SYNTHESES OF METHYL 2,4-DIBENZAMIDO-2,4-DIDEOXY-α-D-GLUCO-PYRANOSIDE AND -GALACTOPYRANOSIDE

M. W. HORNER, L. HOUGH, AND A. C. RICHARDSON
Department of Chemistry, Queen Elizabeth College, London, W8 7AH (Great Britain)
(Received July 23rd, 1970; accepted for publication, August 13th, 1970)

ABSTRACT

Reaction of methyl 2-benzamido-3,6-di-*O*-benzoyl-2-deoxy-4-*O*-mesyl-α-D-glucopyranoside (**1**) with azide afforded the 4-azidogalactopyranoside **2** which was converted into methyl 2,4-dibenzamido-2,4-dideoxy-α-D-galactopyranoside (**4**) by sequential hydrogenation and de-*O*-benzoylation, during which O→N benzoyl migration occurred. The *gluco* analogue **10** was similarly prepared from methyl 2-benzamido-3,6-di-*O*-benzoyl-2-deoxy-4-*O*-mesyl-α-D-galactopyranoside (**7**), which was synthesised from methyl 2-benzamido-2-deoxy-α-D-galactopyranoside by selective dimolar benzoylation followed by mesylation of the resulting 3,6-dibenzoate.

INTRODUCTION

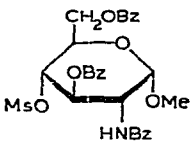
The isolation of diamino sugars from natural sources[1] has stimulated interest in their synthesis. Two 2,4-diaminohexose derivatives have been isolated from natural products. A 4-acetamido-2-amino-2,4,6-trideoxy-hexose occurs in a polysaccharide of *Bacillus licheniformis*[2], and has been tentatively designated[3] as the L-*altro* isomer. 2,4-Diamino-2,3,4,6-tetradeoxy-D-*arabino*-hexose (kasugamine) was later reported[4] as a component of the antibiotic Kasugamycin. Two syntheses of kasugamine have been described, one involving azide displacement of sulphonic esters at both the 2- and 4-positions of a hexopyranoside[5], and the other[6] employing non-carbohydrate starting material. 2,4-Diamino-2,4-dideoxy-D-glucose has also been prepared *via* ammonolysis of 1,6-anhydro-2,4-di-*O*-tosyl-β-D-glucopyranose, a reaction which proceeds by way of the 3,4- and 2,3-epoxides[7].

In this connection, we report our studies of the synthesis of 2,4-diamino derivatives of gluco- and galacto-pyranosides from derivatives of 2-amino-2-deoxy-D-glucose and -D-galactose *via* 4-sulphonates.

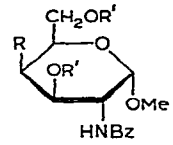
RESULTS AND DISCUSSION

Methyl 2-benzamido-3,6-di-*O*-benzoyl-2-deoxy-4-*O*-mesyl-α-D-glucopyranoside (**1**) is readily prepared by selective dimolar benzoylation of methyl 2-benzamido-2-deoxy-α-D-glucopyranoside followed by mesylation[8]. Sulphonate **1** undergoes bimole-

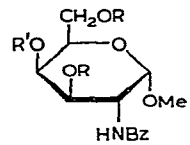
cular displacement with sodium benzoate in *N,N*-dimethylformamide to give the 2-benzamidogalactopyranoside **8**, thereby providing a convenient synthesis of galactosamine derivatives. An analogous displacement on **1** with sodium azide in hexamethylphosphoric triamide has now afforded the corresponding 4-azidogalactopyranoside **2** in 78% yield. Conversion into the 2,4-dibenzamidogalactopyranoside **4**



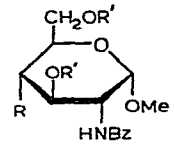
1



2 R = N_3, R' = Bz
3 R = N_3, R' = H
4 R = NHBz, R' = H



5 R = R' = H
6 R = Bz, R' = H
7 R = Bz, R' = Ms
8 R = R' = Bz



9 R = N_3, R' = Bz
10 R = NHBz, R' = H

was effected by hydrogenation with palladium-on-charcoal followed by de-*O*-benzoylation with sodium methoxide. Migration of an *O*-benzoyl group to the 4-amino substituent occurred during the procedure.

The analogous preparation of the 2,4-dibenzamidoglucopyranoside **10** required methyl 2-benzamido-3,6-di-*O*-benzoyl-2-deoxy-4-*O*-mesyl-α-D-galactopyranoside (**7**) as starting material. The axial 4-hydroxyl group in galactopyranosides is the least reactive hydroxyl group towards acylating agents[9], and hence dimolar benzoylation of methyl 2-benzamido-2-deoxy-α-D-galactopyranoside[8] (**5**) afforded the highly crystalline 3,6-dibenzoate in 64% yield, with a little of the tribenzoate **8** and some unchanged starting material.

The 3,6-dibenzoate **6** was converted in good yield into the 4-methanesulphonate **7**, which underwent displacement of the mesyloxy group with sodium azide in hexamethylphosphoric triamide to give the syrupy 4-azide **9** in 45% yield. Catalytic reduction of the 4-azidoglucoside **9**, followed by de-*O*-benzoylation with sodium methoxide, afforded crystalline methyl 2,4-dibenzamido-2,4-dideoxy-α-D-glucopyranoside (**10**) in 62% yield.

The ^{1}H n.m.r. spectral data summarised in Table I are in complete accord with the structures and configurations assigned[8,10].

EXPERIMENTAL

For general procedures, see Ref. 8.

*Methyl 4-azido-2-benzamido-3,6-di-*O*-benzoyl-2,4-dideoxy-α-D-galactopyranoside* (**2**). — A stirred solution of methyl 2-benzamido-3,6-di-*O*-benzoyl-2-deoxy-4-*O*-mesyl-α-D-glucopyranoside[8] (**1**) (10 g) in hexamethylphosphoric triamide (50 ml) was heated with sodium azide (10 g) at 90° (bath) for 24 h. The reaction mixture was then cooled and poured into water, and the resulting crystalline precipitate was filtered off and recrystallised from propan-2-ol to give the 4-azide **2** (7.1 g; 78%), m.p. 171–172°, $[\alpha]_D$ −20° (*c* 0.8, chloroform) (Found: C, 63.3; H, 4.85; N, 10.0. $C_{28}H_{26}N_4O_7$ calc.: C, 63.4; H, 4.9; N, 9.95%).

TABLE I

FIRST-ORDER ^{1}H N.M.R. PARAMETERS[a] AT 100 MHz (τ VALUES) IN DEUTERIOCHLOROFORM (AROMATIC HYDROGEN ATOMS EXCLUDED)

Compound	**2**	**6**	**7**	**9**
H-1	5.08d	5.04d	5.01d	5.08d
H-2	4.95oct	4.87oct	4.97cm	—
H-3	4.30q	4.49q	4.40q	4.35t
H-4	5.75om	5.65om	4.56(br)d	—
H-5	5.71om	5.65om	5.2–5.6cm	—
H-6,6	5.45cm	5.36cm	5.2–5.6cm	6.05cm
OMe	6.59s	6.56s	6.56s	6.58s
N-H	3.56d	3.49d	4.45d	3.45d
$MeSO_2$	—	—	6.88s	—
OH	—	6.70d	—	—
$J_{1,2}$	3.0	3.5	3.5	3.5
$J_{2,3}$	10.5	10.8	10.8	~10
$J_{3,4}$	3.4	2.7	2.8	~10
$J_{4,5}$	—	—	≥1	—
$J_{5,6}$	—	—	—	—
$J_{5,6}$	—	—	—	—
$J_{2,NH}$	9.0	9.0	9.0	9.0

[a]s, singlet; d, doublet; t, triplet or a quartet in which the two middle limbs are almost superimposed; q, quartet; oct, octet; cm, complex octet; om, overlapped multiplet.

Compound **2** was de-*O*-benzoylated in the usual way to give methyl 4-azido-2-benzamido-2,4-dideoxy-α-D-galactopyranoside (**3**), m.p. 188–190° (from ethanol–ether), $[\alpha]_D$ +47° (*c* 1.2, methanol) (Found: C, 52.2; H, 5.5; N, 17.2. $C_{14}H_{18}N_4O_5$ calc.: C, 52.3; H, 5.6; N, 17.4%).

Methyl 2,4-dibenzamido-2,4-dideoxy-α-D-galactopyranoside (**4**). — The 4-azido-dibenzoate **2** (1.3 g) in methanol (50 ml) was hydrogenated at *ca.* 2 atmos. for 20 h, using 10% palladium-on-charcoal (0.1 g). After the removal of the catalyst by filtration through Hyflo-supercell, the filtrate was treated with 0.5M methanolic sodium methoxide (1 ml) and stood at room temperature for 1 h. The solution was then taken to dryness, and the residual thin syrup was boiled several times with light petroleum (to remove methyl benzoate), whereupon crystallisation occurred. Recrystallisation from ethanol gave **4** (0.59 g; 60%), m.p. 258–261°, $[\alpha]_D$ +85° (*c* 1.2, methanol) (Found: C, 63.1; H, 5.8; N, 7.2 $C_{21}H_{24}N_2O_6$ calc.: C, 63.0; H, 6.0; N, 7.0%).

Selective dimolar benzoylation of methyl 2-benzamido-2-deoxy-α-D-galactopyranoside (**5**). — Benzoyl chloride (2.68 ml, 2 molar equivalents) was added dropwise over a period of 30 min. to a stirred solution of **5**[8] (3.3 g) in anhydrous pyridine (33 ml) at −40°. After this temperature had been maintained for a further 2 h, the mixture was stood at room temperature for a further 20 h and then poured into a large volume of ice–water. The crystals were collected and recrystallised twice from ethanol–light petroleum to give the 3,6-dibenzoate **6** (3.6 g; 64%), m.p. 202–205°, $[\alpha]_D$ +118° (*c* 1.1, chloroform) (Found: C, 66.4; H, 5.1; N, 2.8. $C_{28}H_{27}NO_8$ calc.: C, 66.5; H, 5.35; N, 2.75%).

The mother liquors from the recrystallisations were fractionated on a column of silica gel, using ether–light petroleum (2:1 v/v), to give the 3,4,6-tribenzoate **8** (0.18 g; 2.7%), m.p. 144–145°, $[\alpha]_D$ +142° (*c* 1.3, chloroform), identical with an authentic specimen[8]; and a further 0.1 g (1.8%) of the dibenzoate **6**.

*Methyl 2-benzamido-3,6-di-*O*-benzoyl-2-deoxy-4-*O*-mesyl-α-*D*-galactopyranoside* (**7**). — The 3,6-dibenzoate **6** was mesylated in the usual way, and the product was isolated from the reaction mixture by precipitation with water. It had m.p. 182–183° (from propan-2-ol) and $[\alpha]_D$ +86° (*c* 1.1, chloroform) (Found: C, 59.3; H, 5.0; N, 2.5; S, 5.7. $C_{29}H_{29}NO_{10}S$ calc.: C, 59.7; H, 5.0; N, 2.4; S, 5.5%).

*Methyl 4-azido-2-benzamido-3,6-di-*O*-benzoyl-2,4-dideoxy-α-*D*-glucopyranoside* (**9**). — A stirred solution of the 4-methanesulphonate **7** (1.3 g) in hexamethylphosphoric triamide (8 ml) was heated at 70° (bath) with sodium azide (1.3 g) for 40 h. The reaction mixture was then poured into water, and the resulting precipitate was collected and purified by chromatography on silica gel (150 g) with ether–light petroleum (2:1 v/v). The 4-azide **9** was isolated as a syrup (0.64 g; 54%), $[\alpha]_D$ +157° (*c* 1, chloroform) (Found: C, 63.2; H, 4.9; N, 10.4. $C_{28}H_{26}N_4O_7$ calc.: C, 63.4; H, 4.9; N, 10.1%).

*Methyl 2,4-dibenzamido-2,4-dideoxy-α-*D*-glucopyranoside* (**10**). — The 4-azido derivative **9** (0.3 g) was hydrogenated in methanol (50 ml) at 2 atmos. with 10% palladium-on-charcoal catalyst for 20 h. After the removal of the catalyst, the filtrate was treated with 0.5M methanolic sodium methoxide (1 ml), and, after 1 h, concentrated to dryness. The resulting thin syrup was boiled several times with light petroleum which caused crystallisation. The dibenzamido derivative **10** (from ethanol–di-isopropyl ether) (0.14 g; 62%) had m.p. 140–143°, $[\alpha]_D$ +81° (*c* 1, methanol) (Found: C, 62.9; H, 5.9; N, 7.1. $C_{21}H_{24}N_2O_6$ calc.: C, 63.0; H, 6.0; N, 7.0%).

ACKNOWLEDGMENTS

We thank the Science Research Council for a studentship (M. W. H.), and the Physico-Chemical Measurements Unit at Harwell for the 100 MHz ^1H n.m.r. spectral measurements.

REFERENCES

1 D. HORTON, in R. W. JEANLOZ (Ed.), *The Amino Sugars*, Vol. 1A, Academic Press, New York, 1970, p. 185.
2 N. SHARON AND R. W. JEANLOZ, *J. Biol. Chem.*, 235 (1960) 1.
3 U. ZEHAVI AND N. SHARON, *Israel J. Chem.*, 2 (1964) 324.
4 Y. SUHARA, K. MAEDA, H. UMEZAWA, AND M. OHNO, *Tetrahedron Lett.*, (1966) 1239.
5 M. NAKAJIMA, H. SHIBATA, K. KITAHARA, S. TAKAHASHI, AND A. HASEGAWA, *Tetrahedron Lett.*, (1968) 2271.
6 S. YASUDA, T. OGASAWARA, S. KAWABATA, I. IWATAKI, AND T. MATSUMOTO, *Tetrahedron Lett.*, (1969) 3969.
7 R. W. JEANLOZ AND A. M. C. RAPIN, *J. Org. Chem.*, 28 (1963) 2978.
8 M. W. HORNER, L. HOUGH, AND A. C. RICHARDSON, *J. Chem. Soc.* (*C*), (1970) 1336.
9 J. M. WILLIAMS AND A. C. RICHARDSON, *Tetrahedron*, 23 (1967) 1369, 1641.
10 J. HILL, L. HOUGH, AND A. C. RICHARDSON, *Carbohyd. Res.*, 8 (1968) 7, 19; Y. ALI, L. HOUGH., AND A. C. RICHARDSON, *ibid.*, 14 (1970) 181; H. LIBERT, I. SCHUSTER, AND L. SCHMID, *Ber.*, 101 (1968) 1902.