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Dioxolanylium Ions Derived from Carbohydrates. IV. Reaction of Ribofuranose Derivatives with Nucleophiles

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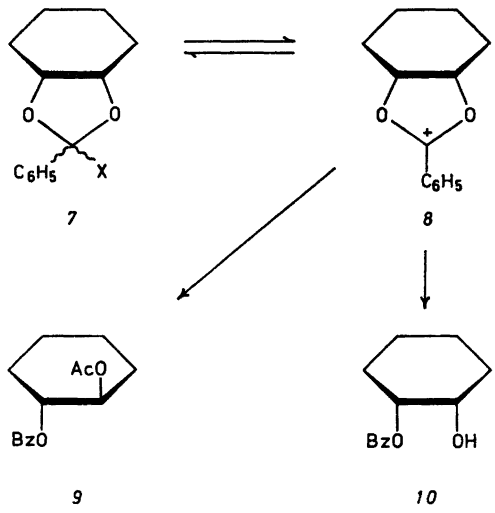
Reaction of methyl 5-*O*-benzoyl- (or 5-*O*-methoxybenzoyl-) 2,3-*O*-benzylidene-β-D-ribofuranoside (*1*) with triphenylmethyl fluoroborate gave a 2,3-benzoxonium ion (*2*) which was in equilibrium with a 3,5-ion (*3*), derived from D-xylofuranose. Treatment of this ion with *p*-toluenesulfonate led to *trans* opening with formation of *p*-toluenesulfonylated D-xylofuranose derivatives. Reaction of *2* with acetate or azide ion gave orthoacid derivatives (*4*) which on subsequent hydrolysis underwent *cis* opening.

In a preceding paper [1] the preparation of benzoxonium ions derived from D-arabinopyranose and their reactivity towards a series of nucleophiles were described. In the present paper this investigation is extended to benzoxonium ions derived from D-ribofuranose.



Treatment of methyl 5-*O*-benzoyl-2,3-*O*-benzylidene-β-D-ribofuranose (*1a*) with triphenylmethyl fluoroborate in acetonitrile yields the benzoxonium ion *2a*. This ion has previously been shown to undergo *cis* opening with water.[3] With bromide ion it gives a 3-bromo-3-deoxy-D-xylofuranose derivative with *trans* opening.[2]

When *2a* was treated with anhydrous sodium acetate a reaction took place at once as seen from the ^{13}C NMR spectrum (a large upfield shift of the signals of C2 and C3). On hydrolysis of the reaction mixture only methyl 2,5- and 3,5-di-*O*-benzoyl-β-D-ribofuranosides were isolated. This indicates that *2a* reacts with acetate to give the orthoacid acetate *4a* (X = OAc) which on hydrolysis undergoes *cis* opening. A similar result was obtained when *2a* was treated with azide ions.

Treatment of the ion *2a* with *p*-toluenesulfonate ion led to *trans* opening and formation of the 3-*O*-tosyl derivative *5*. However, in addition to this product the 5-*O*-tosylate (*6*) was obtained. The latter product cannot arise from the ion *2a*, but must be formed by attack at C5 of the dioxanylium ion *3a*. The amount of dioxanylium ion *3a*, present in equilibrium with *2a*, is small because it could not be observed in the ^1H and ^{13}C NMR spectra of *2a*. Obviously, low concentration of *3a* does not exclude formation of substantial amounts of *6* because the reactivity of *3a* may be higher than that of *2a*.

It has been observed previously that benzoxonium ions are stabilized by a *p*-methoxy-group.[2,4] In an attempt to observe the ion *3* methyl 2,3-*O*-benzylidene-5-*O*-*p*-methoxybenzoyl-β-D-ribofuranoside (*1b*) was treated with trityl fluoroborate in acetonitrile. This gave a

mixture of the cyclic ions *2b* and *3b* containing 16 % of the latter ion as estimated from ^1H and ^{13}C NMR spectra. Hydrolysis of this mixture, followed by deacylation, yielded methyl β-D-xylofuranoside (18 %) and methyl-β-D-ribofuranoside (82 %).

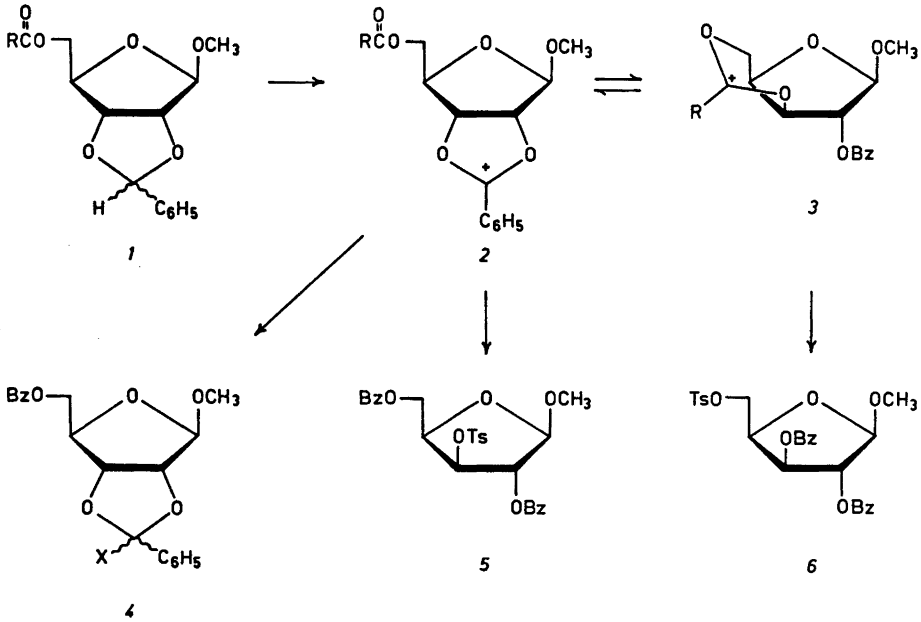
The fact that *2a* and the benzoxonium ion discussed in the preceding paper,[1] do not undergo *trans* opening with acetate ion is somewhat surprising in view of the work of Winstein *et al.* on the acetoxonium ion derived from *cis*-1,2-cyclohexanediol.[5] However, Winstein *et al.* used acetic acid as a solvent at *ca.* 75 °C whereas acetonitrile was used at room temperature in the present work. Carbohydrate benzoxonium ions are not stable at elevated temperatures and it is therefore not possible to compare their reactivity with the results obtained by Winstein *et al.*

It was, however, of interest to see how the benzoxonium ion *8* behaved when treated with acetate ion in acetonitrile. A solution of the ion *8* in acetonitrile was therefore prepared by treatment of 1,2-*O*-benzylidene-*cis*-cyclohexanediol (*7*, X=H) with triphenylmethyl fluoroborate. In a series of experiments *8* was treated with sodium acetate and hydrolysed after varying periods of time. This showed that at room temperature more than 1 month is required for complete *trans* opening of *8* to give *9*. After a short reaction time the *cis* monobenzoate *10* was the main product. When the reaction was followed by ^{13}C NMR spectroscopy it was found that *8* was immediately converted into an intermediate compound on treatment with acetate; the latter compound subsequently rearranged to the *trans* acetate benzoate *9*. Since the intermediate product gave the *cis* monobenzoate *10* on hydrolysis it is probably an orthoacid acetate (*7*, X=OAc).

EXPERIMENTAL

For details about thin layer chromatography, optical rotations, and NMR spectra see the preceding paper.

Preparation of benzoxonium ions. The ions were prepared in acetonitrile solutions as described previously.[2,3] To the solution of the ion were then added 3–5 molar equivalents of the appropriate nucleophile (dried over phosphorus pentoxide or conc. sulfuric acid) and the mixture was stirred at room temperature for the time specified. The mixture was then stirred for 5 min with aqueous $NaHCO_3$ and extracted



a: R = C_6H_5

b: R = *p*-$CH_3OC_6H_4$

with chloroform. The chloroform solution was washed with water, dried and concentrated. Preparative TLC (ether-pentane (1:1) unless otherwise specified) gave triphenylmethane, moving with the solvent front, followed by triphenylcarbinol and the products.

Benzoxonium ion 2a *from methyl 5-O-benzoyl-2,3-O-benzylidene-β-D-ribofuranoside (*1a*).* A solution of this ion (*2a*) was prepared in acetonitrile-d_3. ^{13}C NMR: 106.1 ppm (C1), 93.9 and 93.2 (C2 and C3), 82.0 (C4), 63.2 (C5), 179.3 (>C$^+$−).

Reaction with acetate ion. Benzoxonium ion *2a* from *1a* (483 mg) was stirred with anhydrous sodium acetate (1.0 g) for 24 h. Hydrolysis and chromatography as described above gave 41 mg of unchanged *1a* and 311 mg of a mixture of methyl 2,5- and 3-5-di-*O*-benzoyl-β-D-ribofuranoside.[3] The products were identified by ^{1}H NMR spectroscopy.

In another experiment the ion *2a* was prepared in acetonitrile-d_3 and treated with anhydrous sodium acetate to give a solution of the orthoacid acetate *4a* (X = OAc). ^{13}C NMR: 108.2 ppm (C1), 86.4, 83.3, and 83.3 (C2, C3, and C4), 64.4 (C5).

Reaction with p-*toluenesulfonate ion.* Benzoxonium ion *2a* from 614 mg of *1a* was stirred with tetraethylammonium tosylate (1.0 g) for 3 days. Hydrolysis and chromatography gave, besides unchanged *1a* (50 mg) and methyl 2,5- and 3,5-di-*O*-benzoyl-β-D-ribofuranoside, 323 mg (36 %) of a mixture of two tosylates in about equal amounts. Re-chromatography (using chloroform as an eluent) gave two products.

The fast-moving fraction gave 132 mg of methyl 2,3-di-*O*-benzoyl-5-*O*-*p*-toluenesulfonyl-β-D-xylofuranoside (*6*), m.p. 86 – 88 °C, identical with an authentic specimen described below. The slow-moving fraction, 72 mg, m.p. 118 – 128 °C, consisted of methyl 2,5-di-*O*-benzoyl-3-*O*-*p*-toluenesulfonyl-β-D-xylofuranoside (*5*). Recrystallization from ethyl acetate-pentane and from ethanol-water gave a product with m.p. 127 – 129 °C, identical with an authentic specimen (see below), $[\alpha]_D^{25}$ +16° (*c* 1.1). Anal. $C_{27}H_{26}O_9S$: C, H, S. ^{1}H NMR : δ 5.01 (H1), 5.38 (H2), 5.28 (H3), 4.84 (H4), 4.62 (H5), 4.61 (H5′); J_{12} = 0.8 Hz, J_{23} = 2.2, J_{34} = 5.7, J_{45} = 5.2, $J_{45'}$ = 6.7.

Reaction of methyl β-D-xylofuranoside [6] (526 mg) with *p*-toluenesulfonyl chloride (721 mg) in pyridine (10 ml) for 8 h at 0 °C and 16 h at 25 °C gave 469 mg (43 %) of crude methyl 5-*O*-*p*-toluenesulfonyl-β-D-xylofuranoside. This was benzoylated with benzoyl chloride in pyridine to give 704 mg of a syrupy product. Preparative TLC (chloroform) gave 527 mg (68 %) of *6* as a syrup which crystallized on standing, m.p. 86 – 87 °C, $[\alpha]_D^{25}$ +35° (*c* 2.4). Anal. $C_{27}H_{26}O_9S$: C, H, S. ^{1}H NMR: δ 5.08 (H1), 5.43 (H2), 5.72 (H3), 4.84 (H4), 4.38 (H5), 4.33 (H5′); J_{12} < 0.5 Hz, J_{23} = 1.4, J_{34} = 5.8, J_{45} = 6.3, $J_{45'}$ = 6.5. $J_{55'}$ = 10.2.

Benzoylation of methyl 2-*O*-benzoyl-β-D-xylofuranoside [7] (468 mg) with benzoyl chloride (0.13 ml) in pyridine (10 ml) for 2 days at 0 °C gave a syrup. Preparative TLC (ether-pentane 3:1) yielded 234 mg (40 %) of methyl 2,5-di-*O*-benzoyl-β-D-xylofuranoside and 62 mg of recovered 2-*O*-benzoate. Reaction of the 2,5-dibenzoate with *p*-toluenesulfonyl chloride (500 mg) in pyridine (5 ml) for 3 days at room temperature and work-up in the usual way yielded 317 mg of *5*, m.p. 125 – 127 °C after recrystallization from ethanol-water.

*Methyl 2,3-O-benzylidene-5-O-*p*-methoxybenzoyl-β-D-ribofuranoside (*1b*).* Crude methyl 2,3-*O*-benzylidene-β-D-ribofuranoside [2] (from 1.64 g of methyl β-D-ribofuranoside) was treated with *p*-methoxybenzoyl chloride (2.0 g) in pyridine (10 ml). Work-up in the usual way gave 3.2 g of crude *1b*, m.p. 69 – 75 °C. Recrystallization from ethyl acetate-pentane gave 1.8 g (47 %) of a mixture of diastereomers, m.p. 72 – 75 °C. Anal. $C_{21}H_{22}O_7$: C, H.

*Benzoxonium ion from methyl 2,3-O-benzylidene-5-O-*p*-methoxybenzoyl-β-D-ribofuranoside (*1b*).* A solution containing the ions *2b* and *3b* was prepared in acetonitrile-d_3 as described above and spectral data were obtained from this solution. ^{1}H NMR of *2b*: δ 5.62 (H1), 6.27 and 6.64 (H2 and H3), 5.23 (H4), 4.63 (H5), 4.52 (H5′), 3.46 (glycosidic OCH_3), 3.87 (arom. OCH_3); $J_{12} \simeq 0$ Hz, J_{23} = 6.8, $J_{34} \simeq 0$, J_{45} = 6.3, $J_{45'}$ = 6.8, $J_{55'}$ = 11.8 ^{1}H NMR of *3b* (only the two methoxy-signals could be identified): 3.14 (glycosidic OCH_3), 4.01 (arom. OCH_3). ^{13}C NMR of *2b*: 106.1 ppm (H1), 93.9 and 93.3 (C2 and C3), 82.2 (C4), 62.9 (C5), 182.2 (>C$^+$). ^{13}C NMR of *3b*: 105.8 (C1), 70.5 (C2), 77.7 (C3), 83.2 (C4), 72.1 (C5).

Reaction with water. A mixture of the ions *2b* and *3b*, prepared from *1b* (530 mg), in acetonitrile solution was stirred for 5 min with aqueous $NaHCO_3$. Work-up as described above gave a crude mixture which was deacylated with sodium methoxide in methanol. The solution was neutralized with CO_2 and evaporated to dryness. The residue was suspended in water and extracted with chloroform. The aqueous solution was evaporated to dryness and dissolved in deuterium oxide and the ^{13}C NMR spectrum was recorded. Except for a small signal from carbonate the spectrum showed only the signals of methyl β-D-ribofuranoside (82 %) and methyl β-D-xylofuranoside (18 %).[8] The relative amounts were estimated from the ratio of peak intensities of carbons 1, 2, 3, and 5.

*Reaction of 2-phenyl-4,5-tetramethylenedioxolanylium ion with acetate. cis-*1,2-*O*-Benzylidenecyclohexane [9] (500 mg) was treated with a 10 – 20 % excess of triphenylmethyl fluoroborate for 15 min at room temperature in acetonitrile (10 ml). Anhydrous sodium acetate (1.0 g) was then added and the mixture was stirred at room temperature for the time specified below. The mixture was then stirred for 5 min

with aqueous $NaHCO_3$ and extracted with chloroform. The chloroform solution was dried and concentrated. Preparative TLC (ether-pentane 1:2) gave triphenylmethane (with the solvent front), triphenylcarbinol, *trans*-2-acetoxycyclohexanol benzoate (*9*), and *cis*-2-benzoyloxycyclohexanol (*10*).[10] Three experiments were carried out:

1. 5 h, *9*: 5 – 10 %, *10*: 77 %
2. 5 days, 9: 27 %, 10: 50 %
3. 25 days, 9: 73 %, 10: 16 %

The syrupy *9* was characterized through its NMR spectrum. Besides it was deacylated with sodium methoxide in methanol to give *trans*-1,2-cyclohexanediol, m.p. 102 – 103°C, undepressed in admixture with an authentic sample.[9,10]

In a separate experiment the benzoxonium ion *8* was generated in acetonitrile-d_3 solution. ^{13}C NMR: 88.3 ppm (C1, C2), 23.8 (C3, C6), 16.1 (C4, C5), 181.4 ($\rangle C^+$). A ^{13}C NMR spectrum measured shortly after addition of anhydrous sodium acetate gave the following values: 75.1 (C1, C2), 25.3 (C3, C6), 19.1 (C4, C5).

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