REACTION OF UNSATURATED CARBOHYDRATE DERIVATIVES WITH METHANOL AND BORON TRIFLUORIDE*

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(Received January 15th, 1971)

ABSTRACT

Brief treatment of 3,4-di-*O*-benzoyl-1,2-dideoxy-D-*threo*-pent-1-enopyranose (**1**), or the corresponding D-*erythro* compound (**6**), with methanol in the presence of boron trifluoride gives methyl 4-*O*-benzoyl-2,3-dideoxy-D-*glycero*-pent-2-enopyranoside (**3**) as the main product. On further reaction, methanol is added to the double bond of **3**, and two methyl 2-deoxy-3-*O*-methyl-D-pentosides (**4** and **5**) are obtained. Similar treatment of 3,4-di-*O*-benzoyl-1,2,6-trideoxy-L-*arabino*-hex-1-enopyranose (**9**) with methanol and boron trifluoride yields two methyl 2,6-dideoxy-3-*O*-methyl-L-hexosides (**12** and **13**) via the unsaturated methyl glycoside **11**. The structures of the products were determined by n.m.r. spectroscopy.

INTRODUCTION

Ferrier *et al.*[1,2] have shown that treatment of hex-1-enopyranose derivatives with alcohols in the presence of boron trifluoride yields 2,3-unsaturated glycosides. In connection with other work[3,4], on pent-1-enopyranose derivatives, we applied this method and found that, in order to obtain good yields of methyl 4-*O*-benzoyl-2,3-dideoxy-α,β-D-*glycero*-pent-2-enopyranoside (**3**) from 3,4-di-*O*-benzoyl-1,2-dideoxy-D-*threo*-pent-1-enopyranose (**1**), or from the corresponding *erythro* compound (**6**), it is important to use only a small proportion of boron trifluoride and not more than two equivalents of methanol. The reaction was conducted in an inert solvent, usually dichloromethane. Under these conditions, the reaction was complete in ~10 minutes, and high yields of **3** were obtained. If, however, 3–4 molar equivalents of methanol were present, the yield of **3** decreased, and products resulting from addition of methanol to the double bond of **3** were formed. As this behavior is analogous to the previously studied reactions of unsaturated pentoses with hydrogen halides[3], it was of interest to investigate this reaction more closely.

RESULTS AND DISCUSSION

Treatment of **1** or **6** with two molar equivalents of methanol in dichloromethane in the presence of boron trifluoride etherate for 10 minutes gave a mixture of

*Dedicated to Dr. Nelson K. Richtmyer in honor of his 70th birthday.

TABLE 1

CHEMICAL SHIFTS (δ-VALUES) IN CHLOROFORM-*d* AND COUPLING CONSTANTS (Hz) OF 2-DEOXYPENTOSE DERIVATIVES

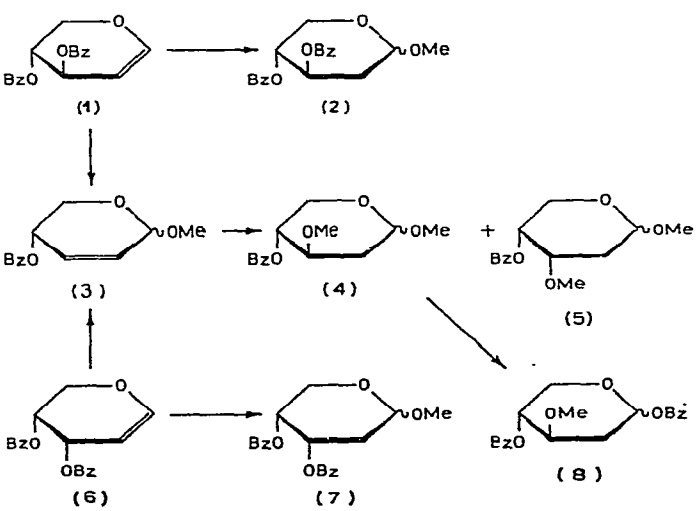
Compound	*H-1*	*H-2a*	*H-2e*	*H-3*	*H-4*	*H-5a*	*H-5e*	$J_{1,2a}$	$J_{1,2e}$	$J_{2a,2e}$	$J_{2a,3}$	$J_{2e,3}$	$J_{3,4}$	$J_{4,5a}$	$J_{4,5e}$	$J_{5a,5e}$	*Conformation*
α-2	4.85	1.97	2.42	5.71	5.31	3.85	4.00	3.0	3.0	13.0	10.0	5.0	9.0	9.0	5.5	11.0	$^4C_1$
β-2	4.70	2.43	2.03	5.43	5.25	4.36	3.66	3.0	6.0	13.0	4.2	7.5	7.0	3.7	6.0	12.0	
α-4	4.75	1.75	2.18	3.76	5.07	3.70	3.91	3.2	3.4	13.4	9.2	4.6	7.6	7.6	4.6	11.0	$^4C_1$
β-4	4.62	2.23	1.82	3.55	5.08	4.22	3.57	3.6	5.0	14.0	4.4	6.6	5.0	3.4	5.0	12.0	
β-5	4.89	1.8	2.1	3.80	5.45	3.90	4.16	3.2	2.0		10.0	6.0	3.0	3	3		
α-8	6.43	2.03	2.41	3.93	5.19	3.96	4.16	3.2	4.0	13.5	8.9	4.1	7.6	8.0	4.5	11.8	$^4C_1$
β-8	6.37	2.36	2.20	3.75	5.18	4.45	3.85	3.2	3.6	14.0	3.5	3.6	4	2.3	3.1	12.2	$^1C_4$

the anomers of the unsaturated methyl glycoside **3** in ~70% yield, together with small amounts of **2** and **7**, which must arise by direct addition of methanol to the double bond of **1** and **7**, respectively. The β anomer of **3** was the preponderant product; both this compound and the α anomer were characterized through their n.m.r. spectra, which have been described and analyzed by Lemieux *et al.*[5].

When compound **1** was treated with 3–4 equivalents of methanol under the same conditions, the unsaturated methyl glycoside **3**, which was initially formed, gradually disappeared while new products were formed. The mixture was processed after 24 hours when, as shown by an n.m.r. spectrum of the mixture, **3** was no longer present; this gave a total yield of ~80% of a mixture of the 2-deoxy-3-*O*-methyl-glycosides (**4** and **5**). The main product, isolated in 62% yield after chromatography, was methyl 4-*O*-benzoyl-2-deoxy-3-*O*-methyl-α-D-*threo*-pentopyranoside (α-**4**). In addition, an 11% yield of the corresponding β anomer (β-**4**) was obtained. Methyl 4-*O*-benzoyl-2-deoxy-3-*O*-methyl-D-*erythro*-pentopyranoside was isolated as the β anomer (β-**5**) in only 11% yield. The same products were obtained when the unsaturated glycoside **3** was treated with methanol and boron trifluoride.

The reaction of pure α-**4** with methanol, catalyzed by boron trifluoride, gave a mixture of the α and β anomers of **4** in the ratio of 6:1. The *erythro* compound **5** was not formed by this reaction, indicating that the ratio between the anomers of **4** and **5** is thermodynamically controlled, whereas the addition of methanol to the double bond of **3** is a kinetically controlled reaction. This conclusion is in contrast to the results obtained[3] for the addition of hydrogen bromide to **3**, which resulted in formation of an equilibrium mixture of 3-bromo-2,3-dideoxy-D-*erythro* and-*threo* compounds.

The structures of the 3-methyl ethers **4** and **5** were assigned from their n.m.r. spectra (see Table I). The structure of the main product (α-**4**) was readily determined from the coupling constants, $J_{4,5a} = J_{3,4} = 7.6$ Hz, $J_{2a,3} = 9.0$, and $J_{1,2} = 3.2$ and 3.4 Hz; these results show that the product is an α-D-*threo* compound which is

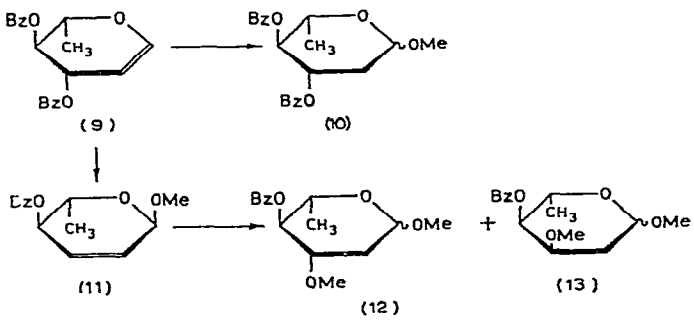


mainly in the $^4C_1$ conformation. The spectrum is closely similar to that of α-**2**, except for the δ-value of H-3. The structure of β-**5** is seen from the small values of $J_{1,2}$, $J_{3,4}$, and $J_{4,5}$ and the large coupling-constant $J_{2a,3} = 10.6$ Hz. These results are only compatible with a β-D-*erythro* compound in the $^1C_4$ conformation, similar to that of β-**7**. The structure of the remaining product (β-**4**) could not be determined unambiguously from the n.m.r. data. The coupling constants indicated that the compound exists as a mixture of two conformers in solution; these could arise either from a β-D-*threo* compound (β-**4**) or from an α-D-*erythro* compound (α-**5**). The fact that the spectrum is similar to that of β-**2**, and rather different from that of (α-**7**)[4], indicates, however, that the product is β-**4**.

Treatment of α-**4** with hydrogen chloride gave a glycosyl chloride which, by reaction with silver benzoate, yielded a mixture of the anomers of 1,4-di-*O*-benzoyl-2-deoxy-3-*O*-methyl-D-*threo*-pentopyranose (**8**). The spectra of the two products were closely similar to those of the methyl glycosides **4**.

In analogy with the results just described, it would be expected that treatment of 3,4-di-*O*-benzoyl-1,2,6-trideoxy-L-*arabino*-hex-1-enopyranose (**9**) with methanol and boron trifluoride should yield 2,6-dideoxy-3-*O*-methyl-hexoses. As such compounds are found as components of the cardiac glucosides[6], it was of interest to investigate this reaction.

Reaction of compound **9** with two molar equivalents of methanol for 15 minutes gave a 73% yield of methyl 4-*O*-benzoyl-2,3,6-trideoxy-α-L-*erythro*-hex-2-enopyranoside (α-**11**); the corresponding β anomer was not found. In addition, the addition product **10** was obtained in 19% yield as a mixture of its anomers. Treatment of **9** with three molar equivalents of methanol and boron trifluoride for 48 hours gave, besides **10**, a mixture of the methyl 2,6-dideoxy-3-*O*-methyl-hexopyranosides (**12** and **13**), which were separated by chromatography. The structures of the products **10**, **11**, **12**, and **13** were readily determined from the n.m.r. spectra (see Table II). The saturated compounds were all found to exist exclusively in the $^1C_4$ conformation.



Treatment of α-**12** with methanol and boron trifluoride led to anomerization only; no epimerization occurred at C-3, in agreement with the results just described for the corresponding pentose derivatives. When this reaction was performed with *O*-deuteriomethanol (MeOD), the same result was obtained; no deuterium was introduced at C-2. Treatment of the 2,3-unsaturated glycoside **11** with *O*-deuterio-

TABLE II

CHEMICAL SHIFTS (δ-VALUES) IN CHLOROFORM-*d* AND COUPLING CONSTANTS (Hz) OF 2,6-DIDEOXYHEXOSE DERIVATIVES

Compound	*H-1*	*H-2a*	*H-2e*	*H-3*	*H-4*	*H-5*	*H-6*	$J_{1,2a}$	$J_{1,2e}$	$J_{2a,2e}$	$J_{2a,3}$	$J_{2e,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$
α-10	4.86	1.95	2.48	5.63	5.24	4.18	1.29	3.6	1.2	13.0	11.3	5.1	9.4	9.4	6.3
β-10	4.62	1.92	2.56	5.40	5.22	3.73	1.36	9.8	2.0	12.2	9.2	5.0	9.3	9.2	6.0
α-12	4.82	1.70	2.30	3.80	4.97	3.90	1.22	3.6	1.3	12.6	11.5	5.0	9.0	9.0	6.0
β-12	4.45	1.70	3.28	3.5	4.96	3.6	1.28	9.8	2.0	12.8	11.4	5.0	9.0	9.0	6.2
α-13	4.72	1.95	2.23	3.87	4.90	4.41	1.25	4.4	1.8	14.6	4.4	3.9	3.0	9.0	6.5
β-13	4.77	1.74	2.20	3.93	4.82	4.16	1.28	9.0	2.3	13.2	2.7	4.2	2.8	9.0	6.3
								$J_{1,2}$	$J_{1,3}$	$J_{1,4}$	$J_{2,3}$	$J_{2,4}$			
α-11	4.92	5.85		5.96	5.34	4.14	1.30	2.1	0.6	1.6	10.0	1.6	1.6	9.2	6.3

methanol and boron trifluoride resulted in formation of the same products as those obtained from methanol. As expected, they all contained one deuterium atom at C-2. An n.m.r. analysis of these four products, α- and β-**12** and α- and β-**13**, showed that the deuterium at C-2 was almost equally distributed between the axial and the equatorial positions. As it was shown that the final products are stable with regard to the configuration at C-3, it is concluded that the addition of methanol to the double bond of **12** is not stereospecific.

EXPERIMENTAL

General procedures. — Melting points are uncorrected. For thin-layer chromatography (t.l.c.), Silica Gel PF_{254} (E. Merck) was used. Preparative t.l.c. was conducted on 1-mm layers on 20 × 40 cm plates. Compounds were detected with u.v. light. N.m.r. spectra were recorded with Varian HA-100 and A-60 instruments, with tetramethylsilane as the internal reference.

*Methyl 3,4-di-*O*-benzoyl-2-deoxy-*D-threo*-pentopyranosides* (**2**). — Authentic samples of the anomers of **2** were prepared from di-*O*-acetyl-1,2-dideoxy-D-*threo*-pent-1-enopyranose (753 mg) by the method described[4] for the corresponding D-*erythro* compound **7**. The crude product (1.21 g) was purified by preparative t.l.c., with 1:1 ether–pentane as the eluant; this gave 875 mg (65%) of **2** as a mixture of its anomers. Crystallization from ether yielded α-**2**, which was recrystallized from ether–pentane; m.p. 115–116°, $[\alpha]_D^{23}$ +31.5° (*c* 1.7, chloroform).

Anal. Calc. for $C_{20}H_{20}O_6$: C, 67.39; H, 5.66. Found: C, 67.25; H, 5.74.

Preparative t.l.c. of the material in the mother liquors gave pure β-**2** as a syrup, $[\alpha]_D^{23}$ −128° (*c* 3.8, chloroform).

Anal. Found: C, 67.17; H, 5.56.

The anomeric structures were readily derived from the n.m.r. spectra (see Table I) and from the optical rotations.

*Methyl 4-*O*-benzoyl-2,3-dideoxy-*D-glycero-*pent-2-enopyranoside* (**3**). — To a solution of compound **1** (515 mg; prepared as in Ref. 3) in dichloromethane (5 ml) was added 1.5 ml of a 1:1:8 mixture of methanol, boron trifluoride etherate, and dichloromethane (solution A). The reaction was monitored by n.m.r. spectroscopy, and it was found that **1** was no longer present after 10 min at room temperature. The solution was then diluted with dichloromethane, washed with aqueous sodium hydrogen carbonate, dried, and evaporated. The product (400 mg) was separated into two fractions by preparative t.l.c. with 1:1 ether–pentane as the eluant. The faster-moving fraction (97 mg) consisted of α-**3** contaminated with ~30% of α-**2**, as shown by the n.m.r. spectrum. The second fraction gave 248 mg (67%) of β-**3**, identical with the product described previously[4,5].

Treatment of 3,4-di-*O*-benzoyl-1,2-dideoxy-D-*erythro*-pent-1-enopyranose[3] (**6**) with solution A in the same way gave 17% of α-**3**, 46% of β-**3**, 14% of β-**7**, and 4% of α-**7**. The products were identified through their n.m.r. spectra. The spectra of α- and β-**7** have been published[4].

*Methyl 4-O-benzoyl-2-deoxy-3-O-methyl-*D-threo- *and* -D-erythro-*pentopyranosides* (**4** *and* **5**). — To a solution of **1** (1.02 g) in dichloromethane (10 ml) was added 5.0 ml of solution A. The solution was kept for 24 h at room temperature; compound **3** was then no longer present, as seen from the n.m.r. spectrum. The solution was then processed as described in the preceding experiment, and the product (915 mg) was separated into four fractions by preparative t.l.c. with 1:1 ether–pentane as the eluant. The fastest fraction gave 113 mg (13%) of α-**2**, m.p. 110–113°. The second fraction yielded 513 mg (62%) of α-**4** as a syrup, $[\alpha]_D^{23}$ +20.8° (*c* 3.5, chloroform).

Anal. Calc. for $C_{14}H_{18}O_5$: C, 63.00; H, 6.77. Found: C, 63.25; H, 6.81.

The third fraction yielded 93 mg (11%) of β-**4** as a syrup, $[\alpha]_D^{23}$ −177° (*c* 1.8, chloroform).

Anal. Found: C, 63.40; H, 6.78;

The last fraction gave 92 mg (11%) of β-**5**, which was crystallized from ether–pentane; m.p. 53–54°, $[\alpha]_D^{23}$ −142° (*c* 1.0, chloroform).

Anal. Found: C, 62.90; H, 6.87.

The products were characterized through their n.m.r. spectra (see Table I).

Treatment of the unsaturated glycoside **3** with solution A in the same way gave 54% of α-**4**, 9% of β-**4**, and 9% of β-**5**. The products were identical with those already described.

When pure α-**4** was treated with solution A for 24 h, a mixture of the anomers of **4** was obtained in 84% yield. The ratio of α to β was 6:1, as measured from the n.m.r. spectrum. No other products could be detected.

*1,4-Di-O-benzoyl-2-deoxy-*3-O-*methyl-*D-threo-*pentopyranoses* (**8**). — A solution of α-**4** (528 mg) in benzene (5 ml) was cooled in ice, and treated with a slow stream of hydrogen chloride for 1 h. Silver benzoate (3.0 g) and acetonitrile (20 ml) were then added, and the mixture was stirred for 2 h at room temperature. The salts were filtered off, the solvent was evaporated, and the residue was dissolved in dichloromethane. The solution was washed with aqueous sodium hydrogen carbonate, dried, and evaporated. The product thus obtained consisted of a mixture of α- and β-**8**, which could not be separated by t.l.c. Crystallization from ether–pentane gave α-**8**, obtained pure after two recrystallizations; m.p. 120–121°, $[\alpha]_D^{23}$ −3.1° (*c* 0.3, chloroform).

Anal. Calc. for $C_{20}H_{20}O_6$: C, 67.39; H, 5.66. Found: C, 67.10; H, 5.72.

Crystallization, from methanol, of the material in the mother liquors gave β-**8**, m.p. 84–87°. Three recrystallizations gave the pure product; m.p. 87–88°, $[\alpha]_D^{23}$ −81.7° (*c* 0.6, chloroform).

Anal. Found: C, 67.92; H 5.98.

*Methyl 4-O-benzoyl-2,3,6-trideoxy-*α-L-erythro-*hex-2-enopyranoside* (α-**11**). — To a solution of compound **9** (524 mg; prepared as in ref. 7) in dichloromethane (5 ml) was added 1.3 ml of solution A. The reaction was monitored by n.m.r. spectroscopy; the starting material **9** had disappeared after 15 min at room temperature. The mixture was then diluted with dichloromethane, washed with aqueous sodium hydrogen carbonate, dried, and evaporated. The product (421 mg) was separated into two

fractions by preparative t.l.c. with 1:1 ether—pentane. The first fraction gave 280 mg (73%) of α-**11**, which was crystallized from ether–pentane; m.p. 43–45°, $[\alpha]_D^{23}$ −215° (*c* 1.5, chloroform).

Anal. Calc. for $C_{14}H_{16}O_4$: C, 67.73; H, 6.51. Found: C, 67.90; H 6.52.

The second fraction gave 107 mg (19%) of a mixture of α- and β-**10**. These were separated by t.l.c., by three elutions with 1:2 ether–pentane. The first fraction gave 40 mg of α-**10**, which was crystallized from ether–pentane; m.p. 88–89°, $[\alpha]_D^{23}$ +1.1° (*c* 1.5, chloroform).

Anal. Calc. for $C_{21}H_{22}O_6$: C, 68.11; H, 5.99. Found: C, 68.27; H, 6.06.

The slower-moving fraction yielded 67 mg of β-**10** as a syrup, $[\alpha]_D^{23}$ +91.1° (*c* 1.2, chloroform).

Anal. Found: C, 68.40; H, 6.20.

*Methyl 4-*O*-benzoyl-2,6-dideoxy-3-*O*-methyl-*L-arabino- *and* -L-ribo-*hexopyranosides* (**12**) *and* (**13**). — To a solution of **9** (995 mg) in dichloromethane (10 ml) was added 4 ml of solution A, and the solution was kept for 48 h at room temperature. It was then processed as already described, to give 900 mg of crude product which was separated into several fractions by preparative t.l.c. with 1:1 ether–pentane as the eluant. The fastest-moving fraction (385 mg) was a mixture which was separated into two fractions by rechromatography using two elutions with benzene; this gave 205 mg (19%) of α-**10**; m.p. 79–80°, and 180 mg (22%) of β-**13**. The latter was recrystallized from ether–pentane; m.p. 74–75°, $[\alpha]_D^{23}$ −10.4° (*c* 3.0, chloroform).

Anal. Calc. for $C_{15}H_{20}O_5$: C, 64.28; H, 7.19. Found: C, 64.18; H, 7.25.

The second fraction (from the chromatographic separation with ether–pentane) gave 270 mg (33%) of α-**12** as a syrup, $[\alpha]_D^{23}$ −82.9° (*c* 3.6, chloroform).

Anal. Found: C, 64.45; H, 7.07.

The third fraction yielded 33 mg (4%) of β-**12**, which was crystallized from ether–pentane; m.p. 81–82°, $[\alpha]_D^{23}$ +57.4° (*c* 0.4, chloroform).

Anal. Found: C, 64.00; H, 7.13.

The last fraction gave 102 mg (12%) of α-**13** as a syrup, $[\alpha]_D^{23}$ −136° (*c* 2.9, chloroform).

Anal. Found: C, 64.55; H, 7.23.

Reaction of α-**12** *with methanol and boron trifluoride.* — To a solution of α-**12** (270 mg) in dichloromethane (3 ml) was added 1 ml of solution A. The solution was kept for 48 h at room temperature, and processed as already described. The n.m.r. spectrum of the crude product (260 mg) showed that it was a mixture of α- and β-**12** in the ratio of 89:11. These were separated by t.l.c., to give 218 mg of α-**12** and 21 mg of β-**12**. None of the isomeric **13** could be detected.

Reactions with O*-deuteriomethanol.* — Treatment of α-**12** with *O*-deuteriomethanol and boron trifluoride as just described gave a mixture of α-**12** and β-**12**. The n.m.r. spectra showed that no deuterium had been introduced.

Reaction of the unsaturated methyl glycoside **11** (500 mg) with *O*-deuteriomethanol and boron trifluoride for 48 h as just described gave 520 mg of crude product. This was separated into the following four products by preparative t.l.c.

with 1:1 ether–pentane; 175 mg (37%) of β-**13**, 145 mg (31%) of α-**12**, 25 mg (5%) of β-**12**, and 46 mg (11%) of α-**13**. The n.m.r. spectra of these products showed that they all contained ~0.8 equivalent of deuterium at C-2, almost equally distributed between the axial and equatorial positions.

ACKNOWLEDGMENT

Microanalyses were performed by Mr. Preben Hansen.

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