Carbohydrate Research, 26 (1973) 357–363

STEREOSPECIFICITY OF THE O→N ACYL MIGRATION IN 2,3,4,6-TETRA-*O*-BENZOYL-β-D-MANNOPYRANOSYLAMINE*

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(Received July 31th, 1972; accepted in revised form, November 2nd, 1972)

ABSTRACT

By heating tetra-*O*-benzoyl-α-D-mannopyranosyl bromide with sodium azide, 2,3,4,6-tetra-*O*-benzoyl-β-D-mannopyranosyl azide (**3**) was obtained. Catalytic hydrogenation of **3** produced 2,3,4,6-tetra-*O*-benzoyl-β-D-mannopyranosylamine (**4**). Ammonolysis of **4** afforded *N*-benzoyl-β-D-mannopyranosylamine (**7**) in good yield (60%) and a mixture of D-mannose and D-mannopyranosylamine (34%). No other compound was characterized. This result shows that, in O-acylated glycosylamines, O→N acyl migration is stereospecific and takes place when there is a *cis* relation between the *O*-acyl group at O-2 and the amino group at C-1.

INTRODUCTION

We have reported[1] that the ammonolysis of 2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosylamine (**1**) produces a small proportion of 1,1-bis(benzamido)-1-deoxy-D-glucitol and traces of *N*-benzoyl-β-D-glucopyranosylamine. The fact that the O→N acyl migration is not favored in the case of **1** is in agreement with results previously described[1]. In the study of the O→N acyl migration in inosamines with configuration *myo* and *scyllo*, Anderson and Lardy[2] observed that the migration is faster in the *myo* than in the *scyllo* isomer; in the *myo* derivative a *cis* relation exists between the amino and the neighboring hydroxyl group, in the *scyllo* derivative a *trans* relation. However, there is only a quantitative difference in the behavior of both compounds, since the proper pH value and a longer reaction time resulted in the complete migration in both isomers.

In the study of the N→O acyl migration in epimeric 2-acetamidocyclohexanols in dilute aqueous hydrochloric acid, McCasland[3] established that the *cis* epimer liberated its amino group five to six times faster than did the corresponding *trans* isomer. The same result was observed with epimeric *N*-acetylinosamines, since under similar conditions the *myo* isomer liberated its amino group five to six times faster than did the *scyllo* isomer, in agreement with the conclusions of Anderson and Lardy[2].

*Dedicated to Professor V. Deulofeu, in honor of his 70th birthday.

†Research member of the Consejo Nacional de Investigaciones Científicas y Técnicas.

Similar observations were reported by Fodor and Kiss[4] with epimeric 2-benzamidocyclohexanols in alcoholic hydrogen chloride. The *cis* diastereoisomer gave a more rapid N→O benzoyl group migration than did the corresponding *trans* compound. The same authors reconverted each of the *O*-acyl compounds obtained into their hydroxyamide starting materials, thus showing retention of configuration for both N→O and O→N acyl migrations.

A case of O→N acyl group migration was reported by White[5], 2-acetamido-2-deoxy-D-glucose (65%) being produced upon ammonolysis at room temperature of 1,3,4,6-tetra-*O*-acetyl-2-amino-2-deoxy-β-D-glucose, where the amino and the *O*-acyl groups at C-1 and C-3 are in a *trans* relationship (eq–eq).

Fodor and Otvös[6] observed that an ethanolic solution of ethyl 3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-β-D-glucopyranoside, kept for 24 h at room temperature, produced a mixture of ethyl 4,6-di-*O*-acetyl-2-amino-2-deoxy-D-glucopyranoside (51%) and ethyl 2-acetamido-4,6-di-*O*-acetyl-2-deoxy-D-glucopyranoside (15%). The small yield of *N*-acetyl derivative was explained by the *trans* relation between the substituents at C-2 and C-3.

Micheel *et al.*[7] studied the O→N acyl migration in *O*-acyl derivatives of 2-amino-2-deoxy-D-glucose and showed that 3,4,6-tri-*O*-acetyl-2-amino-1-*O*-benzoyl-2-deoxy-α-D-glucopyranose hydrobromide yields 3,4,6-tri-*O*-acetyl-2-benzamido-2-deoxy-D-glucose when heated in an aqueous solution of sodium acetate. It had been previously demonstrated[8] that 1,3,4,6-tetra-*O*-acetyl-2-amino-2-deoxy-β-D-glucose hydrochloride was not rearranged to the corresponding acetamido derivative when submitted to the same conditions. This can now be explained in view of the *trans* relation between the *O*-acyl group at C-1 and the amino group at C-2.

In the case of the α and β anomers of 1-*O*-acetyl-2-amino-2-deoxy-3,4,6-tri-*O*-methyl-D-glucopyranose it was determined[7] that the β anomer rearranges to 2-acetamido-2-deoxy-3,4,6-tri-*O*-methyl-D-glucose sixty times slower than does the α anomer; in the latter configuration the *O*-acyl group at C-1 and the amino group at C-2 are in *cis* relationship.

Van den Kamp and Micheel, studying[9] several 1-*O*-acyl-2-amino-2-deoxy-D-glucose derivatives, determined the half-life periods of the O→N acyl group migration and established that, when the *O*-acyl group at C-1 is *cis* (α anomer) to the amino group, the migration is faster than when the *O*-acyl group is *trans* (β anomer).

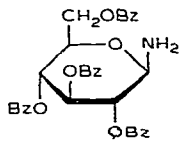
A careful study by Inch and Fletcher[10] of the rearrangement of 2-(*N*-acetylbenzamido)-2-deoxy-D-glucose in chloroform pointed to the fact that a *trans* migration of the benzoyl group from the nitrogen atom at C-2 to the O-3 was not a significant part of the total transformation of the *N*-acetylbenzamido derivative. Furthermore, the fact that all isolated products were α anomers and none of the corresponding β anomers were detected proved that *cis* migration to C-1 predominates.

Finally, results on the stereospecificity of the O→N acyl migration in acylated derivatives of 2-amino-2-deoxy-D-glucopyranose, similar to those reported by us in the present paper, have been reported by Horton *et al.*[11] and our conclusions confirm the conclusions of these authors.

DISCUSSION AND RESULTS

This work was undertaken in order to obtain a better understanding of the O→N acyl migration reaction in connection with our studies on acyl group migration in glycosylamines and those taking place during the ammonolysis of per-*O*-benzoylated monosaccharides. For this purpose we selected 2,3,4,6-tetra-*O*-benzoyl-β-D-mannopyranosylamine (**4**), which has an equatorial amino group at C-1 (β-D-anomer) and an axial benzoyl group at O-2, *i.e.* a *cis* relation between both groups.

The synthesis of **4** was achieved through a route similar to the one previously described[1] for 2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosylamine (**1**). 2,3,4,6-Tetra-*O*-benzoyl-α-D-mannopyranosyl bromide (**2**)[12] was treated with sodium azide in boiling acetonitrile to give 2,3,4,6-tetra-*O*-benzoyl-β-D-mannopyranosyl azide (**3**). The



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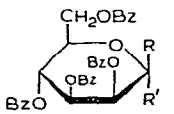
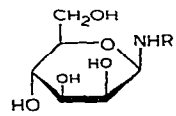


2 R = H, R' = Br
3 R = N_3, R' = H
4 R = NH_2, R' = H
5 R = NHAc, R' = H

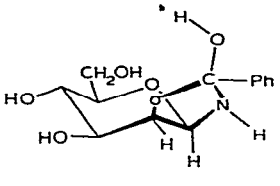


6 R = Ac
7 R = Bz

glycosyl azide **3**, upon catalytic hydrogenation, gave 2,3,4,6-tetra-*O*-benzoyl-β-D-mannopyranosylamine (**4**) in good yield. The n.m.r. spectrum of **4** did not allow assignments of the anomeric configuration, but it was subsequently assigned by transformation of **4** into the known *N*-acetyl-[13] (**6**) and *N*-benzoyl-β-D-mannopyranosylamine[14] (**7**). On acetylation with acetic anhydride–pyridine, the amino compound **4** was transformed into *N*-acetyl-2,3,4,6-tetra-*O*-benzoyl-β-D-mannopyranosylamine (**5**), whose structure was confirmed by debenzoylation to the known[13] **6**. Benzoylation of compound **4** to the corresponding peracylated derivative, and treatment without purification with sodium methoxide and methanol gave the known[14] *N*-benzoyl-β-D-mannopyranosylamine (**7**). Ammonia in methanol at room temperature converted compound **4** into crystalline *N*-benzoyl-β-D-mannopyranosylamine (**7**), isolated in 60% yield, together with products identified by paper chromatography as D-mannopyranosylamine, D-mannose, *N*-benzoyl-D-mannopyranosylamine, and traces of a substance having R_F 0.85. Chromatography of this residue on a cellulose column gave 40 mg of **7** and a mixture (0.42 g; 35%) of D-mannose and D-mannopyranosylamine. The formation of **7** in high yield (60%) by the ammonolysis of **4** proves that the O→N acyl migration is favored when there is a *cis* relation (axial–equatorial) between the acyl group at O-2 and the amino group at C-1. On the other hand, it is noteworthy that in the ammonolysis of **4** no 1,1-bis(benzamido)-1-deoxy-D-mannitol was produced, whereas it was the principal product (20–21%) obtained after reaction of the per-*O*-benzoylated-D-mannopyranose with ammonia in methanol[14]. Our results show that the O-acyl migration to C-1 occurs very rapidly with the concomitant formation of product **7**, which is stable under the reaction conditions.

It is remarkable that, in the ammonolysis of **1**, traces of *N*-benzoyl-β-D-glucopyranosylamine were detected; this result could be explained by the fact that in compound **1** there is a *trans* relation between the acyl group at O-2 and the amino group at C-1. However, the same relation between the amino group and the neighboring *O*-acyl groups is present in 2-acetamido-deoxy-1,3,4,6-tetra-*O*-acetyl-β-D-glucose, but the ammonolysis of this compound under conditions similar to those used for **1** gave 2-acetamido-2-deoxy-D-glucose (65%)[5]. At present, we are unable to give an explanation of this result which in fact differs from all other conclusions reported in the introduction.

The difference between the two glycosylamines **1** and **4** is the orientation of the *O*-acyl group at C-2 which is equatorial in **1** and axial in **4**. Thus, the O→N acyl migration in glycosylamines is stereospecific, as it takes place only with the anomer corresponding to a *cis* migration. The O→N acyl migration has been explained[1–15] by the formation of an orthoacid ester amide between neighboring groups. Inspection of molecular models showed that an orthoacid ester amide **8** could be easily obtained from a β-D-anomer of the *manno* series, with little strain on the pyranoid ring of the sugar. This intermediate **8** would rearrange to produce **7**. Fodor *et al.*[17], on basis of spectroscopical studies, postulated the formation of an orthoacid ester amide, similar to **8**, to explain the rearrangement of ethyl 3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-β-D-glucopyranose into ethyl 2-acetamido-4,6-di-*O*-acetyl-2-deoxy-β-D-glucopyranose.



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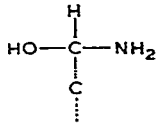

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N-Acyl-D-glycosylamines are also obtained in the ammonolysis of per-*O*-acylated monosaccharides; their formation has been explained[15,18,19] as proceeding through an aminol **9** which, by intramolecular O→N acyl migration, gives *N*-acylglycosylamines and 1,1-bis(acylamido)-1-deoxyalditols. According to our results we can postulate that a partially *O*-acylated aminol **9**, cyclizing to an *O*-acylated glycosylamine having an *O*-benzoyl group at O-2, would be an important intermediate in the formation of *N*-acylglycosylamines having the *manno* configuration.

A possible objection to our conclusions on the formation of **7** from **4** is that we are not yet able to assure that the *N*-benzoyl group of **7** was the one originally attached at O-2. This problem is being studied by the use of isotopic tracers in our laboratories.

EXPERIMENTAL

General. — Evaporations were performed under diminished pressure. Melting points were determined with a Fisher–Johns block and are uncorrected. I.r. spectra

were obtained with a Perkin–Elmer Infracord spectrophotometer. N.m.r. spectra were recorded, for solutions in chloroform-*d* unless otherwise stated, with a Varian A-60 n.m.r. spectrometer with tetramethylsilane as the internal reference standard. Paper chromatography was conducted on Whatman No. 1 paper for analytical chromatography. T.l.c. was performed on Silica Gel (E. Merck). The following solvent systems were used: (A) ethyl acetate–pyridine–water–benzene (5:3:3:1, v/v, top layer); (B) 24:1 (v/v) benzene–2-propanol. Paper chromatograms were sprayed with the Petronici–Safina reagent[20]. Iodine vapor was used for detection after t.l.c.

2,3,4,6-Tetra-O-*benzoyl-β*-D-*mannopyranosyl azide* (**3**). — To a solution of 2,3,4,6-tetra-*O*-benzoyl-α-D-mannopyranosyl bromide (**2**), $[\alpha]_D^{20}$ +10.8° (*c* 2.0, chloroform)[12] (24.0 g), in dry acetonitrile (120 ml) was added sodium azide (7.20 g). The mixture was heated at reflux for 3 h after which t.l.c. (solvent B) indicated the conversion of **2** into **3**. The hot suspension was filtered from salts, and the filtrate was evaporated to dryness. The solid residue (20.0 g) was twice recrystallized from abs. ethanol to give pure **3** (12.0 g), m.p. 130–130.5°; $[\alpha]_D^{20}$ +13.0° (*c* 0.61, chloroform); i.r. data: ν_{max}^{KBr} 2105 (N_3) and 1715 cm^{-1} (C=O); n.m.r. data: τ 4.07 (d, $J_{1,2}$ 3 Hz, H-1 ax, β-D-anomer), 3.80 (t, *J* 10.5 Hz, attributed to H-4 because of its *trans* diaxial orientation in respect to both neighboring protons), 5.14–5.50 (complex, H-6,6′, H-5), and 4.17–4.45 (m, H-3 and H-2).

Anal. Calc. for $C_{34}H_{27}N_3O_9$: C, 65.69; H, 4.38; N, 6.76. Found: C, 65.66; H, 4.39; N, 6.65.

2,3,4,6-Tetra-O-*benzoyl-β*-D-*mannopyranosylamine* (**4**). — The azide **3** (1.14 g) was dissolved in ethyl acetate (15 ml) and hydrogenated at 1.7 torr over W_2-Raney nickel (1.4 ml) for 20 h at room temperature. The catalyst was filtered off, the filtrate was evaporated, and the syrupy residue (0.96 g) was dissolved in boiling abs. ethanol. The cooled solution gave needles (0.78 g), m.p. 154–156°. Two recrystallizations from the same solvent yielded pure **4**, 156–157°; $[\alpha]_D^{20}$ −134.8° (*c* 0.77, chloroform); i.r. data: ν_{max}^{KBr} 3400–3100 (–NH_2) and 1700 cm^{-1} (C=O); n.m.r. data: τ 3.97 (t, *J* 10 Hz, attributed as just described to H-4), 4.35 (q, $J_{2,3}$ 3 Hz, $J_{3,4}$ 10 Hz, H-3), 8.00 (s, 2H, vanishes upon deuterated water treatment, amino group).

Anal. Calc. for $C_{34}H_{29}NO_9$: C, 68.56; H, 4.91; N, 2.85. Found: C, 68.28; H, 5.11; N, 2.18.

N-*Acetyl-2,3,4,6-tetra*-O-*benzoyl-β*-D-*mannopyranosylamine* (**5**). — Acetic anhydride (0.9 ml) was added to a solution of compound **4** (0.18 g) in pyridine (0.6 ml) cooled to 0°. The mixture was kept for 24 h at this temperature and then for the same time at room temperature. The suspension was poured into ice–water. The resulting solid was filtered off after 2 h, the white powder (0.18 g) was dissolved in boiling abs. ethanol (4.0 ml) and treated with Norit. The boiling suspension was filtered and the product crystallized to give pure **5** (0.13 g), m.p. 166–167°; $[\alpha]_D^{20}$ −84.0° (*c* 0.89, chloroform); i.r. data: ν_{max}^{KBr} 3100 (–NH–), 1710 (C=O), 1540 and 1650 cm^{-1} (–CONH–).

Anal. Calc. for $C_{36}H_{31}NO_{10}$: C, 67.81; H, 4.90; N, 2.20. Found: C, 67.61; H, 4.95; N, 2.07.

N-*Acetyl-β-*D-*mannopyranosylamine* (**6**). — Compound **5** (0.08 g) was dissolved by shaking it in dry methanol (3 ml) containing 0.5M sodium methoxide (0.5 ml). After 6 h the solution was neutralized by addition of Dowex-50 W resin[21]. The insoluble material was filtered off and the filtrate was evaporated to dryness. The solid (23 mg) was dissolved in abs. ethanol (2.0 ml) and the addition of the same volume of dry ether produced crystalls of **6** (18 mg; 65%), m.p. 201–204°, $[\alpha]_D^{22}$ −46.8° (*c* 1.0, water), in accordance with reported values. The i.r. spectrum of **6** was identical with that of an authentic sample.

N-*Benzoyl-β-*D-*mannopyranosylamine* (**7**). — Benzoyl chloride (0.05 ml) was added to a solution of compound **4** (0.12 g) in pyridine (1 ml) cooled to −10°. The mixture was kept for 3 h at the same temperature and then for 48 h at 0°. The suspension was poured into ice–water. The microcrystalline solid (0.12 g) was debenzoylated without prior purification, as previously described, to yield needles (0.04 g; 84%), m.p. 250–253° (dec). The solid (0.04 g) was recrystallized from 70% ethanol, to give pure **7** (0.03 g), m.p. 253–254° (dec.), $[\alpha]_D^{20}$ +6.3° (*c* 0.8, pyridine), in accordance with the reported values[13]. The i.r. spectrum was identical with the one from an authentic sample. The n.m.r. spectrum of **7** was obtained in dimethyl sulfoxide-d_6 and showed, after addition of deuterium chloride, the following bands: τ 4.69 (q^{15}, $J_{1,2}$ H-2, and $J_{1,NH}$ 9 Hz, N-H), and 1.82 (d, *J* 9 Hz, -NH); the quartet at 4.69 collapses into a doublet and the signal at 1.82 disappears on treatment with deuterium oxide; similar results were recently reported[16].

*Ammonolysis of 2,3,4,6-tetra-*O*-benzoyl-β-*D-*mannopyranosylamine* (**4**). — Compound **4** (4.00 g) was suspended in 16% (v/v) methanolic ammonia (100 ml) and dissolved by shaking the suspension for 30 min. After 4 h, a new solid was formed and the suspension was kept for 18 h at room temperature. The mixture was cooled in ice–water and, after filtration, a crystalline precipitate (1.17 g), m.p. 251–253° (dec.) was obtained. The filtrate was evaporated to dryness to give a residue (0.93 g). Crystallization of the precipitate from 70% ethanol (700 ml) gave pure **7** (0.91 g), m.p. 252–255° (dec.), $[\alpha]_D^{20}$ +6.0° (*c* 0.15, pyridine). The ethanolic mother liquors yielded a second crop of crystalls of **7** (0.22 g), m.p. 252–255° (dec.). The residue was extracted at room temperature with ethyl acetate (3 × 30 ml) to remove benzamide. Paper chromatography of the residue (solvent A) showed that it contained D-mannopyranosylamine (R_F 0.35), D-mannose (R_F 0.40), *N*-benzoyl-D-mannopyranosylamine (R_F 0.72), and a very light, non-reductive spot (R_F 0.85). The dry residue (0.52 g), insoluble in ethyl acetate, was chromatographed on a 3 × 50 cm column of cellulose powder (Whatman–Chromedia CF11) with solvent A; 20 fractions (80 ml each) were collected and monitored by paper chromatography. From fraction 6 was obtained a solid, which was recrystallized from 70% ethanol to give pure **7** (0.04 g), m.p. 252–255° (dec.). The total yield of **7** was 1.17 g (60%). From fractions 8–20 was obtained a mixture (0.42 g; 35%) of D-mannose and D-mannopyranosylamine.

ACKNOWLEDGMENTS

I thank Dr. B. B. de Deferrari for the microanalysis and Mr. J. J. Ferrer for recording the n.m.r. spectra.

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