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Reaction of Some Pentofuranose Derivatives with Dibromomethyl Methyl Ether. Preparation of Some 2-Bromo-2-deoxy-pentofuranoside Derivatives

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When methyl tri-*O*-acetyl-α-D-arabinofuranoside, or tetra-*O*-acetyl-β-D-ribofuranose, was treated with dibromomethyl methyl ether and zinc bromide di-*O*-acetyl-2-bromo-2-deoxy-α-D-arabinofuranosyl bromide was formed. Analogous treatment of tri-*O*-acetyl-1-*O*-benzoyl-β-D-xylofuranose gave di-*O*-acetyl-2-bromo-2-deoxy-β-D-xylofuranosyl bromide. Benzoylated arabino- and xylo-furanoses also yielded 2-bromo-2-deoxy-furanosyl bromides. Benzoylated ribo- and lyxo-furanoses did not react with dibromomethyl methyl ether. The unstable 2-bromo-2-deoxy-furanosyl bromides were converted into the corresponding methyl furanosides by treatment with methanol.

In a previous paper the reaction of acetylated and benzoylated pentopyranoses with dibromomethyl methyl ether (DBE) was described.[1] It was found that with zinc bromide as a catalyst 2-bromo-2-deoxy-xylopyranose derivatives were obtained from acylated xylo-, arabino-, and lyxo-pyranoses. Acetylated ribopyranose on the other hand, gave 2-bromo-2-deoxy-arabinopyranose derivatives. This investigation has now been extended to pentofuranoses.

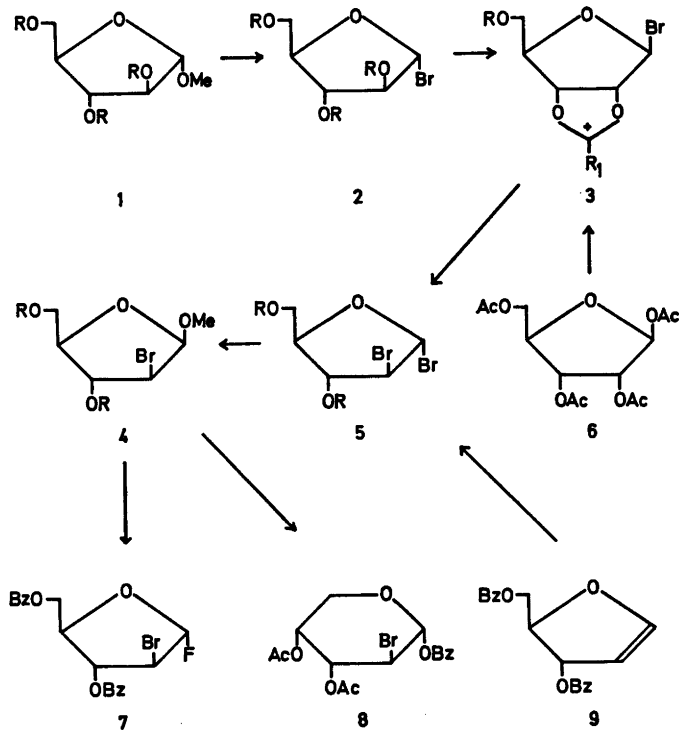
Treatment of methyl tri-*O*-benzoyl-α-D-arabinofuranoside (*1b*) with DBE and zinc bromide in chloroform for 15 min gave a high yield of the furanosyl bromide (*2b*) and a similar result was obtained with tetra-*O*-benzoyl-α-D-xylofuranose (*10*). Acetylated methyl furanosides also gave the corresponding furanosyl bromides when treated briefly with DBE-$ZnBr_2$ as seen from ^{1}H NMR spectra of the reaction mixtures. The bromides were not isolated because of their instability.

More prolonged treatment with DBE led to formation of 2-bromo-2-deoxy-derivatives, analogous to the results found in the pyranose series.[1] Thus reaction of *1b* with DBE-$ZnBr_2$ for 16 h gave a rather unstable product which, as seen from a ^{1}H NMR spectrum (Table 1), was the 2-bromo-2-deoxy-D-arabinosyl bromide (*5b*). Treatment with methanol gave the methyl furanoside (*4b*) in 50 % yield. In the same manner *10* gave a crude bromo-deoxy-bromide (*14b*), which was converted into a mixture of the anomeric methyl furanosides (*15b*), obtained in *ca.* 50 % yield. The tribenzoylated ribo- or lyxo-furanosyl bromides did not give 2-bromo-2-deoxy-compounds on prolonged treatment with DBE-$ZnBr_2$.

The acetate *1a*, when treated in the same way, gave *5a* (Table 1) which was converted into *4a*, contaminated with a small amount of the α-anomer. The same product was obtained in *ca.* 50 % yield by treating tetra-*O*-acetyl-β-D-ribofuranose (*6*) with DBE-$ZnBr_2$.

The xylofuranose derivative (*12*) analogously yielded the unstable bromide (*14a*) and subsequently a mixture of the anomeric methyl furanosides (*15a*). These could not be separated and were therefore only characterized through their ^{1}H NMR spectra (Table 1).

In order to prove the structure of *4b* the unsaturated compound *9* was treated with bromine and the product was reacted with methanol. This gave two products one of which was *4b* and thus proves the configuration at C3 and C4 of *4b*. The $J_{1,2}$ value (Table 1) shows that the substituents at C1 and C2 are

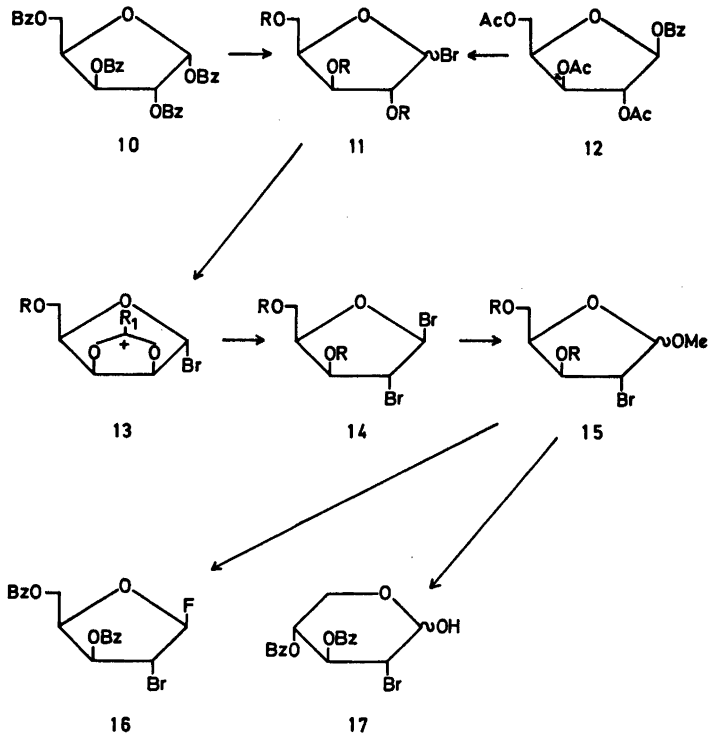


a) R = CH_3CO

b) R = C_6H_5CO

Table 1. Proton chemical shifts and coupling constants of pentofuranose derivatives.

Compound	δ-values H1	H2	H3	H4	H5	H5′	Coupling constants (Hz) $J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{4,5}'$	$J_{5,5}'$	
2b	6.63	5.97	5.66		4.7–5.0		0.7	0	3.5				$J_{13} \simeq 0.5$
5b	6.72	4.92	5.72		4.6–5.0		~0.5	0	3.5				$J_{13} \simeq 0.5$
5a	6.66	4.78	5.3		4.3–4.7		0	0.5	4.0				$J_{13} \simeq 0.5$
7	6.07	4.44	5.66		4.6–4.9		0	0.8	3.0				J_{1F} 61; J_{2F} 7.9; J_{4F} 0
4b	5.00	4.42	5.84	4.4	4.74	4.57	4.4	8.6	5.6	4.6	6.0	11.9	
4a	4.96	4.24	5.44		4.0–4.5		4.4	8.5	5.2				
14b	6.67	4.94	5.97	5.21	4.77	4.77	0	0	5.3	5.3	5.3		
14a	6.61	4.85	5.66	4.99	4.5	4.5	0	0	5.1	6.3	6.3		
16	6.03	4.42	5.85	5.14	4.71	4.71	0	~0	5.0	5.8	5.8		J_{1F} 65; J_{2F} 6.0; J_{4F} 6.0
β-15b	5.27	4.30	5.77	5.02	4.67	4.58	~0.5	1.6	5.5	5.5	5.5	11.8	
α-15b	5.10	4.44	5.96	4.81	4.5	4.5	4.2	6.9	6.7	4.8	4.8		
β-15a	5.20	5.45					0.5	2.0	5.4				
α-15a	5.03	5.59					4.1	7.2	7.2				
12	6.44	5.41	5.52	4.76	4.4	4.3	0	1.3	5.4	5.2	6.8	11.8	



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cis-oriented. Brief treatment of *4b* with anhydrous hydrogen fluoride gave the furanosyl fluoride (*7*) which has $J_{1,2}=0$ Hz and therefore must have bromide and fluorine *trans*-oriented. It furthermore has $J_{4,F}=0$ Hz, which shows that fluorine and H4 are *cis*-oriented.[2] There results are only compatible with the structure *4b*. It was further confirmed by its conversion to the known[1] pyranose derivative *8*. The structure of *4a* was proved by its preparation from *4b* *via* a debenzoylation and acetylation.

The *β*-anomer of *15b* has physical data identical with those of a known product.[3] The *α*-anomer was converted into the known pyranose derivative (*17*),[1] thus proving the configuration at C2, C3, and C4. Treatment of *α*-*15b* with hydrogen fluoride gave the *β*-fluoride 16, the anomeric structure of which was found from the $J_{1,2}$ and $J_{4,F}$ values of 0 and 6.0 Hz, respectively.

The anomeric acetates *15a* were not obtained pure, but their structures are evident from the ^{1}H NMR spectra which are very similar to those of *15b* (Table 1).

The 2-bromo-2-deoxy-bromides (*5* and *14*) are probably formed *via* the 2,3-dioxolanylium ions (*3* and *13*), respectively, by an intramolecular migration of the bromine from C1 to C2 as proposed previously in the pyranose series.[1] The ions *3* and *13* may be formed by two different mechanisms depending on the stereochemistry at C2 and C3. When these are *trans*-oriented, as in arabino- and xylo-furanose derivatives, the reaction with DBE probably proceeds *via* a 1,2-dioxolanylium ion which subsequently rearranges to a 2,3-ion, (*3* or *13*). When C2 and C3 are *cis*-oriented the 2,3-ion is probably formed by a mechanism similar to that by which *cis*-1,2-diacetoxycyclohexane reacts with hydrogen fluoride.[4]

The mechanism will be discussed further in a forthcoming paper, in which the reactions of model compounds with DBE are described.

EXPERIMENTAL

Melting points are uncorrected. Preparative TLC was performed on 1 mm layers of silica gel (Merck PF_{254}). ^1H NMR spectra were measured on Varian A-60 and HA-100 instruments or on a Bruker HX-90E instrument in deuteriochloroform solution with tetramethylsilane as internal reference. ^{19}F NMR spectra were obtained on the Bruker instrument. Optical rotations were measured on solutions in chloroform.

2,3,5-Tri-O-*acetyl-1*-O-*benzoyl-β*-D-*xylofuranose* (12). 3,5-Di-*O*-acetyl-1,2-*O*-isopropylidene-α-D-xylofuranose [5] (1.50 g) in acetyl bromide (1.5 ml) was kept at room temp. for 1.5 h. Evaporation gave a mixture of the anomeric tri-*O*-acetyl-D-xylofuranosyl bromides as a syrup. A ^1H NMR spectrum showed H1 of the β-anomer as a singlet at δ 6.3 and H1 of the α-anomer as a doublet at δ 6.85, $J_{1,2}$ 4.6 Hz.

The bromide was treated with silver benzoate in acetonitrile to give 1.5 g of a product which was purified by preparative TLC (ether-pentane 3:1) to give pure *12* as a syrup, $[\alpha]_D^{25}$ −46.8° (*c* 4.8). (Found: C 56.87; H 5.34. Calc. for $C_{18}H_{20}O_9$: C 56.84; H 5.26).

Tri-O-*benzoyl*-α-D-*arabinofuranosyl bromide* (2b). Methyl tri-*O*-benzoyl-α-D-arabinofuranoside [6] (1.09 g) in chloroform (2 ml) was stirred with dibromomethyl methyl ether [7] (DBE) (1.0 ml) and anhydrous zinc bromide (100 mg) for 15 min at room temp. The mixture was then diluted with dichloromethane and washed with 4 N hydrochloric acid until the organic phase was clear; it was then washed with aqueous sodium hydrogen-carbonate, dried ($MgSO_4$) and evaporated. The residue was crystallized from ether-pentane to give 1.06 g (89 %) of *2b*, m.p. 97—100 °C. An additional recrystallization gave m.p. 101—102 °C, $[\alpha]_D^{20}$ +80.1° (*c* 1.7) (reported [6] m.p. 103—104 °C (corr.), $[\alpha]_D^{20}$ +85°). A ^1H NMR spectrum of the material in the mother liquor showed that no β-bromide was present.

Tri-O-*benzoyl*-D-*xylofuranosyl bromide* (11). Treatment of tetra-*O*-benzoyl-α-D-xylofuranose [8] (530 mg) with DBE (1.0 ml) and $ZnBr_2$ (85 mg) in chloroform (1.5 ml) as described above gave 505 mg of a syrup. A ^1H NMR spectrum showed that the product was a mixture of the two anomeric bromides *11* containing *ca.* 80 % α-anomer. The two products could not be separated.

Methyl di-O-*benzoyl-2-bromo-2-deoxy-β*-D-*arabinofuranoside* (4b). *A.* A solution of *1b* (5.0 g) in chloroform (10 ml) was stirred with DBE (10 ml) and $ZnBr_2$ (300 mg) for 16 h at room temp. Work-up as described above gave a syrup (a ^1H NMR spectrum is shown in Table 1) which was dissolved in methanol (200 ml) and stirred for 24 h with silver carbonate (8 g). The mixture was then filtered and evaporated. The residue was dissolved in ether, filtered through carbon and evaporated. Crystallization from ether-pentane gave 2.27 g (50 %) of 4b, m.p. 107—108 °C, $[\alpha]_D^{20}$ −98.0° (*c* 2.8). One additional recrystallization gave a product with m.p. 109—109.5 °C, $[\alpha]_D^{20}$ −98.6° (*c* 2.7). (Found: C 55.29; H 4.55; Br 18.21. Calc. for $C_{20}H_{19}BrO_6$: C 55.19; H 4.37; Br 18.39).

B. Freshly prepared di-*O*-benzoyl-1,2-dideoxy-D-*erythro*-pent-1-enofuranose (*9*) [9] (0.57 g) in benzene (15 ml) was cooled to +5 °C and bromine (0.5 ml) in benzene (10 ml) was added during 15 min. Evaporation of the solvent gave a residue which, as seen from a ^1H NMR spectrum, was a 1:1 mixture of the two *trans*-addition products. The mixture was stirred with methanol (20 ml) and silver carbonate (1.0 g) for 1 h. Filtration through carbon and evaporation gave a residue which was purified by preparative TLC (ether-pentane 1:2) to give 446 mg (58 %) of a 1:1 mixture of two methyl glycosides as seen from ^1H NMR spectra.

Crystallization from ether-pentane gave 129 mg of (4b), m.p. 106—107 °C, $[\alpha]_D^{20}$ −96.0° (*c* 2.5). A ^1H NMR spectrum and a mixed m.p. proved the identity with the product described above.

The material in the mother liquor was a mixture which could not be separated completely by chromatography. A ^1H NMR spectrum showed that methyl 3,5-di-*O*-benzoyl-2-bromo-2-deoxy-α-D-ribofuranoside was the main component. It gave the following spectral data: δ 5.13 (H1), 4.38 (H2), 5.55 (H3). $J_{1,2}$ 4.1 Hz, $J_{2,3}$ 6.9 Hz, $J_{3,4}$ 3.1 Hz.

Methyl di-O-*acetyl-2-bromo-2-deoxy-β*-D-*arabinofuranoside* (4a). *A.* Methyl tri-*O*-acetyl-α-D-arabinofuranoside [10] (587 mg) in chloroform (1.5 ml) was treated with DBE (1.5 ml) and $ZnBr_2$ (200 mg) for 16 h at room temp. An additional 1.5 ml of DBE was then added and the mixture was stirred for 24 h. Work-up as described above gave 0.8 g of a dark syrup which was treated with methanol (50 ml) and silver carbonate (1.0 g). The product (427 mg) was purified by preparative TLC (ether-pentane 3:1) to give 280 mg (45 %) of a mixture of anomeric glycosides. A ^1H NMR spectrum showed that 90—95 % was the β-anomer (*4a*). Crystallization from ether-pentane gave 175 mg of *4a*, m.p. 79—80 °C, $[\alpha]_D^{21}$ −107° (*c* 2.5).

B. Tetra-*O*-acetyl-β-D-ribofuranose (1.01 g) in chloroform (1.5 ml) was treated with DBE (1.5 ml) and $ZnBr_2$ (317 mg) for 16 h. After treatment with methanol and silver carbonate the product (750 mg) was purified by preparative TLC (ether-pentane 3:1) to give 503 mg (51 %) of a mixture of anomers. Crystallization from ether-pentane gave 427 mg of *4a*, m.p. 80—81 °C, $[\alpha]_D^{21}$ −107° (*c* 2.0). Further recrystallization did not change these values.

(Found: C 38.40; H 4.92; Br 25.70. Calc. for $C_{10}H_{15}BrO_6$: C 38.59; H 4.87; Br 25.68).

The α-anomer could not be obtained pure, but a ^{1}H NMR spectrum of the material in the mother liquor gave the following data: δ 5.20 (H1), 5.26 (H3); $J_{2,3}$ 2 Hz, $J_{3,4}$ 4 Hz, in agreement with reported values.[11]

*Methyl di-*O*-benzoyl-2-bromo-2-deoxy-*D*-xylofuranoside* (15b). A solution of *10* (1.07 g) in chloroform (2.0 ml) was treated with DBE (2.0 ml) and $ZnBr_2$ (567 mg) for 16 h. This gave 1.1 g of crude di-*O*-benzoyl-2-bromo-2-deoxy-β-D-xylofuranosyl bromide (*14*) (^{1}H NMR spectral data are shown in Table 1) which was at once treated with methanol and silver carbonate as described above. The product (630 mg) was separated into two fractions by preparative TLC (ether-pentane 1:2).

The fast moving fraction gave 97 mg (12 %) of *β-15b* which was crystallized from ether-pentane, m.p. 66—67 °C, $[\alpha]_D^{21}$ −4.8° (*c* 1.5) (reported [3] m.p. 67.5—68 °C, $[\alpha]_D$ −6°). (Found: C 55.08; H 4.84; Br 18.17. Calc. for $C_{20}H_{19}BrO_6$: C 55.19; H 4.36; Br 18.36).

The next fraction contained 351 mg (43 %) of *α-15b* as a syrup, $[\alpha]_D^{21}$ +163.1° (*c* 5.9). (Found: C 54.99; H 4.34; Br 18.20).

*Methyl di-*O*-acetyl-2-bromo-2-deoxy-*D*-xylofuranoside* (15a). Reaction of *12* (605 mg) in 1 ml of chloroform with DBE (1.5 ml) and $ZnBr_2$ (200 mg) for 16 h gave di-*O*-acetyl-2-bromo-2-deoxy-β-D-xylofuranosyl bromide (*14a*) as an unstable, dark syrup (Table 1). The bromide was treated with silver carbonate in methanol and the product thus obtained was purified by preparative TLC (ether-pentane 1:1). This gave 218 mg (44 %) of *15a* as a mixture of anomers in an α:β ratio of 3:1. They could not be separated, but ^{1}H NMR data were obtained from the mixture (Table 1).

*Di-*O*-benzoyl-2-bromo-2-deoxy-α-D-arabinofuranosyl fluoride* (7). A solution of *4b* (244 mg) in anhydrous hydrogen fluoride (5 ml) was kept at 0 °C for 15 min. Dichloromethane was then added and the mixture was poured on ice. The organic phase was washed with aqueous sodium hydrogen carbonate, dried and evaporated. The residue (230 mg) was purified by preparative TLC (ether-pentane 1:3) to give 164 mg (70 %) of *7*, m.p. 92—93 °C. One recrystallization from ether-pentane gave a product with m.p. 94—95 °C, $[\alpha]_D^{20}$ −15.4° (*c* 2.1). (Found: C 54.08; H 3.93; Br 18.71. Calc. for $C_{19}H_{16}BrFO_5$: C 53.92; H 3.81; Br 18.88). ^{1}H NMR data are given in Table 1. A ^{19}F NMR spectrum gave ϕ = −106.5 ppm (using internal trichlorofluoromethane).

*Di-*O*-benzoyl-2-bromo-2-deoxy-β-D-xylofuranosyl fluoride* (16). Treatment of 335 mg of (*α-15b*) with hydrogen fluoride in the same way, followed by preparative TLC gave 135 mg (41 %) of *16*. Recrystallization from ether-pentane gave the pure product, m.p. 68—70 °C, $[\alpha]_D^{20}$ +10.4° (*c* 3.3). (Found: C 53.84; H 3.98; Br 18.70). ^{19}F NMR data: ϕ = −103.0 ppm.

Conversion of 4b *into 3,4-di-*O*-acetyl-1-*O*-benzoyl-2-bromo-2-deoxy-α-*D*-arabinopyranose* (8). Sodium (200 mg) was dissolved in methanol (10 ml) and 400 mg of *4b* was added. The mixture was stirred for 30 min and it was then neutralized with Amberlite IR-120 and evaporated. The residue was boiled for 5 h with 0.1 N HCl and the solution was neutralized with Amberlite IR-4B and evaporated. After two evaporations with pyridine the residue was acetylated with acetic anhydride (2 ml) in pyridine (10 ml). Work-up in the usual way gave 204 mg of tri-*O*-acetyl-2-bromo-2-deoxy-D-arabinopyranose which was treated with DBE (0.3 ml) and $ZnBr_2$ (20 mg) in chloroform (0.5 ml) for 1 h. Work-up as described above and treatment of the crude product with silver benzoate (1.0 g) in acetonitrile (10 ml) yielded 170 mg of a product which was purified by preparative TLC (ether-pentane 1:1). This gave 83 mg (20 %) of *8* which was recrystallized from ether-pentane, m.p. 144—145 °C, $[\alpha]_D^{20}$ −5.57° (*c* 2.3). A ^{1}H NMR spectrum and a mixed m.p. proved its identity with a product described previously.[1]

Conversion of α-15b *into 3,4-di-*O*-benzoyl-2-bromo-2-deoxy-*D*-xylopyranose* (17). 350 mg of *α-15b* was debenzoylated and hydrolyzed with 0.1 N HCl as described above. The 2-bromo-2-deoxy-D-xylose thus obtained was benzoylated with benzoyl chloride in pyridine to give tri-*O*-benzoyl-2-bromo-2-deoxy-D-xylopyranose. Treatment of this with DBE and $ZnBr_2$ gave the pyranosyl bromide, which was hydrolyzed with aqueous acetone in the presence of silver carbonate. This gave crude *17* which was purified by preparative TLC and recrystallized to yield 49 mg of the pure product, m.p. 141—143 °C, $[\alpha]_D^{20}$ −44.2° (5 min) → −32.5° (5 days) (*c* 0.2). The product was identical with that described previously.[1]

Conversion of the benzoate 4b *into the acetate* 4a. 538 mg of *4b* was debenzoylated with methanolic sodium methoxide as described above. The product, obtained after evaporation of the methanol, was extracted with pentane to remove most of the methyl benzoate. Acetylation with acetic anhydride in pyridine gave 409 mg of crude *4a* which was crystallized from ether-pentane, 272 mg (71 %), m.p. 79.5—80.5 °C, $[\alpha]_D^{20}$ −106.5° (*c* 4.0). A mixed m.p. and a ^{1}H NMR spectrum proved its identity with the product described above.

Microanalyses were performed by Dr. A. Bernhardt, Mikroanalytisches Laboratorium.

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