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Note

Selective benzoylation of 1,5-anhydro-D-glucitol*

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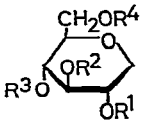
Selective esterification[1] of glycosides is an important procedure for synthesis of specifically protected glycosides useful as intermediates for the preparation of keto sugars, amino sugars, and disaccharides. We have recently reported[2] partial sulfonylation of 1,5-anhydro-D-glucitol and have invoked stereoelectronic factors to explain the preferential reactivity of hydroxyl groups in glycosides. As an extension of these studies, this communication describes selective benzoylation of 1,5-anhydro-D-glucitol (**1**).

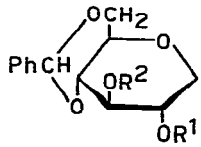
Selective benzoylation of **1** with 3 molar equivalents of benzoyl chloride in pyridine at −40° gave a mixture containing one major and several minor components. Chromatography of the mixture afforded four crystalline products (*A–D*) and one syrupy compound (*E*).

Component *A*, eluted first, was isolated in 7% yield. It showed no hydroxyl absorption in its i.r. spectrum, therefore indicating that it is the 2,3,4,6-tetrabenzoate **2**.

The second component *B* was obtained as the major product in 63% yield.



	R^1	R^2	R^3	R^4
1	H	H	H	H
2	Bz	Bz	Bz	Bz
3	Bz	Bz	Ms	Bz
4	Bz	Bz	H	Bz
5	Ms	Bz	Bz	Bz
6	H	Bz	Bz	Bz
7	Ms	Bz	Ms	Bz
8	H	Bz	H	Bz
9	Bz	Ms	Ms	Bz
10	Bz	H	H	Bz
11	Ms	Ms	Bz	Bz



	R^1	R^2
12	Bz	Bz
13	Ms	OH
14	Ms	Bz
15	Bz	OH
16	OH	OH

*Dedicated to Professor Stephen J. Angyal on the occasion of his retirement.

Its ^{1}H-n.m.r. data indicated it to be a tribenzoate. In order to determine the positions of the benzoyl groups, *B* was treated with methanesulfonyl chloride in pyridine to give the corresponding monosulfonate, which was identified as 1,5-anhydro-2,3,6-tri-*O*-benzoyl-4-*O*-mesyl-D-glucitol (**3**). Comparison of the ^{1}H-n.m.r. spectrum of **2** with that of **3** showed an upfield (~0.5 p.p.m.) shift of the H-4 resonance of **3**. This shift is consistent with the known behavior[3] of a hydrogen atom on a carbon atom attached to a sulfonyloxy group and thus indicates the mesyloxy group to be at C-4. The structure of **3** was further confirmed by its unequivocal synthesis from 1,5-anhydro-2,3-di-*O*-benzoyl-4,6-*O*-benzylidene-D-glucitol[4] (**12**). Debenzylidenation of **12** followed by selective benzoylation at O-6 of the product gave the 2,3,6-tribenzoate **4**. Treatment of **4** with mesyl chloride in pyridine gave **3**. This result indicates that mesylation in pyridine occurs without migration of benzoyl groups. On the basis of these results, *B* is identified as the 2,3,6-tribenzoate **4**.

The third fraction *C*, obtained in 8% yield, was a tribenzoate. Treatment of *C* with methanesulfonyl chloride gave 1,5-anhydro-3,4,6-tri-*O*-benzoyl-2-*O*-mesyl-D-glucitol (**5**). Comparison of the ^{1}H-n.m.r. spectrum of **5** with that of **2** showed that the H-2 resonance of **5** was upfield (~0.5 p.p.m.) because of the shielding effect of the mesyl group at C-2, in agreement with the assigned structure **5**. Compound **5** was further characterized by comparison with an authentic sample prepared from 1,5-anhydro-4,6-*O*-benzylidene-2-*O*-mesyl-D-glucitol[5] (**13**). Hydrolysis of the benzylidene acetal of **13**, followed by perbenzoylation of the product, yielded the 2-sulfonate **5**. Hence *C* is the 3,4,6-tribenzoate **6**.

The fourth component *D* was a dibenzoate isolated in 16% yield. Its structure was proved by preparing the *O*-mesyl derivative, which was shown to be 1,5-anhydro-3,6-di-*O*-benzoyl-2,4-di-*O*-mesyl-D-glucitol (**7**) by a sequence of debenzylidenation, 6-*O*-benzoylation, and mesylation, starting from 1,5-anhydro-3-*O*-benzoyl-4,6-*O*-benzylidene-D-glucitol[4] (**14**). Therefore, *D* is the 3,6-dibenzoate **8**.

Component *E*, isolated in 6% yield, was also a dibenzoate. Its dimesyl derivative was identical with 1,5-anhydro-2,6-di-*O*-benzoyl-3,4-di-*O*-mesyl-D-glucitol (**9**), as prepared from 1,5-anhydro-2-*O*-benzoyl-4,6-*O*-benzylidene-D-glucitol[4,6] (**15**) by debenzylidenation followed by 6-*O*-benzoylation and permesylation. Compound **9** was distinguishable from the remaining 2,3-disulfonate **11**, obtained as syrup from 1,5-anhydro-4,6-*O*-benzylidene-D-glucitol[7] (**16**) by permesylation followed by debenzylidenation and perbenzoylation. Accordingly, *E* is the 2,6-dibenzoate **10**.

Benzoylation with 2 molar equivalents of the same reagent followed by chromatographic separation yielded four of the products (*B*–*E*) in yields of 8, 1, 34, and 5%, respectively.

The isolation of **4** and **8**, respectively, as the major products from tri- and dimolar benzoylation of **1** shows that the hydroxyl groups are acylated in the order 6-OH > 3-OH > 2-OH > 4-OH. The finding that the 4-OH group is resistant to benzoylation is consistent with the results obtained with methyl α-D-glucopyranoside[8], and methyl 6-deoxy-α- and -β-D-glucopyranosides[3], and is attributable to steric hindrance[8] by the 5-benzoyloxymethyl or 5-methyl group. It is noteworthy that the

3-OH group in **1** is more reactive towards benzoyl chloride than the other ring-hydroxyl groups, especially the least sterically-hindered (2-OH) group adjacent to the deoxy group at C-1. This result indicates that deoxygenation has no activating effect on a neighboring hydroxyl group in benzoylation. This finding is in accord with the result[9] of selective benzoylation of **16**, namely, the order of reactivity is 3-OH > 2-OH. Selective benzoylation of **16** was first reported[6] in 1959 by Newth, who concluded that the order of reactivity of its hydroxyl groups was the reverse: 2-OH > 3-OH. This misleading interpretation probably arose by a judgment based on the isolation of **13** as the only major, crystalline product from the mixture. In selective benzoylation[10] of benzyl α-D-xylopyranoside, the order of reactivity of the secondary hydroxyl groups was reported as 2-OH > 4-OH > 3-OH. The greater reactivity of the 2-OH group was rationalized from the activating effect of the *cis*-OR substituent, favoring intramolecular hydrogen-bonding. The lowest reactivity of the 3-OH group towards benzoyl chloride was interpreted in terms of gauche interactions between the benzoyloxy group at C-2 and the 4-OH group at C-4. This viewpoint explains the preponderance of **3** over **6**. However, the preponderance of **8** over **10** cannot be similarly rationalized. A greater reactivity of the 3-OH group toward benzoyl chloride in pyridine has been reported for methyl 6-deoxy-β-D-glucopyranoside[2] and methyl 4,6-*O*-benzylidene-β-D-glucopyranoside[11]. This observation suggests the presence of a certain rate-accelerating effect on the hydroxyl group at C-3 toward benzoyl chloride in glycopyranosides that have the *gluco* configuration and lack *cis*-OR groups.

EXPERIMENTAL

General methods. — Melting points were determined with a Yanagimoto hot-stage apparatus and are uncorrected. Optical rotations were measured with a Yanagimoto OR-50 polarimeter. The ^{1}H-n.m.r. spectra were recorded with a Hitachi R-24 60-MHz instrument in chloroform-*d* with tetramethylsilane as the internal standard, unless otherwise stated. T.l.c. was performed on Silica Gel G-60 (Merck) and column chromatography on Silica Gel 60 (70–230 mesh, Merck).

Benzoylation of 1,5-anhydro-D-glucitol (**1**). — (*a*) *With three equivalents.* Benzoyl chloride (2.12 mL, 3.0 mol) was added dropwise during 15 min to a stirred solution of **1** (1 g) in anhydrous pyridine (40 mL) at −40°. The bath temperature was kept for 3 h at −20°, for 48 h at 0°, and the mixture was then stirred for 2 days at room temperature. Water was then added and the mixture was extracted with chloroform. The extract was washed successively with dilute hydrochloric acid, saturated sodium hydrogencarbonate, and water. The chloroform solution was dried (sodium sulfate) and evaporated to a syrup that was chromatographed on silica gel (250 g). Stepwise elution with the solvent systems: benzene–ethyl acetate, 9:1, 4:1, 2:1, 1:1 (v/v), and pure ethyl acetate, gave six fractions; the tetrabenzoate **2** (206 mg, 7%), the 2,3,6-tri- (**4**; 1.814 g, 63%), 3,4,6-tri- (**6**; 182 mg, 8%), the 3,6-di- (**8**; 364 mg, 16%), and 2,6-di- (**10**; 137 mg, 6%) benzoates.

1,5-Anhydro-2,3,4,6-tetra-*O*-benzoyl-D-glucitol (**2**) crystallized from ethanol; m.p. 58–60°, $[\alpha]_D^{18}$ +41.4° (*c* 0.9, chloroform); ^{1}H-n.m.r. data: τ 4.00 (1 H, t, $J_{2,3}$ 9.5 Hz, H-3), 4.32 (1 H, t, $J_{4,5}$ 9.5 Hz, H-4), 4.65 (1 H, m, H-2), 5.89 (1 H, H-5), and 6.37 (1 H, t, $J_{1a,1e} = J_{1a,2}$ 10 Hz, H-1a).

Anal. Calc. for $C_{34}H_{28}O_9$: C, 70.33; H, 4.87. Found: C, 70.14; H, 4.77.

1,5-Anhydro-2,3,6-tri-*O*-benzoyl-D-glucitol (**4**) crystallized from chloroform–ethanol; m.p. 181–183°, $[\alpha]_D^{24}$ +72.7° (*c* 2.3, chloroform).

Anal. Calc. for $C_{27}H_{24}O_8$: C, 68.03; H, 5.09. Found: C, 67.98; H, 5.35.

1,5-Anhydro-3,4,6-tri-*O*-benzoyl-D-glucitol (**6**) crystallized from ethanol; m.p. 152–153°, $[\alpha]_D^{22}$ −8.2° (*c* 1.0, chloroform).

Anal. Calc. for $C_{27}H_{24}O_8$: C, 68.03; H, 5.09. Found: C, 68.23; H, 5.36.

1,5-Anhydro-3,6-di-*O*-benzoyl-D-glucitol (**8**) crystallized from ethanol; m.p. 161–162°, $[\alpha]_D^{20}$ +51.9° (*c* 1.2, chloroform).

Anal. Calc. for $C_{20}H_{20}O_7$: C, 64.50; H, 5.42. Found: C, 64.74; H, 5.46.

1,5-Anhydro-2,6-di-*O*-benzoyl-D-glucitol (**10**) could not be crystallized; $[\alpha]_D^{21}$ +27.4° (*c* 1.1, chloroform).

(*b*) *With two equivalents.* Treatment of **1** (1 g) with benzoyl chloride (1.46 mL, 2.1 mol) in pyridine (40 mL) followed by chromatographic fractionation of the resulting product on silica gel as described in (*a*) gave four fractions; the 2,3,6-tri- (**4**; 236 mg, 8%) and 3,4,6-tri- (**6**; 36 mg, 1%) benzoates, and the 3,6-di- (**8**; 768 mg, 34%) and 2,6-di- (**10**; 114 mg, 5%) benzoates.

*1,5-Anhydro-2,3,6-tri-*O*-benzoyl-4-*O*-mesyl-D-glucitol* (**3**). — (*a*). A solution of the 2,3,6-tribenzoate **4** (100 mg) in pyridine (1 mL) was cooled in an ice bath, and methanesulfonyl chloride (0.1 mL) was added dropwise. Stirring for 18 h at 4° followed by conventional isolation gave a solid that recrystallized from ethanol to afford **3** (60 mg, 52%), m.p. 167–168°, $[\alpha]_D^{17}$ +104° (*c* 1.0, chloroform); ^{1}H-n.m.r. data: τ 4.13 (1 H, t, $J_{2,4} = J_{3,4}$ 9.5 Hz, H-3), 4.60 (1 H, sextet, $J_{1e,2}$ 5 Hz, H-2), 4.98 (1 H, q, $J_{5,6}$ 4, $J_{6,6'}$ 10 Hz, H-6), 6.11 (1 H, m, H-5), 6.47 (1 H, t, $J_{1a,1e} = J_{1a,2}$ 10 Hz, H-1a), and 7.10 (3 H, s, SO_2CH_3).

Anal. Calc. for $C_{28}H_{26}O_{10}S$: C, 60.63; H, 4.73; S, 5.78. Found: C, 60.56; H, 4.93; S, 5.98.

(*b*). A suspension of 1,5-anhydro-2,3-di-*O*-benzoyl-4,6-*O*-benzylidene-D-glucitol[4] (**12**, 208 mg) in 1% methanolic hydrogen chloride (6 mL) was stirred for 20 min at room temperature. The clear solution obtained was made neutral with silver carbonate, filtered, and the filtrate evaporated. The resulting residue was dissolved in pyridine (2 mL) and treated with one molar equivalent of benzoyl chloride (0.05 mL) in an ice–salt bath. The mixture was stirred for 2 h at −5° and then overnight at room temperature. T.l.c. (4:1 benzene–ether) showed complete conversion of the starting material into a single product (R_F 0.6). Conventional isolation gave a crystalline residue (136 mg, 63%) that recrystallized from ethanol to give the 2,3,6-tribenzoate **4**, m.p. 180–182°. The i.r. and ^{1}H-n.m.r. spectra were indistinguishable from those of **4** obtained by procedure (*a*).

A portion of the foregoing benzoate (65 mg) was treated with methanesulfonyl

chloride (0.1 mL) as described in (*a*). Evaporation of the solvent afforded a syrup (72 mg, 96%) that crystallized from chloroform–ethanol to give **3**, m.p. 166–167°, identical with the material prepared as described in (*a*).

*1,5-Anhydro-3,4,6-tri-*O*-benzoyl-2-*O*-mesyl-*D*-glucitol* (**5**). — (*a*). The tribenzoate **6** (34 mg) was treated with methanesulfonyl chloride in pyridine as already described. The mixture was processed conventionally and the resulting syrup (35 mg, 88%) crystallized from ethanol to give **5**, m.p. 136–138°, $[\alpha]_D^{20}$ +1.4° (*c* 1.4, chloroform); ^{1}H-n.m.r. data: τ 4.30 (1 H, t, $J_{3,4}$ 9 Hz, H-3), 4.53 (1 H, t, $J_{4,5}$ 9 Hz, H-4), 5.13 (1 H, m, H-2), 6.10 (1 H, m, H-5), 6.42 (1 H, t, $J_{1a,1e}$ 11 Hz, H-1a), and 7.18 (3 H, s, SO_2CH_3).

Anal. Calc. for $C_{28}H_{26}O_{10}S$: C, 60.63; H, 4.73; S, 5.78. Found: C, 60.86; H, 4.73; S, 6.03.

(*b*). 1,5-Anhydro-4,6-*O*-benzylidene-2-*O*-mesyl-D-glucitol[5] (**13**, 223 mg) was debenzylidenated in 1% methanolic hydrogen chloride (6 mL) as described for **4**. The resultant residue was dissolved in pyridine (2 mL) and benzoylated with benzoyl chloride. The mixture was processed to give a syrup (230 mg, 81%) that crystallized from ethanol to afford **5**, m.p. 140–142°, identical with the product described in (*a*).

*1,5-Anhydro-3,6-di-*O*-benzoyl-2,4-di-*O*-mesyl-*D*-glucitol* (**7**). — (*a*). The 3,6-dibenzoate **8** (100 mg) was mesylated to give **7** (130 mg, 92%) as an amorphous solid that was crystallized from chloroform–ethanol; m.p. 78–82°, $[\alpha]_D^{15}$ +56.3° (*c* 1.0, chloroform); ^{1}H-n.m.r. data: τ 4.32 (1 H, t, $J_{2,3}$ 10 Hz, H-3), 5.02 (1 H, t, $J_{3,4}$ 10 Hz, H-4), 6.05 (1 H, m, H-5), 6.42 (1 H, t, $J_{1a,1e} = J_{1a,2}$ 11 Hz, H-1a), 7.13, and 7.18 (6 H, 2s, SO_2CH_3).

Anal. Calc. for $C_{22}H_{24}O_{11}S_2$: C, 49.99; H, 4.59; S, 12.13. Found: C, 49.95; H, 4.43; S, 12.16.

(*b*). 1,5-Anhydro-3-*O*-benzoyl-4,6-*O*-benzylidene-2-*O*-mesyl-D-glucitol[5] (**14**, 141 mg) was debenzylidenated conventionally. The resultant syrup was selectively benzoylated with benzoyl chloride at the primary hydroxyl group as described for **4**. The benzoylated material obtained without isolation was treated with methanesulfonyl chloride (0.15 mL) at 0° and the mixture was stirred overnight at 4°. Isolation followed by crystallization from ethanol yielded **7** (110 mg, 64%), m.p. 75–78°. The ^{1}H-n.m.r. and i.r. spectra of the products prepared by the two methods were identical.

*1,5-Anhydro-2,6-di-*O*-benzoyl-3,4-di-*O*-mesyl-*D*-glucitol* (**9**). — (*a*). The 2,6-dibenzoate **10** (136 mg) was mesylated to give **9** (143 mg, 74%), m.p. 207–208° (from ethanol), $[\alpha]_D^{15}$ +72.7° (*c* 1.0, chloroform); ^{1}H-n.m.r. data (in dimethyl sulfoxide-d_6): τ 6.68 and 6.83 (6 H, 2 s, SO_2CH_3).

Anal. Calc. for $C_{22}H_{24}O_{11}S_2$: C, 49.99; H, 4.59; S, 12.13. Found: C, 49.70; H, 4.69; S, 12.28.

(*b*). Debenzylidenation of 1,5-anhydro-2-*O*-benzoyl-4,6-*O*-benzylidene-D-glucitol[4] (**15**, 348 mg) followed by selective benzoylation at the 6-hydroxyl group and mesylation as described for **7** afforded **9** (377 mg, 73%), m.p. 205–206° (from

chloroform–ethanol), which was identical (^{1}H-n.m.r. and i.r. spectra) with the product obtained in (*a*).

*1,5-Anhydro-4,6-di-*O*-benzoyl-2,3-di-*O*-mesyl-*D*-glucitol* (**11**). — 1,5-Anhydro-4,6-*O*-benzylidene-D-glucitol[7] (**16**, 100 mg) was mesylated and the product debenzylidenated and then perbenzoylated conventionally to give **11** (78 mg, 37%) as a syrup that could not be crystallized; $[\alpha]_D^{20}$ +18.4° (*c* 3.5, chloroform); ^{1}H-n.m.r. data: τ 4.48 (1 H, t, $J_{3,4} = J_{4,5}$ 9 Hz, H-4), 4.90 (1 H, t $J_{2,3}$ 9 Hz, H-3), 6.88, and 6.95 (6 H, 2s, SO_2CH_3).

Anal. Calc. for $C_{22}H_{24}O_{11}S_2 \cdot H_2O$: C, 48.34; H, 4.80; S, 11.73. Found: C, 48.63; H, 4.42; S, 11.41.

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