AMMONOLYSIS OF 2,3,4,6-TETRA-*O*-BENZOYL-D-GLUCOPYRANOSYLAMINE

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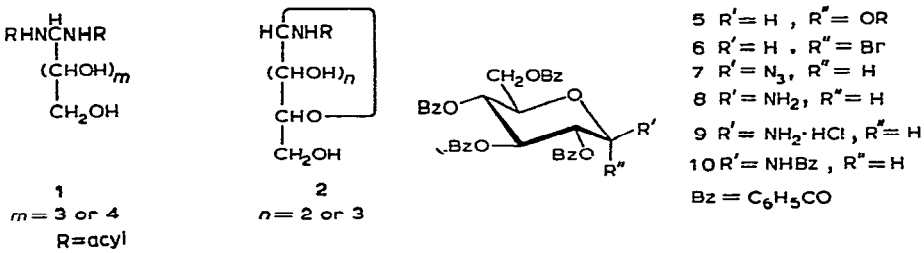
ABSTRACT

The reaction of tetra-*O*-benzoyl-α-D-glucopyranosyl bromide with sodium azide afforded 2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl azide (**7**). Hydrogenation of **7** produced 2,3,4,6-tetra-*O*-benzoyl-D-glucopyranosylamine (**8**), characterized as its hydrochloride (**9**). Ammonolysis of **8** produced 1,1-bis(benzamido)-1-deoxy-D-glucitol in very low yield (1.4%), traces of *N*-benzoyl-D-glucopyranosylamine, and a mixture (95%) of D-glucose and D-glucosylamine. This result strongly supports the concept that O → N acyl migrations are not favored in this reaction of a tetra-*O*-benzoyl-D-glucosylamine.

INTRODUCTION

It is known that, when submitted to the action of ammonia in methanol, acylated aldoses yield the 1,1-bis(acylamido)-1-deoxy-alditol **1** and *N*-acylglycosylamine **2**. The formation of **1** and **2** has been explained as resulting from an intramolecular, O → N acyl migration[1,2].



Isbell and Frush[1] proposed that, before any acyl migration can take place, the acylated aldose is transformed into the acylated *aldehydo* form, *e.g.* **3**. On reaction with ammonia, **3** would be converted into an aldehyde-ammonia (*e.g.* **4**) which might retain some of the *O*-acyl groups.

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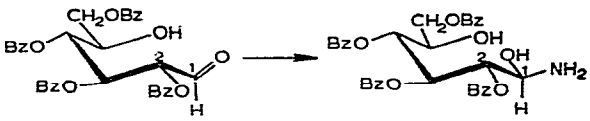

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The ammonolysis reaction has been studied *in extenso* by Deulofeu and co-workers[3–5]. By ammonolysis of labeled 1,2,3,4,6-penta-*O*-benzoyl-D-glucose (**11**) and 2,3,4,6-tetra-*O*-benzoyl-D-glucopyranose (**12**) (containing, at different positions, benzoyl groups labeled with ^{14}C on the carbonyl group), Gros *et al.*[3] demonstrated that the benzoyl group at O-1 does not participate in the formation of **1** (R = Bz). It was also established that the apparent contribution of each benzoyl group to the formation of the bis (benzamido) compound **1** was very similar for both **11** and **12**.

DISCUSSION AND RESULTS

The foregoing facts showed that the benzoyl group at O-1 is eliminated prior to formation of the *aldehydo* form **3**. Although this reaction is fast (as could be expected from the low electron density[6] of the oxygen atom on C-1) during the elimination of the 1-*O*-benzoyl group, acyl groups on other oxygen atoms may undergo nucleophilic attack by ammonia and solvent molecules; as a result, in the acyclic form **4**, a smaller number of acyl groups would remain available for the migration.

Consequently, it was considered that a per-*O*-benzoylaldosylamine (having a free amino group on C-1), that is, a compound having the nitrogen function already present and having all of the *O*-benzoyl groups available, would, upon ammonolysis, yield products **1** and **2** in a much higher yield. Were that supposition correct, such a compound might be postulated as an intermediate in the ammonolysis reaction.

A convenient route for the synthesis of per-*O*-acylglycosylamines is provided by the reduction of the corresponding *O*-acylglycosyl azides[7]. Bertho[8] synthesized the first per-*O*-acetyl-D-glycosyl azide from a per-*O*-acetyl-D-glycosyl halide by a reaction involving nucleophilic displacement of the halide atom by the azide ion. By subsequent catalytic hydrogenation, the azido sugar was transformed into the per-*O*-acyl-D-glycosylamine[9].

In order to apply this procedure to the synthesis of compound **8**, penta-*O*-benzoyl-α-D-glucopyranose (**5**) was transformed into 2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranosyl bromide (**6**) by the well-known method of Hudson and co-workers[10].

Treatment of compound **6** with sodium azide in boiling acetonitrile gave 2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl azide (**7**); the β-D-*gluco* configuration was confirmed by its n.m.r. spectrum, in which the signal for the anomeric proton appeared as a doublet at τ 5.17 ($J_{1,2}$ 8 Hz).

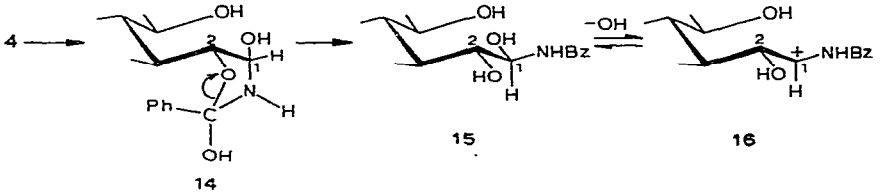
On catalytic hydrogenation, the glycosyl azide **7** afforded, in almost quantitative yield, 2,3,4,6-tetra-*O*-benzoyl-D-glucopyranosylamine (**8**) as a glass that was homogeneous by t.l.c.; compound **8** was characterized as its hydrochloride (**9**). On

treatment with benzoyl chloride in pyridine, compounds **8** and **9** were transformed into the known[11] *N*-benzoyl-2,3,4,6-tetra-*O*-benzoyl-*β*-D-glucopyranosylamine (**10**).

Ammonolysis of **8** in methanol produced a complex mixture which, after application of a combination of cellulose-column chromatography and preparative, paper chromatography, afforded 159 mg (1.4%) of 1,1-bis(benzamido)-1-deoxy-D-glucitol (**1**), and traces of *N*-benzoylglucosylamine (**2**) were characterized by paper chromatography (solvent A) and t.l.c. (solvent C). The rest of the ammonolysis product consisted of a mixture of D-glucose and D-glucosylamine (yield 95%).

The very low yields of **1** and **2** permit the following conclusions: (*a*) compound **8**, which is an *O*-acylated pyranoid glycosylamine having a free amino group on C-1, is not an adequate intermediate for the O→N acyl migration in the ammonolysis of per-*O*-acyl-D-glucose; (*b*) the low yields of **1** contrast with the yield (28%) obtained for the same compound in the ammonolysis of 2,3,4,6-tetra-*O*-benzoyl-D-glucopyranose; (*c*) products having structures similar to that of **8** are not important intermediates in the formation of 1,1-bis(benzamido)-1-deoxy-D-glucitol (**1**, R = Bz), although they participate to a small extent.

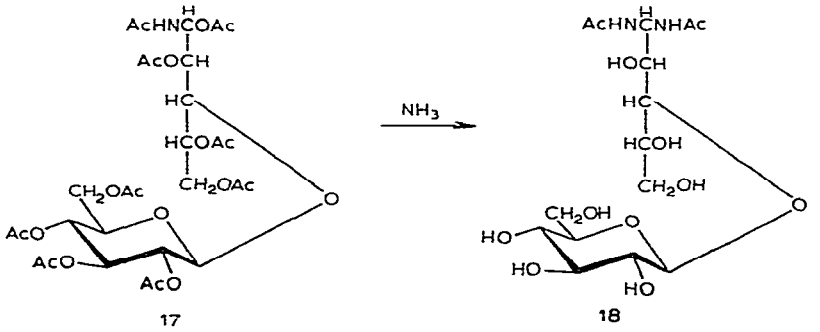
According to the mechanism proposed[1], the *N*-acylation of **4** to **15** results from an O→N acyl migration, as shown in Scheme 1.



SCHEME 1

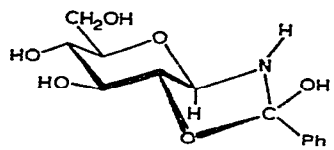
A species such as **15** may be in equilibrium with the carbonium ion **16** proposed by Gros *et al.*[3].

Farkas *et al.*[12] heated octa-*O*-acetylcellobionyl azide with acetic anhydride, and isolated compound **17** which, by reaction with ammonia, was transformed into 1,1-bis(acetamido)-1-deoxy-3-*O*-*β*-D-glucopyranosyl-D-arabinitol (**18**) in 51% yield. Compound **18** had originally been prepared by ammonolysis of octa-*O*-acetylcellobiononitrile (yield 24.2%)[13].



Without doubt, such a partially acylated acyclic compound as **17**, having a 1-acylamido group produced either by the Isbell–Frush or some other mechanism, may be considered to be formally derived from such structures as **15** or **16**, and to be an intermediate in the production of the diamidoalditols (**1**) and *N*-acylglycosylamines (**2**).

On the other hand, inspection of molecular models showed that it should be possible to obtain from compound **8** an ortho acid type of ester amide (**19**) without modifying the pyranoid ring of the sugar. Such a compound as **19** would be almost



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strainless and readily formed; this hypothetical intermediate should then afford compound **2** through an O → N acyl migration, without opening of the pyranoid ring.

Van de Kamp and Micheel[14] described O → N acyl migration from C-1 to C-2 in 1-*O*-acetyl-2-amino-2-deoxy-3,4,6-tri-*O*-methyl-α-D-glucopyranose hydrobromide and 1-*O*-acetyl-2-amino-2-deoxy-3,4,6-tri-*O*-methyl-β-D-glucopyranose hydrochloride on treatment with weakly alkaline reagents; the corresponding 2-acetamido compounds were obtained. It was also demonstrated that the rate of acyl migration for the α anomer was higher than for the β anomer, as would be expected from the respective configurations[15].

However, as compound **2** was detected only as a trace product, after the ammonolysis of **8**, the ortho acid ester amide cannot be an important intermediate in the reaction. Accordingly, we postulate that the formation of **1** and **2** involves a sequence of reactions in which the products of the principal steps are such acyclic compounds as **4**, **15**, and **16**.

It is reasonable to presume that, with such species as **15** and **16**, two competitive reactions occur, namely, (*a*) fixation of a second acylamido group (to produce the bis(acylamido)alditol **1**), and (*b*) cyclization to produce the *N*-acylglycosylamine **2**. According to the results with the D-*gluco* derivatives, the introduction of a second benzamido group is faster than the cyclization.

EXPERIMENTAL

General. — Melting points were determined with a Fisher–Johns block, and are uncorrected. Solvents were removed under diminished pressure at 40°. I.r. spectra were recorded with a Perkin–Elmer Infracord spectrophotometer. P.m.r. spectra were recorded, for solutions in chloroform-*d*, with a Varian A-60 n.m.r. spectrometer, with tetramethylsilane as the internal reference standard. T.l.c. was performed on Silica Gel (E. Merck). Paper chromatography was conducted on Whatman No. 1

paper for analytical chromatography, and on Whatman No. 3MM paper for preparative purposes, by the descending technique. The following solvent systems were used: (A) ethyl acetate–pyridine–water–benzene [5:3:3:1 (v/v); top layer]; (B) 99:1 (v/v) benzene–isopropyl alcohol; and (C) 3:3:4 (v/v) benzene–chloroform–isopropyl alcohol. Paper chromatograms were sprayed with the Petronici–Safina reagent[16]. Iodine vapors were used for detection after t.l.c.

*1,2,3,4,6-Penta-*O*-benzoyl-α-*D*-glucopyranose* (**5**). — Compound **5** was prepared by the method described[10] in the literature. Our product showed $[\alpha]_D^{20}$ +130°; lit.[10], $[\alpha]_D$ +136.8°.

*2,3,4,6-Tetra-*O*-benzoyl-α-*D*-glucopyranosyl bromide* (**6**). — Compound **6** was prepared from **5** by the method of Hudson *et al.*[10]. Our compound had m.p. 128–129°, $[\alpha]_D^{20}$ +127.4° (*c* 1.2, chloroform) in agreement with the reported values[10].

*2,3,4,6-Tetra-*O*-benzoyl-β-*D*-glucopyranosyl azide* (**7**). — To a solution of compound **6** (14.65 g) in dry acetonitrile (100 ml) was added sodium azide (4.50 g). The suspension was gently refluxed and stirred for 3 h. T.l.c. (solvent B) then indicated the complete conversion of **6** into **7**. The hot suspension was filtered from inorganic salts, and the filtrate was evaporated to dryness. The solid residue was twice recrystallized from absolute ethanol, to give pure **7** (9.15 g), m.p. 115–116°, $[\alpha]_D^{22}$ +42.0° (*c* 1.0, chloroform); i.r. data: ν_{max} 2105 (N_3) and 1715 cm^{-1} (C=O); n.m.r. data: τ 5.17 (1-proton doublet, $J_{1,2}$ 8 Hz, axial H-1 of the β-D anomer).

Anal. Calc. for $C_{34}H_{27}N_3O_9$: C, 65.70; H, 4.34; N, 6.76. Found: C, 65.92; H, 4.30; N, 6.80.

*2,3,4,6-Tetra-*O*-benzoyl-*D*-glucopyranosylamine hydrochloride* (**9**). — The azide **7** (13.20 g) in ethyl acetate (150 ml) was hydrogenated at 1.7 torr over nickel(Raney) (W_2) (14 ml) for 20 h at room temperature. The catalyst was filtered off, and the filtrate was evaporated. A glassy material (10.81 g) was obtained that was homogeneous by t.l.c. (solvent B). A solution of the amino compound **8** (0.60 g) in boiling absolute ethanol (5.5 ml) was filtered through Celite, the filtrate was cooled, and concentrated hydrochloric acid (0.02 ml) was added, to give fine needles of **9** (275 mg); m.p. 145–146°, $[\alpha]_D^{20}$ +73.2° [*c* 0.71, 8:2 (v/v) *p*-dioxane–water].

Anal. Calc. for $C_{34}H_{30}ClNO_9$; C, 64.60; H, 4.75; Cl, 5.62; N, 2.21. Found: C, 64.47; H, 5.04; Cl, 5.72; N, 2.19.

N-*Benzoyl-2,3,4,6-tetra-*O*-benzoyl-β-*D*-glucosylamine* (**10**). — (*a*) *From* **9**. Benzoyl chloride (0.1 ml) was added to a solution of compound **9** (200 mg) in pyridine (2.5 ml) cooled to −10°. The mixture was kept for 3 h at −10° and then poured onto ice–water. The resulting solid was dissolved in chloroform, and the solution was washed successively with M sulfuric acid, aqueous sodium hydrogen carbonate, and water, dried (sodium sulfate), and evaporated to dryness. Recrystallization from ethanol gave pure compound **10** (150 mg), m.p. 114–116°, $[\alpha]_D^{22}$ +22.8° (*c* 0.6, chloroform), in agreement with the values reported in the literature[11].

(*b*) *From* **8**. Benzoylation of compound **8** (100 mg) under the conditions just described yielded compound **10** (63 mg), m.p. 114–116°, $[\alpha]_D^{20}$ +21.0° (*c* 0.6, chloroform) in accordance with the properties of an authentic sample.

*Ammonolysis of 2,3,4,6-tetra-*O*-benzoyl-*D*-glucopyranosylamine.* — Compound **8** (17.10 g) was suspended in methanolic ammonia [270 ml of 16% (v/v)] and dissolved by shaking for 30 min. The solution was kept for 18 h at room temperature, and evaporated to dryness, and the residue (16.50 g) was dried, and extracted with ethyl acetate (5 × 75 ml) to remove benzamide, giving a solid (6.50 g). A portion was submitted to paper chromatography. The chromatograms showed components having R_F 0.30 (glucopyranosylamine), 0.42 (glucose), and ~0.80 (elongated spot). 1,1-Bis(benzamido)-1-deoxy-D-glucitol (**1**, R = Bz) has R_F 0.84, and *N*-benzoyl-D-glucopyranosylamine (**2**, R = Bz) has R_F 0.77 (solvent A). The solid (6.50 g) was chromatographed on a column (110 × 4.5 cm) of cellulose powder (Whatman, Standard grade) with solvent A; 113 fractions (50 ml each) were collected. From fractions 16–20 was obtained a solid that was dissolved in boiling ethanol (3 ml); on standing at room temperature, 170 mg of crystals were obtained. Recrystallization from ethanol yielded 159 mg (1.4%) of a pure compound, m.p. 205–208°, $[\alpha]_D^{20}$ +3.0° (*c* 1.0, pyridine), that was identified as 1,1-bis(benzamido)-1-deoxy-D-glucitol (**1**). Fractions 22–28 (50 mg) were freed of two unidentified contaminants by preparative paper chromatography (solvent A). After elution of the zones by the usual procedure, it was possible, by analytical paper chromatography (solvent A), to detect four spots; these had R_F 0.30 (glucopyranosylamine), 0.42 (glucose), 0.77 (**2**), and 0.84 (**1**); this result was confirmed by t.l.c. (solvent C). Fractions 33–113 yielded a mixture (4.70 g; 95%) of D-glucose and D-glucosylamine.

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REFERENCES

1 H. S. Isbell and H. L. Frush, *J. Amer. Chem. Soc.*, 71 (1949) 1579.
2 R. C. Hockett, V. Deulofeu, and J. O. Deferrari, *J. Amer. Chem. Soc.*, 72 (1950) 1840.
3 E. G. Gros, M. A. Ondetti, J. F. Sproviero, V. Deulofeu, and J. O. Deferrari, *J. Org. Chem.*, 27 (1962) 924.
4 E. G. Gros and V. Deulofeu, *J. Org. Chem.*, 29 (1964) 3647.
5 A. Lezerovich, E. G. Gros, J. F. Sproviero, and V. Deulofeu, *Carbohyd. Res.*, 4 (1967) 1.
6 A. Salinas and J. F. Sproviero, *Carbohyd. Res.*, 16 (1971) 243.
7 F. Micheel and A. Klemer, *Advan. Carbohyd. Chem.*, 16 (1961) 85.
8 A. Bertho (with H. Nüssel), *Ber.*, 63 (1930) 836.
9 A. Bertho (with M. Beutler), *Ann.*, 562 (1949) 229.
10 R. K. Ness, H. G. Fletcher, Jr., and C. S. Hudson, *J. Amer. Chem. Soc.*, 72 (1950) 2200.
11 A. S. Cerezo, J. F. Sproviero, V. Deulofeu, and S. Delpy, *Carbohyd. Res.*, 7 (1968) 395.
12 I. Farkas, I. F. Szabó, and R. Bognár, *Acta Chim. Acad. Sci. Hung.*, 59 (1969) 419, and references cited therein.
13 J. O. Deferrari, M. E. Gelpi, and R. A. Cadenas, *J. Org. Chem.*, 30 (1965) 2328.
14 F. P. Van de Kamp and F. Micheel, *Chem. Ber.*, 90 (1957) 2054.
15 S. J. Angyal and C. G. MacDonald, *J. Chem. Soc.*, (1952) 686.
16 C. Petronici and G. Safina, *Conserve Deriv. Agrum.*, 2, No. 5 (1953) 3; *Chem. Abstr.*, 47 (1953) 11297.