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# Reaction of Acylated Pentoses with Acyl Bromide. Preparation of Some Bromo-deoxy Pentoses

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When tri-*O*-acetyl-D-xylopyranosyl bromide was reacted with acetyl bromide and zinc bromide bromine was introduced stereospecifically at C2 to give di-*O*-acetyl-2-bromo-2-deoxy-D-xylopyranosyl bromide (*7a*). Further treatment of the latter compound with acetyl bromide and zinc bromide gave 2,4-dibromo-2,3,4-trideoxy-D,L-*glycero*-pent-2-enopyranosyl bromide (*11*), isolated as the 1-hydroxy-compound (*10*) after hydrolysis. Analogous results were obtained when tri-*O*-benzoyl-D-xylopyranosyl bromide was treated with benzoyl bromide and zinc bromide. Other acetylated or benzoylated pentopyranoses did not give well defined products when treated with acyl bromide and zinc bromide.

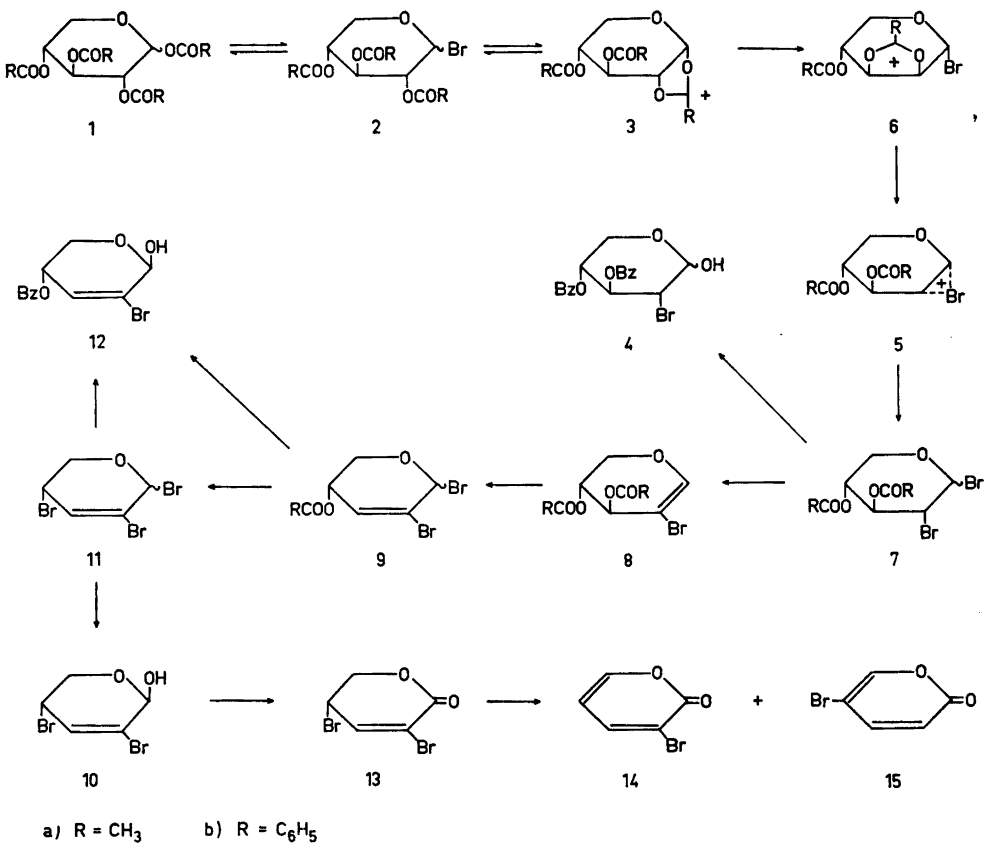
In previous papers the reaction of acylated pentopyranoses and furanoses with dibromomethyl methyl ether was studied.[1,2] It was found that brief treatment with the dibromo ether in the presence of zinc bromide gave glycosyl bromides. The latter on further reaction were converted into 2-bromo-2-deoxy-pentosyl bromides in stereospecific displacement reactions. This property of dibromomethyl methyl ether is probably connected with its ability to form an oxocarbonium ion which is the reactive species.[3,4] Since acyl halides also form oxocarbonium ions under acidic conditions it was decided to study the behaviour of acetyl and benzoyl bromide towards acylated carbohydrates.

Acetylated glycosyl bromides have previously been prepared by the reaction of free sugars or acetylated sugars with acetyl bromide.[5] Treatment of tetra-*O*-acetyl-β-D-xylopyranose (*β-1a*) with acetyl bromide and zinc bromide gave tri-*O*-acetyl-α-D-xylopyranosyl bromide (*α-2a*). In the absence of zinc bromide, or in the presence of a weaker catalyst such as boron trifluoride, the unstable β-bromide (*β-2a*) was first formed as seen from $^1$H NMR spectra of the reaction mixtures. It subsequently underwent anomerization to the more stable α-bromide. With stronger catalysts, such as zinc bromide, mercuric chloride, or sulfuric acid, the β-bromide could not be detected, probably because of rapid anomerization.

The reaction of the tetraacetate (*1a*) with acetyl bromide and zinc bromide gives, besides the bromide (*2a*), acetic anhydride. Separate experiments showed that the bromide (*2a*) reacted with acetic anhydride and zinc bromide to give the α-tetraacetate (*α-1a*). It is therefore necessary to use a rather large excess of acetyl bromide in order to convert *1a* completely into *2a*. When (*β-1a*) was treated with acetyl chloride and zinc chloride tri-*O*-acetyl-α-D-xylopyranosyl chloride was obtained in good yield.

When the bromide *2a* was treated with acetyl bromide and zinc bromide for 3 days further reactions took place and the known 2-bromo-2-deoxy-D-xylopyranosyl bromide[1] (*7a*) was formed as seen from $^1$H NMR spectra of the reaction mixture. The dark colour of the reaction mixture showed that extensive decomposition took place. Work up and treatment with silver benzoate gave a low yield of 3,4-di-*O*-acetyl-1-*O*-benzoyl-2-bromo-2-deoxy-β-D-xylopyranose together with the elimination product *8a* and tri-*O*-acetyl-1-*O*-benzoyl-β-D-xylopyranose.

Since benzoates are generally more stable than acetates the reaction of tri-*O*-benzoyl-α-D-xylopyranosyl bromide (*α-2b*) with benzoyl bromide and zinc bromide was also investigated. This gave a considerably better yield of the 2-bromo-




2-deoxy-bromide (*7b*), isolated as the crystalline 3,4-di-*O*-benzoyl-2-bromo-2-deoxy-D-xylose (*4*) after hydrolysis.

When tetra-*O*-acetyl-β-D-xylopyranose was treated with acetyl bromide in the presence of a larger amount of zinc bromide than that used in the experiments described above the reaction went even further to give the unstable tribromo-compound (*11*). After hydrolysis of the crude product 2,4-dibromo-2,3,4-trideoxy-β-D,L-*glycero*-pent-2-enopyranose (*10*) was isolated in 37 % yield. The same compound was obtained in 51 % yield by treatment of tri-*O*-benzoyl-α-D-xylopyranosyl bromide with benzoyl bromide and zinc bromide. A similar treatment of 3,4-di-*O*-benzoyl-2-bromo-2-deoxy-D-xylopyranosyl bromide (*7b*) also gave *10*, showing that *7* is an intermediate in the conversion of *2* into *10*.

Tri-*O*-acetyl- and tri-*O*-benzoyl-arabino-, -ribo-, and -lyxopyranosyl bromides did not give 2-bromo-2-deoxy-compounds by treatment with acetyl and benzoyl bromide, respectively. All the compounds underwent a slow decomposition, but no pure products could be isolated.

The 2-bromo-2-deoxy-xylopyranosyl bromides (*7*) are probably formed *via* the dioxolanylium ions *3* and *6* and the bromonium ion *5* as proposed for the analogous reaction with dibromomethyl methyl ether.[1,4] This mechanism requires that the acyloxy-groups at C2 and C3 are *trans*-oriented and thus explains why tri-*O*-acyl-lyxo- and -ribopyranosyl bromides do not give 2-bromo-2-deoxy compounds. It does, however, not explain the lack of reactivity of the corresponding arabinosyl bromides.

The conversion of *7* into the unsaturated tribromo-compound *11* must necessarily involve a number of intermediates. It was found that 3,4-di-*O*-benzoyl-2-bromo-1,2-dideoxy-D-*threo*-pent-1-enopyranose (*8b*), obtained from *7b* by treatment with diethylamine, could be converted into *10* in 63 % yield by treatment with

*Table 1.* Proton chemical shifts ($\delta$) and coupling constants (Hz).

| Compound | H1 | H3 | H4 | H5 | H5′ | $J_{13}$ | $J_{34}$ | $J_{35}$ | $J_{35'}$ | $J_{45}$ | $J_{45'}$ | $J_{55}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *8b*[a] | 7.02 | 5.74 | 5.39 | 4.45 | 4.14 | 0 | 2.5 | 1.5 | ~0.5 | 2.5 | 1.5 | 12.0 |
| *10*[b] | 5.36 | 6.47 | 4.79 | 4.46 | 3.92 | ~0.5 | 5.5 | | 1.1 | 2.6 | 1.1 | 13.3 |
| *12*[b] | 5.36 | 6.49 | 5.24 | 4.41 | 3.96 | ~0.5 | 5.5 | | 1.1 | 2.9 | 1.1 | 13.0 |
| *13*[b] | | 7.59 | 5.18 | 5.00 | 4.67 | | 5.9 | | 1.4 | 3.0 | 1.9 | 13.3 |

$^{13}$C chemical shifts ($\delta$) and $^{1}J\{C-H\}$ values (Hz).

| Compound | C1 | C2 | C3 | C4 | C5 | $J_{C1-H1}$ | $J_{C3-H3}$ | $J_{C4-H4}$ | $J_{C5-H5}$ |
|---|---|---|---|---|---|---|---|---|---|
| *8b*[a] | 147.5 | 94.7 | 68.7 | 68.3[c] | 63.7[c] | 194 | 155 | 155 | 149 |
| *10*[a] | 91.1 | 125.8 | 130.0 | 44.3 | 62.6 | 170 | 175 | 158 | 148 |
| *12*[a] | 92.0 | 130.9 | 126.8 | 67.5 | 61.0 | 171 | 167 | 151 | 150 |

[a] In deuteriochloroform; [b] in acetone-$d_6$; [c] may be reversed.

benzoyl bromide and zinc bromide for 24 h. The primary product of this reaction is *11* which is subsequently hydrolyzed during work-up. When *8b* was treated with benzoyl bromide and zinc bromide for only 10 min *9b* was formed in high yield, as seen from an NMR spectrum of the reaction mixture, and the corresponding 1-hydroxy-compound *12* could be isolated in 80 % yield after hydrolysis.

From these experiments it is concluded that the conversion of *7* into *11* takes place *via 8* and *9*. The presence of *8* was not observed directly, probably because it, as shown above, reacts rapidly with benzoyl bromide and zinc bromide to give *9*.

The structures of the products *10* and *12* were derived from their $^{1}$H NMR and $^{13}$C NMR spectra (Table 1). Only one anomer was observed of the two compounds. The small values of $J_{45}$ and $J_{45'}$ indicated that both compounds adopt the $^{5}H_{0}$ conformation with equatorial H4. The rather large value of $J_{34}$ (5.5 Hz) also shows that H4 is equatorial.[6] The small allylic coupling, $J_{13}$, indicates that H1 is equatorial [6-8] and hence that the hydroxygroup and the substituent at C4 are *trans*-oriented. The dibromo-compound *10* was obtained as a racemic form only whereas *12* was optically active. Thus the racemization takes place during the conversion of *9* to *11*. Reaction of *10* with silver benzoate yielded racemic *12*.

In order to confirm the structure of *10* it was oxidized to the lactone *13*, which gave spectral data in agreement with its structure. Reaction of *13* with triethylamine yielded a mixture of the known bromo-pyrones *14* and *15*.

The structures of *9* and *11*, together with those of similar compounds, will be discussed in detail in a forthcoming paper.

Treatment of tri-*O*-acetyl-α-D-xylopyranosyl chloride or of other pentosyl chlorides with acetyl chloride and zinc chloride did not result in formation of chloro-deoxy derivatives.

## EXPERIMENTAL

Melting points are uncorrected. Preparative TLC was performed on 1 mm layers of silica gel (Merck $PF_{254}$). $^{1}$H NMR spectra were measured on Varian A-60 and HA-100 instruments or on a Bruker HX-90E instrument using tetramethylsilane as internal reference. $^{13}$C NMR spectra were obtained as previously described.[9] Optical rotations were measured on solutions in chloroform.

*Tri-O-acetyl-α-D-xylopyranosyl bromide* (α-2a). A mixture of tetra-*O*-acetyl-β-D-xylopyranose (*β-1a*) (995 mg), acetyl bromide (5 ml), and anhydrous zinc bromide (100 mg) was stirred for 10 min at room temperature. It was then diluted with dichloromethane (100 ml), washed with 4 N hydrochloric acid and with aqueous sodium hydrogencarbonate, dried ($MgSO_4$) and evaporated. The residue (1.1 g) was crystallized from ether-pentane to give 833 mg (79 %) of

α-*2a*, m.p. 92 – 95 °C. One recrystallization gave a product with m.p. 96 – 97 °C, $[\alpha]_D^{20}$ +206° (*c* 2.3) (reported [19] m.p. 102 °C, $[\alpha]_D$ +212°). A $^1$H NMR spectrum further confirmed the structure.

*Tri*-O-*acetyl*-α-D-*xylopyranosyl chloride* was prepared in the same way by treating *β-1a* (1.01 g) with acetyl chloride (5 ml) and zinc chloride (80 mg) for 10 min. Work up and crystallization from ether-pentane gave 616 mg (67 %) of product, m.p. 93 – 96 °C. Two additional recrystallizations gave a product with m.p. 99 – 100 °C, $[\alpha]_D^{20}$ +167.8° (*c* 3) (reported [11] m.p. 105 °C, $[\alpha]_D$ +171.2°).

*Reaction of tri*-O-*acetyl*-α-D-*xylopyranosyl bromide with acetyl bromide.* To a solution of α-*2a* (983 mg) in dichloromethane (3 ml) was added acetyl bromide (1 ml) and zinc bromide (965 mg) and the mixture was stirred for 3 days at +5 °C. Dichloromethane (50 ml) was then added and the solution was washed with 4 N hydrochloric acid and aqueous sodium hydrogencarbonate, dried ($MgSO_4$) and evaporated. The residue (1.0 g) was dissolved in acetonitrile (50 ml) and stirred with silver benzoate (2.0 g) for 16 h at room temperature. The mixture was filtered through carbon and evaporated, the residue was dissolved in dichloromethane, washed with aqueous sodium hydrogencarbonate and dried. Evaporation gave a syrup (900 mg) which was separated into 5 fractions by preparative TLC using ether-pentane (2:1) as eluent.

The fastest moving fraction (100 mg) was a mixture of products as seen from a $^1$H NMR spectrum and was not investigated further. The second fraction (70 mg) consisted mainly of 3,4-di-*O*-acetyl-2-bromo-1,2-dideoxy-D-*threo*-pent-1-enopyranose (*8a*).[1] It was only characterized through its NMR spectrum. The third fraction gave 208 mg (18 %) of 3,4-di-*O*-acetyl-1-*O*-benzoyl-2-bromo-2-deoxy-*β*-D-xylopyranose, recrystallized from ether-pentane, m.p. 119 – 121 °C, $[\alpha]_D^{20}$ −24.7° (*c* 2.6). A mixed m.p. and an NMR spectrum proved its identity with the product described previously.[1] The fourth fraction gave 217 mg (20 %) of tri-*O*-acetyl-1-*O*-benzoyl-*β*-D-xylopyranose, recrystallized from ether – pentane, m.p. 144 – 145 °C, $[\alpha]_D^{20}$ −68.1° (*c* 2.0) (reported [12] m.p. 147 – 148 °C, $[\alpha]_D$ −68.2°). The last fraction (48 mg) consisted of hexa-*O*-acetyl-aldehyde-D-xylose as seen from an NMR spectrum.[13]

*3,4-Di*-O-*benzoyl-2-bromo-2-deoxy*-D-*xylopyranose (4).* A solution of tri-*O*-benzoyl-α-D-xylopyranosyl bromide [1] (5.03 g) in dichloromethane (5 ml) was stirred with benzoyl bromide (10 ml) and zinc bromide (2 g) for 5 days at +5 °C. The mixture was then diluted with dichloromethane (100 ml) and stirred for 3 h with 100 ml of 4 N hydrochloric acid. The organic phase was washed with hydrochloric acid and aqueous sodium hydrogencarbonate, dried and evaporated. The semicrystalline residue (10 g) was shown by $^1$H NMR and TLC to be a mixture of *7b* and benzoic anhydride. It was dissolved in acetone (100 ml) and water (10 ml) and stirred with silver carbonate (5 g) over night. The mixture was then filtered through carbon and evaporated, dissolved in dichloromethane, washed with water, dried and evaporated. The residue (7.4 g) was separated into 2 fractions by chromatography on a column of silica gel using chloroform as eluent.

The first fraction consisted of benzoic anhydride. The next fraction gave 2.0 g (50 %) of *4*, m.p. 143 – 146 °C, $[\alpha]_D^{20}$ −51.5° (10 min) → −29.7° (4 days) (*c* 3.2). An NMR spectrum was identical with that of the product described previously.[1]

*2,4-Dibromo-2,3,4-trideoxy-β*-D,L-glycero-*pent-2-enopyranose (10). A. From tetra*-O-*acetyl-β*-D-*xylopyranose.* To a solution of *β-1a* (5.0 g) in dichloromethane (15 ml) was added acetyl bromide (5 ml) and zinc bromide (2.3 g) and the mixture was refluxed for 3 h (the same result was obtained when the mixture was stirred for 3 days at room temperature). The solution was then poured into a mixture of ice (50 g), conc. hydrochloric acid (50 ml), and ether (100 ml) and stirred for 30 min. The ether phase was washed with 4 N hydrochloric acid and aqueous sodium hydrogencarbonate, dried, filtered through carbon, and evaporated. The residue (2.56 g) was crystallized from tetrachloromethane to give 967 mg (24 %) of *10* as colourless needless, m.p. 187 – 190 °C, $[\alpha]_D^{20}$ 0.0° (*c* 5, acetone). Recrystallization gave the pure product, m.p. 187 – 188 °C. (Found: C 23.19; H 2.06; Br 62.12. Calc. for $C_5H_5Br_2O_2$: C 23.37; H 1.96; Br 62.21). Preparative TLC of the material in the mother liquor gave an additional 517 mg (13 %) of *10*.

*B. From tri*-O-*benzoyl*-α-D-*xylopyranosyl bromide.* A solution of α-*2b* (5.01 g) in dichloromethane (5 ml) was stirred for 5 days at room temperature with benzoyl bromide (10 ml) and zinc bromide (2.0 g). Work up as described above gave 5.8 g of a product which was separated into two fractions by chromatography on a column of silica gel using chloroform as eluent. The first fraction consisted of benzoic anhydride. The second fraction was a mixture of *10* and benzoic acid. It was dissolved in dichloromethane, washed with aqueous sodium hydrogencarbonate and dried. Evaporation of the solvent gave 1.25 g (51 %) of *10* which was recrystallized from tetrachloromethane, m.p. 186 – 189 °C. An NMR spectrum showed that it was identical with the product described above.

*C. From di*-O-*benzoyl-2-bromo-2-deoxy-β*-D-*xylopyranosyl bromide.* A solution of *β-7b* [1] (501 mg) in dichloromethane (0.5 ml) was stirred with benzoyl bromide (1 ml) and zinc bromide (330 mg) for 4 days at room temperature. Work up and chromatography as described above gave 146 mg (55 %) of *10*, m.p. 185 – 187 °C.

*D. From 3,4-di*-O-*benzoyl-2-bromo-1,2-dideoxy*-D-threo-*pent-1-enopyranose.* The same product

was obtained in 63 % yield by treatment of *8b* with benzoyl bromide and zinc bromide for 24 h as described above, m.p. 185 – 188 °C, $[\alpha]_D^{22}$ 0.0° (*c* 4, acetone).

*4-O-Benzoyl-2-bromo-2,3-dideoxy-β-*D-glycero*-pent-2-enopyranose (12).* A solution of *8b* (501 mg) in dichloromethane (0.5 ml) was stirred at room temperature for 10 min with benzoyl bromide (1 ml) and zinc bromide (245 mg). Work up as described above and purification by preparative TLC (chloroform) gave 295 mg (80 %) of *12*, m.p. 134 – 140 °C, $[\alpha]_D^{20}$ +99° (*c* 3.0). One recrystallization from ether-pentane gave a product with m.p. 135 – 137 °C, $[\alpha]_D^{20}$ +102° (*c* 1.2.) (Found: C 48.28; H 3.79; Br 26.94. Calc. for $C_{12}H_{10}BrO_4$: C 48.34; H 3.78; Br 26.81).

*Racemic* 12. A solution of *10* (499 mg) in acetonitrile (10 ml) was stirred for 1 h at room temperature with silver benzoate (1.03 g). The mixture was then filtered through carbon, evaporated, dissolved in dichloromethane, washed with aqueous sodium hydrogencarbonate, dried and evaporated. The residue (438 mg) was separated into two fractions by preparative TLC (ether-pentane 1:1).

The fast moving fraction gave 310 mg (54 %) of racemic *12* which was recrystallized from ether-pentane, m.p. 146 – 148 °C. A $^1$H NMR spectrum and an IR spectrum in chloroform solution were identical with those of the D-form described above. IR spectra of the two forms in the solid phase (KBr) were different.

The second fraction gave 55 mg (14 %) of 1-*O*-benzoyl-3,4-dideoxy-pent-3-enopyranosulose, m.p. 71 – 72 °C (recorded [14] m.p. 74 – 75 °C). NMR and IR spectra were identical with those of the product previously described.

*3,4-Di-O-benzoyl-2-bromo-1,2-dideoxy-*D-threo*-pent-1-enopyranose (*8b*).* A solution of *7b* (1.017 g) in dichloromethane (2 ml) was reacted with diethylamine (2 ml) for 15 min at 0 °C. The solution was then diluted with dichloromethane (50 ml), washed with 4 N hydrochloric acid and aqueous sodium hydrogencarbonate, dried and evaporated. The residue was crystallized from ether-pentane to give 634 mg (78 %) of *8b*, m.p. 136 – 137 °C. One recrystallization gave m.p. 138 – 139 °C, $[\alpha]_D^{20}$ −296° (*c* 1.3). (Found: C 56.49; H 4.04; Br 19.50. Calc. for $C_{19}H_{15}BrO_5$: C 56.59; H 3.75; Br 19.82).

*Racemic 3,5-dibromo-5,6-dihydro-2-pyrone (13).* A solution of *10* (505 mg) in dichloromethane (20 ml) was stirred at room temperature for 3 h with water (50 ml) saturated with bromine. The organic phase was then washed with 5 % aqueous sodium thiosulfate and water, dried and evaporated. The product (469 mg) was purified by preparative TLC (ether-pentane 3:1) to give 330 mg (66 %) of *13*, m.p. 61 – 64 °C. Recrystallization from ether-pentane gave the pure product, m.p. 64 – 65 °C. (Found: C 23.57; H 1.65; Br 62.32. Calc. for $C_5H_4Br_2O_2$: C 23.47; H 1.58; Br 62.45). An IR spectrum (KBr) showed a carbonyl band at 1730 cm$^{-1}$; a UV spectrum gave $\lambda_{max}$ 250 nm, $\varepsilon$ 7700 (acetonitrile).

*3- and 5-Bromo-2-pyrone, (14 and 15), respectively.* A solution of *13* (101 mg) in dichloromethane (10 ml) was cooled to 0 °C and triethylamine (0.5 ml) was added. After 16 h at 0 °C the solution was evaporated and the residue was separated into two fractions by preparative TLC (ether-pentane 2:1).

The fast moving fraction gave 17 mg (25 %) of *15*, m.p. 58 – 60 °C (reported [15] m.p. 60 – 61 °C). The next fraction gave 44.5 mg (64 %) of *14*, m.p. 62 – 63 °C after recrystallization from ether – pentane (reported [15] m.p. 63.5 – 64 °C). UV, IR, and NMR spectra of both products were in agreement with those published.[15,16]

Microanalyses were made by Dr. A. Bernhardt's Microanalytical Laboratory.

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