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Note

Selective benzoylation of 1,5-anhydro-L-arabinitol

YÔTARO KONDO
Department of Agricultural Chemistry, Tottori University, Tottori 680 (Japan)
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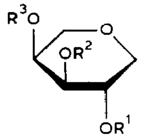
Our previous publications reported selective benzoylation of 1,5-anhydroxylitol[1], -galactitol[2], and -glucitol[3]. As an extension of the studies, this communication describes selective benzoylation of 1,5-anhydro-L-arabinitol (**1**).

Selective benzoylation of **1** with 2 molar equivalents of benzoyl chloride in pyridine at −40° gave the 2,3,4-tribenzoate **2** (25%), the 2,4-dibenzoate **3** (4%), a mixture of the 2,3-dibenzoate **4** and the 3,4-dibenzoate **5** (64%), and a mixture of the 3-benzoate **7** and the 4-benzoate **8** (7%), as shown by quantitative t.l.c. Chromatography on silica gel afforded the four fractions just described.



	R^1	R^2	R^3
1	H	H	H
2	Bz	Bz	Bz
3	Bz	H	Bz
4	Bz	Bz	H
5	H	Bz	Bz
6	Bz	H	H
7	H	Bz	H
8	H	H	Bz
9	Bz	Ts	Bz
10	Ts	Bz	Bz
11	Bz	Bz	Ts
12	Bz	Ts	Ts
13	Ts	Bz	Ts
14	Ts	Ts	Bz
15	Ts	Ts	Ts

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The structure of **3** was confirmed by conversion into the known 1,5-anhydro-2,4-di-*O*-benzoyl-3-*O*-*p*-tolylsulfonyl-L-arabinitol[4] (**9**). Interestingly, the proportion of **3** unusually increased during fractionation by column chromatography. When a mixture of **4** and **5**, which behaves as a single compound in t.l.c. was subjected to re-chromatography, new **3** was obtained, besides a mixture of **4** and **5**. Therefore, it is clear that **4** was converted into **3** by an acyl migration in the course of the column chromatography. It is probable that compounds **3** and **5** are stable, and that the rate of acyl migration, if any, of **3** and **5** is very low. Thus, **5** was successfully isolated from the mixture by repeated column chromatography. The yield of **4** and **5** was, therefore, found to be 20 and 44% (in the respective molar proportions).

The position of the benzoyl groups of **5** was ascertained by ^{1}H-n.m.r. spectroscopy. The signals of H-3 and H-4 in **5** appeared to low field of all other ring-proton resonances, because of the deshielding effect of benzoyl groups on the methine protons attached to the same carbon atoms. The structure of **5** was further confirmed by tosylation, giving the known 1,5-anhydro-3,4-di-*O*-benzoyl-2-*O*-*p*-tolylsulfonyl-L-arabinitol[4] (**10**). Compound **4** could not be isolated in pure form; however, the structure of **4** was confirmed as the known 1,5-anhydro-2,3-di-*O*-benzoyl-4-*O*-*p*-tolylsulfonyl-L-arabinitol[4] (**11**) by tosylation of a mixture of **4** and **5**, followed by fractional recrystallization.

Compounds **7** and **8** could also not be separated as single compounds by repeated column chromatography, and each was contaminated with a little of the other; but structural elucidation of **7** and **8** was obtained by ^{1}H-n.m.r. spectroscopy. The signals of H-3 of **7** and H-4 of **8** occurred at the most-downfield of the ring-proton resonances, showing that these protons must be geminal to deshielding benzoyl groups. The structures of **7** and **8** were further confirmed by preparing the known *O*-tosyl derivatives[4] **13** and **14**.

Monomolar benzoylation of **1** gave **3** (3%), a mixture of **4** and **5** (23%), **6** (4%), and a mixture of **7** and **8** (70%), as shown by t.l.c. analysis. The molar ratio of the partially benzoylated products was further determined by ^{1}H-n.m.r. spectroscopy, from the relative intensities of the methyl proton of the tosyloxy groups of the tosylated benzoate mixture, in comparison with those of authentic specimens[4]. The benzoylated mixture was, without isolation, directly tosylated, because confusion as to the distribution in the partially benzoylated products might be caused by acyl migrations occurring during column chromatography. Thus, the tosylated mixture was found to consist of **9** + **10** + **11** (25%), **12** (6%), **13** (43%), **14** (9%), and **15** (17%). Therefore, the yield of the monomolar-benzoylation products was in the order: **3** + **4** + **5** (30%), **6** (7%), **7** (52%), and **8** (11%), on a relative molar basis.

In dibenzoylation of **1**, the highest yield of **5** (44%), and the preponderance of **4** + **5** (64%) over **3** + **4** (24%) and **3** + **5** (48%) showed that the relative reactivity of the hydroxyl groups in **1** is OH-3 > OH-4 > OH-2. This order is in agreement with the results of monobenzoylation of **1**, in which serious differences in the reactivity of the OH-2 and OH-3 groups are not observed. This result contrasts with those reported for dibenzoylation of benzyl[5] and methyl[6] β-L-arabinopyranoside, which were in the order OH-2,3 > OH-4.

The high reactivity of the OH-3 group in **1** could be rationalized by intramolecular hydrogen-bonding between axial and equatorial hydroxyl groups. It is noteworthy that the axial OH-4 group is more reactive than the equatorial OH-2 group, because it is well known[5-9] that axial hydroxyl groups are more sterically hindered than equatorial ones, and therefore acylation of axial hydroxyl groups decelerates in comparison with that of equatorial hydroxyl groups. A similar high reactivity of the axial hydroxyl group was found in selective tosylation of **1** as reported[4] previously. This finding may be explained by the previous suggestions[2,4] that intramolecular hydrogen-bonding has an accelerating effect on the axial hydroxyl group also. However, this accelerating effect would, by steric hindrance, be weakened on the axial rather than on the equatorial hydroxyl group.

EXPERIMENTAL

General methods. — Unless otherwise indicated, the general experimental conditions were the same as those described previously[1]. Optical rotations were measured with a Jasco DIP-181 polarimeter using chloroform, unless stated otherwise, and ^{1}H-n.m.r. spectra were recorded with a Hitachi R-24 60-MHz instrument for solutions in chloroform-*d*, with tetramethylsilane as the internal standard.

Selective benzoylation of 1,5-anhydro-L-arabinitol (**1**). — (*a*). *With two equivalents.* A solution of **1** (500 mg) in dry pyridine was cooled to −40°, and then benzoyl chloride (0.96 mL, 2.2 mol. equiv.) was added in portions, with stirring, during 15 min. The solution was kept for 3 h at −20°, and for 48 h at 0°, and then stirred for 48 h at room temperature. After addition of water, the mixture was extracted with chloroform, and the extract was washed successively with dilute hydrochloric acid, saturated sodium hydrogencarbonate, and water, dried (sodium sulfate), and evaporated to a syrup which was chromatographed on silica gel (250 g).

Elution with 9:1 benzene–acetone gave 1,5-anhydro-2,3,4-tri-*O*-benzoyl-L-arabinitol (**2**) (329 mg, 20%), which crystallized from ethanol; m.p. 121–122°, $[\alpha]_D^{26}$ +221.7° (*c* 2.4).

Anal. Calc. for $C_{26}H_{22}O_9$: C, 69.94; H, 4.97. Found: C, 70.10; H, 5.07.

Elution with 4:1 benzene–acetone yielded 1,5-anhydro-2,4-di-*O*-benzoyl-L-arabinitol (**3**) (116 mg, 9%), which could not be crystallized; $[\alpha]_D^{18}$ +165.9° (*c* 4.8). Compound **3** (116 mg) was tosylated with *p*-toluenesulfonyl chloride (194 mg) in pyridine (3 mL) for 5 days at room temperature. After crystallization from chloroform–ethanol, **9** (115 mg, 68%) was obtained as long needles. The physical constants and ^{1}H-n.m.r. data for this compound were in accord with those given previously[4].

Elution with 2:1 benzene–acetone afforded a partly crystalline product which was contaminated with **3**. Column chromatography was repeated twice on silica gel, and gave **3** (129 mg, 10%) and 1,5-anhydro-3,4-di-*O*-benzoyl-L-arabinitol (**5**) (443 mg, 35%). Compound **5** crystallized from ethanol; m.p. 136–138°, $[\alpha]_D^{27}$ +150.2° (*c* 2.0); ^{1}H-n.m.r.: δ 5.52 (q, 1 H, $J_{3,4} = J_{4,5a} = J_{4,5e} = 2.8$ Hz, H-4), 5.22 (q, 1 H, $J_{2,3}$ 7.2 Hz, H-3), and 3.03 (broad s, 1 H, OH-2).

Anal. Calc. for $C_{19}H_{18}O_6$: C, 66.66; H, 5.30. Found: C, 66.67; H, 5.29.

Treatment of **5** (100 mg) with *p*-toluenesulfonyl chloride (170 mg) for 5 days, followed by crystallization and recrystallization from 2-propanol–ethanol–petroleum ether afforded **10** (109 mg, 75%); m.p. 137–139°. The ^{1}H-n.m.r. spectrum was identical with that of an authentic sample[14], reported previously.

Elution with 1:1 benzene–acetone gave a mixture of 1,5-anhydro-3-*O*-benzoyl-L-arabinitol (**7**) and 1,5-anhydro-4-*O*-benzoyl-L-arabinitol (**8**) as a syrup (78 mg, 9%). The ^{1}H-n.m.r. spectrum of the mixture indicated the ratio of **7** and **8** to be 1:2. Repeated column-chromatography of the mixture afforded two main fractions, namely, **7** {$[\alpha]_D^{32}$ +96.0° (*c* 1.4, ethanol); ^{1}H-n.m.r.: δ 5.10 (q, 1 H, $J_{2,3}$ 7, $J_{3,4}$ 3 Hz, H-3)} and **8** {$[\alpha]_D^{20}$ +87.7° (*c* 0.8); ^{1}H-n.m.r.: δ 5.30 (broad s, 1 H, H-4)}. Separate treatment of **7** and **8** with *p*-toluenesulfonyl chloride gave 1,5-anhydro-3-*O*-benzoyl-2,4-di-*O*-*p*-tolylsulfonyl-L-arabinitol (**13**) and 1,5-anhydro-4-*O*-benzoyl-2,3-di-*O*-*p*-tolylsulfonyl-L-arabinitol (**14**), respectively, the physical constants and ^{1}H-n.m.r. data for which were identical with those of the authentic samples[4] prepared previously.

(*b*) *With one equivalent.* Compound **1** (500 mg) was treated with benzoyl chloride (0.52 mL, 1.2 mol. equiv.) in pyridine (20 mL), as described in (*a*). The reaction mixture was extracted with chloroform, and processed as usual. A portion of this solution was subjected to quantitative t.l.c. analysis. Evaporation of the solution gave a syrup which was fractionated on a column of silica gel, as described in (*a*), to give four fractions, namely, a mixture of **3**, **4**, and **5** (166 mg, 13%), **6** (8 mg, 1%), **7** (95 mg, 11%), and **8** (44 mg, 5%). Compounds **7** and **8** were each contaminated with a little of the other, as already described. The syrupy compound **6** was not further investigated, because of its low yield, but it must be the (remaining) 1,5-anhydro-2-*O*-benzoyl-L-arabinitol.

The same treatment of **1** (500 mg) with one molar equivalent of benzoyl chloride as already described, and direct tosylation with *p*-toluenesulfonyl chloride (263 mg, 3 mol. equiv.) for 5 days at room temperature, gave the corresponding tosylates of **1, 3, 4, 5, 6, 7,** and **8**, the molar ratios of which were determined directly by ^{1}H-n.m.r. spectroscopy[4].

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