl-α-D-arabinofuranoside (I).—Methyl 2,3,5-tri-*O*-benzoyl-α-D-arabinofuranoside[9,20] (50 g.) was debenzoylated with sodium methoxide in methanol. After neutralization (CO_2 or Amberlite IR-120), the methanol was removed *in vacuo* and the residue was dissolved in water. Methyl benzoate was removed by extraction with dichloromethane and the aqueous solution concentrated to a sirup from which ethanol and pyridine were successively evaporated. The sirupy methyl α-D-arabinofuranoside was dissolved in 300 ml. of pyridine and the solution was treated with 68.7 g. of *p*-nitrobenzoyl chloride. After standing overnight at room temperature, the reaction mixture was treated with a small amount of water to destroy the remaining *p*-nitrobenzoyl chloride, diluted with dichloromethane, and worked up in the usual manner. Seed crystals were obtained by rubbing a sample of the sirupy material with ether. Crystallized from 150 ml. of hot ethyl acetate and then leached with 150 ml. of ethanol, the product (49.7 g., 77%) had m.p. 137–139° and $[\alpha]^{20}D$ −29.3° (*c* 1.6, CH_2Cl_2). Recrystallization from ethyl acetate–ether failed to change these values. Subsequent recovery of further material, m.p. 135–137°, raised the total yield to 86%.

Anal. Calcd. for $C_{27}H_{21}N_3O_{14}$ (611.49): C, 53.03; H, 3.46; N, 6.87. Found: C, 53.20; H, 3.67; N, 6.81.

In one experiment crude methyl α-D-arabinofuranoside as obtained directly from the reaction of D-arabinose with acidic methanol[6] was *p*-nitrobenzoylated to give I in 25% yield.

2,3,5-Tri-*O*-*p*-nitrobenzoyl-α-D-arabinofuranosyl Bromide (II).—Methyl 2,3,5-tri-*O*-*p*-nitrobenzoyl-α-D-arabinofuranoside (1.00 g.) was dissolved in 2 ml. of dichloromethane and the solution was diluted with 5 ml. of a solution of hydrogen bromide in glacial acetic acid (32% HBr). Crystallization of II proceeded at room temperature; after 1.5 hr., ether (40 ml.) was added, and the mass was broken up, collected by filtration, washed successively with ether and pentane, and dried *in vacuo* over sodium hydroxide. The crude product was obtained as a white powder: 1.015 g. (94%), m.p. 169–171° dec., $[\alpha]^{20}D$ +42.5° (CH_2Cl_2). After two recrystallizations from dichloromethane–ether, the bromide showed m.p. 171–173° dec. and $[\alpha]^{20}D$ +46° (*c* 2.0, CH_2Cl_2).

Anal. Calcd. for $C_{26}H_{18}BrN_3O_{13}$ (660.37): C, 47.29; H, 2.75; Br, 12.10; N, 6.36. Found: C, 47.27; H, 3.00; Br, 11.95; N, 6.63.

2,3,5-Tri-*O*-*p*-nitrobenzoyl-α-D-arabinofuranosyl Chloride (III).—Methyl 2,3,5-tri-*O*-*p*-nitrobenzoyl-α-D-arabinofuranoside (1.0 g.) was dissolved in 1.5 ml. of dichloromethane and the solution was diluted with 18 ml. of glacial acetic acid, cooled in ice, and saturated with hydrogen chloride. After 2.5 hr. at 0°, the solution was left at room temperature for 2 days and then diluted with dichloromethane. It was washed with water and saturated aqueous sodium bicarbonate and dried with magnesium sulfate; concentration then gave a sirup which, from 5:6 dichloromethane–ether, gave 0.291 g. (29%) of product. Two recrystallizations from the same mixture of solvents afforded pure material, m.p. 182–184°, $[\alpha]^{20}D$ +0.5° (*c* 1.35, CH_2Cl_2).

Anal. Calcd. for $C_{26}H_{18}ClN_3O_{13}$ (615.91): C, 50.70; H, 2.95; Cl, 5.76; N, 6.82. Found: C, 50.89; H, 3.29; Cl, 5.81; N, 6.63.

Hydrolysis of 2,3,5-Tri-*O*-*p*-nitrobenzoyl-α-D-arabinofuranosyl Bromide (II).—A solution of 10.3 g. of 2,3,5-tri-*O*-*p*-nitrobenzoyl-α-D-arabinofuranosyl bromide in 600 ml. of acetonitrile was diluted with 25 ml. of water and observed polarimetrically: $\alpha^{20}D$ (1 dm.) +0.03° (4 min.) → −0.30° (30 min.) → −0.30° (65 min.). The reaction mixture was then diluted with 1 l. of dichloromethane and extracted successively with water and aqueous sodium bicarbonate. Moisture was removed with magnesium sulfate and the solution was concentrated *in vacuo* to a crystalline magma which was triturated with warm dichloromethane and collected by filtration. As obtained in this fashion, the **1,3,5-tri-*O*-*p*-nitrobenzoyl-β-D-arabinofuranose** (IV) appeared to be essentially pure: 2.47 g., 27%, m.p. 183–191°,[26] $[\alpha]^{20}D$ +6.3° (*c* 0.6, dioxane).

Anal. Calcd. for $C_{26}H_{19}N_3O_{14}$ (592.46): C, 52.27; H, 3.20; N, 7.03. Found: C, 52.51; H, 3.20; N, 7.04.

From dioxane, IV readily crystallized as a solvate which lost 9.12% of its weight when heated *in vacuo* at 100°; on a solvent-free basis the solvate showed $[\alpha]^{20}D$ +6.3° (*c* 0.62, dioxane).

The mother liquor from the preparation of IV was freed of solvent to give a glass, $[\alpha]^{20}D$ −56.7° (*c* 1.0, dioxane), −58° (*c* 1.0, acetone), whose identity as **2,3,5-tri-*O*-*p*-nitrobenzoyl-D-arabinofuranose** (V) was shown through its behavior with acetyl bromide as well as through comparison with a sample prepared by the deliberate rearrangement of IV as described later in this paper. A sample (554 mg.) of the glass was dissolved in 3 ml. of acetyl bromide and the solution was kept at room temperature overnight. The crystals which precipitated were twice recrystallized from dichloromethane–ether (Darco G-60): 400 mg. (65%), m.p. 171–172°, $[\alpha]^{20}D$ +44° (*c* 0.8, CH_2Cl_2). The infrared spectrum was identical with that of II prepared from I.

Preparation of II from IV *via* 2,3,5-Tri-*O*-*p*-nitrobenzoyl-D-arabinofuranose (V).—1,3,5-Tri-*O*-*p*-nitrobenzoyl-β-D-arabinofuranose (103.4 mg.) was dissolved in dry acetone to make a total volume of 10 ml.; the solution mutarotated $[\alpha]^{20}D$ −6.38° (6 min.) to −60.0° (8 and 26 hr.). The acetone was evaporated from the solution and the sirupy residue was dissolved in 1.5 ml. of acetyl bromide. After standing overnight, the solution was diluted with ether and the crystalline product was removed: 92 mg., 80%. After two recrystallizations from dichloromethane–ether, the product had m.p. 170–171° and $[\alpha]^{20}D$ +46° (*c* 0.8, CH_2Cl_2); its infrared spectrum was identical with that of II prepared from I.

Rate of Conversion of IV into V and of 1,3,5-Tri-*O*-benzoyl-β-D-arabinofuranose into 2,3,5-Tri-*O*-benzoyl-D-arabinofuranose.—1,3,5-Tri-*O*-*p*-nitrobenzoyl-β-D-arabinofuranose (IV, 69.5 mg.) was dissolved in dry acetone to a volume of 5 ml. and the rotation of the solution in a 1-dm. polarimeter tube was observed: $\alpha^{20}D$ +0.120° (extrap.) → −0.785° (8.5 hr., constant). With intermediate values, these rotations gave a first-order reaction constant (min., decimal log) of 11×10^{-3} and $t_{1/2} = 27$ min.

A comparable experiment, using an acetone solution (10 ml.) of 1,3,5-tri-*O*-benzoyl-β-D-arabinofuranose (145.4 mg.) in a

(25) Melting points are corrected. N.m.r. spectra were obtained in deuteriochloroform solution using a Varian A-60 spectrometer and tetramethylsilane as an internal standard; τ-values (tetramethylsilane = 10.0) for selected proton resonances are given with probable assignments.

(26) A sample of IV which had been heated at 210° for 20 sec. showed $[\alpha]^{20}D$ −27°. It is probable that the broad melting point range of IV results from concomitant acyl migration.

2-dm. polarimeter tube, gave the following: $\alpha^{20}D$ −0.500° (extrap.) → −1.26° (*ca.* 6 days, constant). The derived first-order rate constant (min., decimal log) was 0.37×10^{-3}.

2-*O*-Acetyl-3,5-di-*O*-*p*-nitrobenzoyl-α-D-arabinofuranosyl Bromide (VI).—1,3,5-Tri-*O*-*p*-nitrobenzoyl-β-D-arabinofuranose (191.4 mg.) was dissolved in 3 ml. of acetyl bromide and the solution was kept at room temperature overnight to give a precipitate of 47 mg. (88%) of *p*-nitrobenzoic acid, identified by its m.p. 235–239° and its infrared spectrum. The filtrate was diluted with 5.5 ml. of ether–pentane (3:2) and then with 3 ml. of pentane; on chilling the solution, crystals were deposited: 131 mg. (74%), m.p. 120–124°, $[\alpha]^{20}D$ +107° (CH_2Cl_2). After one recrystallization from dichloromethane–ether–pentane, the product had m.p. 128–129° and $[\alpha]^{20}D$ +105° (*c* 0.4, CH_2Cl_2) (a further recrystallization failed to change the melting point); n.m.r. data, τ 3.48 (H-1), 4.25 (H-2), 4.56 (H-3), and multiplet at *ca.* 5.2 (H-4 and 2H-5).

Anal. Calcd. for $C_{21}H_{17}BrN_2O_{11}$ (553.31): C, 45.59; H, 3.10; Br, 14.44; N, 5.06. Found: C, 45.75; H, 3.32; Br, 14.27; N, 5.16.

2-*O*-(Methylsulfonyl)-1,3,5-tri-*O*-*p*-nitrobenzoyl-β-D-arabinofuranose (VII).—1,3,5-Tri-*O*-*p*-nitrobenzoyl-β-D-arabinofuranose (1.5 g.) was added to a cooled and stirred solution of 0.4 ml. of methanesulfonyl chloride in 4 ml. of pyridine. After 3.5 hr. the reaction mixture was diluted with dichloromethane and extracted with 3 *N* sulfuric acid. A precipitate was removed by filtration and the organic layer was washed with aqueous sodium bicarbonate. The dichloromethane was evaporated and the residue was combined with the above-mentioned precipitate. The crude product was rubbed with aqueous sodium bicarbonate and then washed with water and, finally, ethanol. From warm acetonitrile solution the product crystallized: 1.14 g. (67%), m.p. 200–204° dec., $[\alpha]^{20}D$ −10.2° (*c* 1.0, pyridine). After two recrystallizations from acetonitrile, the ester showed m.p. 205–206° dec. and $[\alpha]^{20}D$ −12.4° (*c* 0.5, pyridine).

Anal. Calcd. for $C_{27}H_{21}N_3O_{16}S$ (675.56): C, 48.00; H, 3.13; N, 6.22; S, 4.75. Found: C, 48.24; H, 3.41; N, 6.42; S, 4.75.

Methyl β-D-Ribopyranoside (VIII) from VII.—One gram of the methanesulfonate (VII) was suspended in 15 ml. of 0.33 *N* sodium methoxide in methanol, and the mixture was stirred for 5 days. The remaining alkali was neutralized with carbon dioxide and the solution, after filtration, was concentrated. On the addition of water to the residue, a crystalline precipitate (543 mg.) separated, m.p. 91–94°; methyl *p*-nitrobenzoate melts at 96°. The aqueous layer was extracted with dichloromethane, deionized, and concentrated to a sirup which was dried *in vacuo*. Trituration with ethyl acetate and seeding caused crystallization. A portion of the crystals (*ca.* 10 mg.) was removed, washed on a porous plate with ethyl acetate, and dried: m.p. 76–79°, $[\alpha]^{20}D$ −107° (*c* 0.44, H_2O), infrared spectrum identical with that of methyl β-D-ribopyranoside. The remainder of the semicrystalline mass was benzoylated to give a sirup which was chromatographed on a column of silicic acid. A fraction, eluted with ether–hexane (1:1), crystallized from a small amount of the same solvent mixture: 88 mg. (12%), $[\alpha]^{20}D$ −69.6° (*c* 2.0, $CHCl_3$), m.p. 107–110°. Authentic methyl β-D-ribopyranoside tribenzoate has m.p. 109–110°, shows $[\alpha]^{20}D$ −69.5° in chloroform,[27] and does not depress the melting point of the product made here.

2-*O*-Nitro-1,3,5-tri-*O*-*p*-nitrobenzoyl-β-D-arabinofuranose (IX).—1,3,5-Tri-*O*-*p*-nitrobenzoyl-β-D-arabinofuranose (3.00 g.) was added in portions to a stirred mixture of acetic anhydride (30 ml.) and fuming nitric acid (3.35 ml.) cooled in ice. After 4 hr. at 0° the semisolid mass was transferred quickly to 2 l. of a mixture of ice and water containing 23 g. of sodium acetate. The suspension was stirred for several hours and filtered, and the residue was washed thoroughly with water and dried *in vacuo*. The white powder thus obtained was dissolved in 125 ml. of dichloromethane and the crude product was adsorbed on a column (6 × 14 cm.) of silicic acid. Elution with dichloromethane afforded a fraction which thin layer chromatography (silica gel) showed to be homogeneous. Partial concentration of the solution afforded pure IX: 1.46 g., m.p. 184–186°, $[\alpha]^{20}D$ −53.8° (*c* 0.37, acetone). The substance showed strong absorption at 1658 cm.$^{-1}$, typical of an *O*-nitro compound. A second crop (0.25 g., m.p. 183–184°, $[\alpha]^{20}D$ −52.5° in acetone), obtained by the addition of ether to the mother liquor, raised the total yield to 53%.

Anal. Calcd. for $C_{26}H_{23}N_4O_{16}$ (642.46): C, 48.61; H, 2.82; N, 8.72. Found: C, 48.32; H, 2.94; N, 8.44.

2-*O*-Nitro-3,5-di-*O*-*p*-nitrobenzoyl-α-D-arabinofuranosyl Bromide (X).—2-*O*-Nitro-1,3,5-tri-*O*-*p*-nitrobenzoyl-β-D-arabinofuranose (200 mg.) was dissolved in dichloromethane (12 ml.) and the solution treated with a 32% solution of hydrogen bromide in glacial acetic acid. After standing for 8 min. at room temperature, the reaction mixture was diluted with more dichloromethane, washed successively with ice–water and cold aqueous sodium bicarbonate, and dried with magnesium sulfate. Solvent was removed and the sirupy residue was crystallized from dichloromethane–ether (2:5): 109 mg. (63%), m.p. 143–145°, $[\alpha]^{20}D$ +103.6° (*c* 0.6, CH_2Cl_2). Recrystallization from the same solvent mixture failed to change either melting point or rotation of the substance.

Anal. Calcd. for $C_{19}H_{14}BrN_3O_{12}$ (556.26): C, 41.03; H, 2.54; Br, 14.37; N, 7.55. Found: C, 41.19; H, 2.48; Br, 14.37; N, 7.59.

The Anomeric 2-O-Nitro-3,5-di-*O*-*p*-nitrobenzoyl-D-arabinofuranosyl Chlorides (XI and XII).—2-*O*-Nitro-3,5-di-*O*-*p*-nitrobenzoyl-α-D-arabinofuranosyl bromide (100 mg.) was dissolved in anhydrous benzene (15 ml.) in an all-glass, 2-dm. polarimeter tube: $\alpha^{20}D$ +1.235°. Silver chloride (200 mg.), freshly prepared by the method of Schlubach,[22] was added and the changing rotation of the solution was observed as shown (see Fig. 1).[28] After falling to a minimum value of $\alpha^{20}D$ +0.207°, the rotation rose, becoming constant at $\alpha^{20}D$ +0.520°; a similar curve was obtained when dichloromethane was used instead of benzene.

The bromide X (600 mg.) was dissolved in *ca.* 100 ml. of dichloromethane in a 4-dm. polarimeter tube and the solution was treated with freshly prepared active silver chloride (1.2 g.). The suspension was agitated from time to time and the optical rotation was observed; after *ca.* 2 hr. the solution showed a minimum rotation corresponding to $[\alpha]^{20}D$ +19° (based on the glycosyl chloride formed). The silver salts were removed by filtration through Celite and the solution was concentrated to a sirup which was dissolved in a mixture of dichloromethane (4 ml.) and ether (4 ml.) and the solution was immediately seeded with XII.[29] After 1 hr. at room temperature, the appearance of the crystalline precipitate began to change and the solution was decanted. A second identical batch was prepared, and the two were combined. The crude XII thus obtained was recrystallized from 3:2 dichloromethane–ether in precisely the same way[30] and then recrystallized in the normal fashion (without seeding) from 1:1 dichloromethane–ether to yield brilliant elongated plates (180 mg., 17%): m.p. 192–194°, $[\alpha]^{20}D$ −88.2° in dichloromethane. After another recrystallization from 1:1 dichloromethane–ether, the pure **2-*O*-nitro-3,5-di-*O*-*p*-nitrobenzoyl-β-D-arabinofuranosyl chloride** (XII) showed m.p. 193–194° and $[\alpha]^{20}D$ −88.5° (*c* 0.6, CH_2Cl_2).

Anal. Calcd. for $C_{19}H_{14}ClN_3O_{12}$ (511.80): C, 44.59; H, 2.76; Cl, 6.93; N, 8.21. Found: C, 44.29; H, 2.81; Cl, 7.24; N, 8.17.

In a similar experiment, addition of more ether to the original mother liquor afforded **2-*O*-nitro-3,5-di-*O*-*p*-nitrobenzoyl-α-D-arabinofuranosyl chloride** (XI) in 23% yield: m.p. 121–123°, $[\alpha]^{20}D$ +67° (*c* 1.0, CH_2Cl_2). In another experiment, X (640 mg.) was stirred in dichloromethane solution (10 ml.) with 500 mg. of aged silver chloride to give a sirupy mixture of XI and XII. From dichloromethane–ether (1:2) 154 mg. of this sirup yielded 48 mg. of XI: m.p. 122–124°, $[\alpha]^{20}D$ +68° (CH_2Cl_2, *c* 0.5) (further recrystallization failed to change these values); n.m.r. data, τ 3.60 (H-1), 4.15 (H-2), doublet at 4.40 ($J_{3,4} \sim 3$ c.p.s.), and 5.15 (H-4 and H-5).

Anal. Calcd. for $C_{19}H_{14}ClN_3O_{12}$ (511.80): C, 44.59; H, 2.76; Cl, 6.93; N, 8.21. Found: C, 44.89; H, 2.70; Cl, 6.74; N, 8.08.

(27) R. Jeanloz, H. G. Fletcher, Jr., and C. S. Hudson, *J. Am. Chem. Soc.*, **70**, 4055 (1948).

(28) With the proportions used here, the rate of the reaction was unaffected by occasional shaking.

(29) Seed crystals of XII were originally obtained in an experiment where the minimum rotation was $[\alpha]^{20}D$ ±0°, precipitation of this anomer from dichloromethane–ether being spontaneous.

(30) By seeding with XII and decanting the solution when the morphology of the solid phase changes, fairly pure XII may be obtained when XII represents as little as 19% of the mixture of the two anomers.

Evaporation of the mother liquor and addition of pentane afforded a second crop of IX (44 mg., m.p. 121–123°, $[\alpha]^{20}D$ +66° in CH_2Cl_2), raising the total yield of XI from the sirup to 60%.

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Preparation and Hydrolysis of Methyl 1-Thio-β-D-xylothiopyranoside[1]

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Rates of acid-catalyzed hydrolysis for methyl 1-thio-β-D-xylothiopyranoside are compared with those of other β-D-xylopyranoside analogs. The thiosugars hydrolyze at a faster rate than their oxygen counterparts. The hydrolysis seems to proceed through a cyclic carbonium ion structure.

It has been shown[2] that the rate of acid-catalyzed hydrolysis of methyl β-D-xylothiopyranoside is approximately 28 times faster than the methyl 1-thio-β-D-xylopyranoside. This high rate of hydrolysis of the thiopyranoside has been explained by Whistler and Van Es[2] by the inductive effect of sulfur-releasing electrons to the glycosidic oxygen producing extensive protonation with subsequent loss of the aglycone alcohol and formation of a transient carbonium ion at C-1 of the six-membered ring. The faster hydrolysis rate of the D-xylopyranosides with sulfur as the ring heteroatom is taken as strong additional evidence that the hydrolysis proceeds through a ring carbonium ion rather than an acyclic carbonium ion. Formation of a cyclic carbonium ion is favored by the greater ease of protonation of the glycosidic bridge atom and by the ease with which the ring sulfur can adapt itself to the conformational requirements of the transition structure in which it and carbon atoms C-1, C-2, and C-5 must be planar (Fig. 1).

The hydrolysis rate of methyl 1-thio-β-D-xylothiopyranoside is found now to be nearly the same as that for methyl β-D-xylothiopyranoside (Table I). Hence

TABLE I

RATE OF ACID-CATALYZED HYDROLYSIS

	Min.$^{-1}$ × 10^3
Methyl β-D-xylopyranoside[a] (I)	1.80
Methyl 1-thio-β-D-xylopyranoside[b] (II)	0.915
Methyl β-D-xylothiopyranoside[b] (III)	26.1
Methyl 1-thio-β-D-xylothiopyranoside (IV)	18.3

[a] H. S. Isbell and H. L. Frush, *J. Res. Natl. Bur. Std.* **24**, 125 (1940). [b] See ref. 2.

both glycosides III and IV with sulfur in the ring hydrolyze at nearly the same rate which is 14 to 20 times faster than the analogous D-xylosides I and II with oxygen in the ring. Hydrolysis of D-xylosides III and IV lead to the same transition structures if the carbonium ion formed remains in a six-membered ring. Such identical structures usually help to effect similar hydrolysis rates (Fig. 2). Two different transient structures, however, develop from compounds III and IV if acyclic structures are formed in the transition state. Two different transition structures, most likely, would cause differences in the hydrolysis rates (Fig. 3).

The similarity in rates of hydrolysis between structures I and II and between III and IV is apparent, and quite clearly illustrates the large effect of the ring heteroatom on the hydrolysis rates of sugar glycosides.

The faster hydrolysis of III compared with that of IV may be explained by the inductive effect of the ring sulfur causing extensive protonation of the glycosidic oxygen to produce a high concentration of the conjugate acid. In compound IV a slightly slower rate of hydrolysis is observed due to competitive protonation of the two sulfur atoms which decreases the amount of conjugate acid effective in the hydrolysis.

Thus, the above evidence that acid-catalyzed hydrolysis of glycosides proceeds through formation of a cyclic carbonium ion is in agreement with conclusions of Banks, Meinwald, Rhind-Tutt, Sheft, and Vernon[3] based on an observed oxygen isotope effect and with the explanation of the hydrolysis kinetics of 1-thio-β-D-glycopyranosides given by Bamford, Capon, and Overend.[4]

Compound IV is easily prepared from 2,3,4-tri-*O*-acetyl-α-D-xylothiopyranosyl bromide[2] by the Koenigs–Knorr[5] reaction using methanethiol and potassium methoxide.[6] Acetylation of IV in pyridine with acetic anhydride gives a crystalline triacetate (V).

Compound IV undergoes a rapid methanolysis in a methanolic–acid media. Thus if potassium methoxide solution from the Koenigs–Knorr reaction is neutralized with Amberlite IR-120 acid resin, the crystalline compound III is isolated.

Experimental

Methyl 1-Thio-β-D-xylothiopyranoside (IV).—2,3,4-Tri-*O*-acetyl-α-D-xylothiopyranosyl bromide[2] (3.6 g.) was dissolved in 50 ml. of anhydrous methanol and cooled to 0°. To this was added 10 ml. of a methanolic potassium methoxide solution made by addition of 3.5 g. of oxide-free potassium to 50 ml. of anhydrous methanol at 0° under nitrogen. Then 5 ml. of methanethiol was added and the solution was allowed to stand at 25° for 3 hr. During this time, potassium bromide precipitated from the reaction mixture. The solution was filtered and concentrated to dryness under reduced pressure. The solid residue was extracted five times with 250-ml. portions of boiling ethyl acetate and the combined extracts were concentrated to dryness. This solid was dissolved in twice its volume of hot ethanol and allowed to crystallize at 5°. The yield was 1 g. (50%), m.p. 130°, $[\alpha]^{25}D$ −49.5° (*c* 1.56, water).

(1) Journal Paper No. 2364 of the Purdue Agricultural Experiment Station, Lafayette, Ind. Presented in part at the 145th National Meeting of the American Chemical Society, New York, N. Y., Sept., 1963.

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(3) B. E. C. Banks, Y. Meinwald, A. J. Rhind-Tutt, I. Sheft, and C. A. Vernon, *J. Chem. Soc.*, 3240 (1961).

(4) C. Bamford, B. Capon, and W. G. Overend, *ibid.*, 5138 (1962).

(5) W. Koenigs and E. Knorr, *Ber.*, **34**, 957 (1901).

(6) H. Zinner, A. Koine, and H. Nimz, *ibid.*, **93**, 2705 (1960).