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The reaction of penta-*O*-benzoyl-D-glucopyranose with piperidine: characterization of the products isolated and study of the reaction mechanism

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Abstract

The reaction of penta-*O*-benzoyl-D-glucopyranose with piperidine gave *N*-(2,3,6-tri-*O*-benzoyl-β-D-glucopyranosyl)piperidine (44.1%), *N*-(2,4,6-tri-*O*-benzoyl-β-D-glucopyranosyl)piperidine (1.5%), *N*-benzoylpiperidine and piperidinium benzoate (approx 1 mol of each of these two products per mol of substrate). When several penta-*O*-benzoyl-D-glucopyranoses containing selectively ^{14}C-labeled benzoyloxy groups were submitted to the same reaction, it was found that *N*-benzoylpiperidine is formed at the expense of benzoyloxy-C-1, piperidinium benzoate arises mainly from benzoyloxy-C-2, and the benzoyloxy groups originally attached to C-3, C-4, and C-6 remain in the major product of the reaction. These results demonstrate that the first compound produced in the reaction is *N*-(3,4,6-tri-*O*-benzoyl-β-D-glucopyranosyl)piperidine, which could not be isolated because it undergoes two consecutive benzoyl migrations: a migration from O-3 to O-2 to give the 2,4,6-tri-*O*-benzoate, followed by a migration from O-4 to O-3 to afford the 2,3,6-tri-*O*-benzoate. A mechanism to explain the formation of piperidinium benzoate from benzoyloxy-C-2 of penta-*O*-benzoyl-D-glucopyranose is proposed.

Keywords: Per-*O*-acylated-D-glucopyranoses; Reaction with piperidine; *N*-(β-D-Glucopyranosyl)piperidine derivatives; O-Deacylation; Acyl migration; Reaction mechanism

1. Introduction

The reaction of penta-*O*-acetyl-D-glucopyranose with piperidine was earlier studied by Vogel [1]. Although no crystalline products could be isolated, he concluded that *O*-deacetylation on C-1 and C-2 had occurred, since his tests for enediol formation in the reaction mixture were positive.

Some 15 years later, Hodge and Rist [2] could isolate a crystalline compound from the same reaction, and proved it to be *N*-(3,4,6-tri-*O*-acetyl-β-D-glucopyranosyl)piperidine (36%). They pointed out that optimum yields were obtained using 3 mol of piperidine per mol of penta-*O*-acetyl-D-glucopyranose, since *N*-acetylpiperidine and piperidinium acetate were also formed.

When extended to octa-*O*-acetylcellobiose [3], this reaction produced *N*-(3,6,2′,3′,4′,6′-hexa-*O*-acetyl-β-cellobiosyl)piperidine. If the reaction with piperidine was halted after a short time [4], the major product was the anomerically unsubstituted hepta-*O*-acetylcellobiose having the α-D configuration.

Apart from its use in the production of 2-*O*-substituted derivatives of D-glucose [2,5]

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or cellobiose [3], the reaction of per-*O*-acetylated sugars with piperidine has received little attention from carbohydrate chemists, and no studies have been undertaken to elucidate the mechanism of O-deacetylation at C-2 of the sugar.

This paper describes the analogous reaction between penta-*O*-benzoyl-D-glucopyranose and piperidine which, unexpectedly, failed to produce *N*-(3,4,6-tri-*O*-benzoyl-β-D-glucopyranosyl)piperidine and afforded an isomeric tribenzoate as the major product. Nevertheless, the use of isotopic tracers revealed that O-debenzoylation had occurred at C-1 and C-2 of the substrate, and provided information as to which of the benzoyloxy groups of penta-*O*-benzoyl-D-glucopyranose were involved in formation of the isolated products.

2. Results and discussion

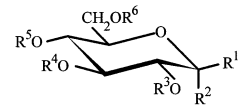
The reaction of penta-*O*-benzoyl-β-D-glucopyranose (**1**) with piperidine in ether for 6 days at room temperature (rt) afforded three benzoylated derivatives of *N*-(β-D-glucopyranosyl)piperidine, which were isolated by chromatographic techniques and characterized by chemical and spectroscopic procedures: *N*-(2,3,6-tri-*O*-benzoyl-β-D-glucopyranosyl)piperidine (**8**), *N*-(2,4,6-tri-*O*-benzoyl-β-D-glucopyranosyl)piperidine (**9**), and *N*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-piperidine (**10**). The respective yields are indicated in Table 1. From the reaction mixture, *N*-benzoylpiperidine and piperidinium benzoate were also obtained, in yields respectively corresponding to 1.02 and 0.90 mol/mol of starting material. The amount of the latter was estimated by measuring the benzoic acid produced.

Table 1
Products from the reaction of acylated D-glucopyranoses with piperidine

Substrate	Products (% yield)					
	8	**9**	**10**	**12**	**13**	**14**
1	44.1	1.5	0.5			
17	53.7	2.3	1.2			
18	52.7	1.8				
7[a]				33.2	1.8	0.5
7[b]					4.1	0.3

[a] The reaction was performed under crystallizing conditions.

[b] The reaction was accomplished under homogeneous conditions.



	R^1	R^2	R^3	R^4	R^5	R^6
1	OBz	H	Bz	Bz	Bz	Bz
2	H	O[^{14}C]COPh	Bz	Bz	Bz	Bz
3	OBz	H	Bz	Bz	[^{14}C]COPh	Bz
4	OBz	H	Bz	Bz	Bz	[^{14}C]COPh
5	O[^{14}C]COPh	H	[^{14}C]COPh	[^{14}C]COPh	Bz	Bz
6	H	O[^{14}C]COPh	Bz	[^{14}C]COPh	[^{14}C]COPh	Bz
7	OAc	H	Ac	Ac	Ac	Ac

When submitted to acid hydrolysis, compound **8** afforded 2,3,6-tri-*O*-benzoyl-α-D-glucopyranose (**15**) as the main product. Benzoylation of **8** produced the perbenzoate **10**. On acetylation, **8** afforded the tribenzoyl monoacetyl derivative **11**. The location of benzoyloxy groups at C-2, C-3, and C-6 was demonstrated by the ^{1}H and ^{13}C NMR spectra of **8** (Tables 2 and 3), that were correlated with the ^{1}H and ^{13}C NMR spectra of perbenzoate **10** and acetate **11** (Tables 4 and 5).

By acid hydrolysis, compound **9** produced the already [8] described 2,4,6-tri-*O*-benzoyl-α-D-glucopyranose (**16**) as the major product. The position of benzoyloxy groups at C-2, C-4, and C-6 was confirmed by the ^{1}H and ^{13}C NMR spectra of **9** (Tables 2 and 3), which were correlated with the ^{1}H and ^{13}C NMR spectra of perbenzoate **10** (Tables 4 and 5).

When compound **10** was submitted to acid hydrolysis, 2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranose (**17**) [8,9] was isolated. The anomeric configuration for compounds **8**, **9**, **10**, **11**, and **15** was assigned by ^{1}H NMR spectroscopy, on the basis of the $J_{1,2}$ value [10]. The β-anomeric configuration obtained for the *N*-D-glucopyranosylpiperidines **8**, **9**, and **10**, and the preferred formation of α anomers when these compounds were converted into the D-glucopyranoses **15**, **16**, and **17** may be rationalized on the basis of electrostatic and steric interactions. It is known that electronegative substituents at the anomeric carbon atom prefer to assume axial rather than equatorial orientations, contrary to ex-

Table 2
^{1}H NMR spectral data for *N*-(β-D-glucopyranosyl)piperidine derivatives

Compound	Chemical shifts (δ, ppm)											
	H-1 (d)[a]	H-2 (t)	H-3 (t)	H-4 (t)	H-5 (m)	H-6[b] (dd)	H-6′[b] (dd)	–N(CH_2CH$_2$)$_2$CH$_2$	–N(CH$_2$CH_2)$_2$CH_2	Ph	OH (bs)	Oac (s)
8[c]	4.22	5.55	5.46	3.80	3.71	4.73	4.62	2.54–2.60 2.97–3.03	1.26–1.40	7.31–7.59 7.91–8.10	3.32[d]	
9	4.20	5.39	4.12	5.30	3.91	4.41	4.60	2.50–2.60 2.92–3.03	1.28–1.45	7.35–7.60 7.97–8.07	2.80[d]	
10[c]	4.34	5.66	5.91	5.58	4.03	4.47	4.60	2.55–2.63 3.01–3.09	1.35–1.45	7.26–7.58 7.81–8.03		
11	4.27	5.60	5.72	5.36	3.90	4.43	4.57	2.55–2.65 3.00–3.10	1.35–1.45	7.32–7.60 7.92–8.12		1.92
12[c]	3.86	3.68	5.11	4.94	3.59	4.22	4.08	2.53–2.62 2.84–2.93	1.45–1.65		2.29[d]	2.02, 2.06, 2.07
13	3.94	5.08	5.02	3.47	3.40	4.42	4.30	2.45–2.59 2.83–2.95	1.35–1.60		2.65[d]	2.03, 2.09, 2.10
14	3.98	5.15	5.21	4.98	3.58	4.23	4.11	2.50–2.60 2.85–2.97	1.40–1.65			2.01, 2.02, 2.03, 2.08

Compound	Coupling constants (Hz)						
	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$[b]	$J_{5,6'}$[b]	$J_{6,6'}$[b]
8[c]	8.8	9.4	9.6	9.0	3.9	2.3	−12.0
9	9.3	9.2	9.3	9.2	5.2	3.1	−11.9
10[c]	9.2	9.3	9.6	9.7	4.9	3.4	−11.9
11	8.9	9.4	9.5	9.6	4.8	2.7	−12.1
12[c]	9.1	9.2	9.5	9.7	4.8	2.6	−12.1
13	8.7	9.1	9.3	9.3	3.9	1.9	−12.1
14	8.8	9.1	9.4	9.8	4.7	2.6	−12.1

[a] Signal multiplicities are given in parentheses.
[b] The assignments of H-6 and H-6′ are shown in Fig. 1.
[c] Signal assignments were confirmed by the two-dimensional ^{1}H–^{1}H chemical-shift correlated spectrum.
[d] Disappeared on deuteration.

Table 3
^{13}C NMR spectral data for *N*-(β-D-glucopyranosyl)piperidine derivatives

Compound	Chemical shifts (δ, ppm)											
	C-1	C-2	C-3	C-4	C-5	C-6	–COPh	–Ph	$-COCH_3$	$-COCH_3$	$-N(CH_2CH_2)_2CH_2$	$-N(CH_2CH_2)_2CH_2$	$-N(CH_2CH_2)_2CH_2$
8[a]	94.52	68.07	77.68	69.98	75.70	63.76	165.54 166.86 167.24	128.21–133.27			49.05	26.20	24.52
9	94.55	71.08	74.98	72.85	73.18	63.71	166.11 166.26 (2)	128.32–133.45			49.06	26.25	24.55
10	94.87	68.37	74.11	70.21	73.33	63.47	165.30 (2) 165.81 166.19	128.22–133.28			49.10	26.18	24.50
11	94.82	68.29	74.36	69.37	73.19	63.13	165.30 165.83 166.20	128.24–133.22	169.49	20.56	49.09	26.19	24.50

[a] Signal assignments were confirmed by the two-dimensional ^{13}C–^{1}H chemical-shift correlated spectrum.

pectations based on steric considerations (anomeric effect). The magnitude of this effect is dependent upon the electronegativity of the substituent directly attached to C-1 [11]. Since nitrogen is less electronegative than oxygen, in *N*-D-glucopyranosylpiperidines the anomeric effect will be comparatively small and steric effects that favor the formation of β anomers will be preponderant.

	R^1	R^2	R^3	R^4
8	Bz	Bz	H	Bz
9	Bz	H	Bz	Bz
10	Bz	Bz	Bz	Bz
11	Bz	Bz	Ac	Bz
12	H	Ac	Ac	Ac
13	Ac	Ac	H	Ac
14	Ac	Ac	Ac	Ac

When compound **17** was treated with piperidine in ether for 6 days at rt, compounds **8**, **9**, and **10** were obtained (Table 1). The reaction produced 0.89 mol of piperidinium benzoate (isolated as benzoic acid) per mol of starting material, but only traces of *N*-benzoylpiperidine were detected by TLC. At the beginning of the reaction, a 1:1 salt-like adduct of 2,3,4,6-tetra-*O*-benzoyl-D-glucopyranose and piperidine (87.4%) crystallized spontaneously from the reaction mixture. The ^{1}H NMR spectrum of the adduct revealed a high degree of hydrogen bonding between the nitrogen atom of piperidine and the oxygen atom from C-1 of the tetrabenzoate. A similar adduct of 2,3,4,6-tetra-*O*-acetyl-D-glucopyranose and benzylamine has been reported [12].

An interconversion between **8** and **9** was observed when these compounds were separately treated with piperidine in ether for 6 days at rt. In contrast, **10** was not altered when it was submitted to the same treatment. Since compounds **8** and **9** are formed from **17** and piperidine, but not from **10** and piperidine, it may be concluded that the *O*-debenzoylation must accompany or precede the formation of the glucosylamine linkage.

When 3,4,6-tri-*O*-benzoyl-α-D-glucopyranose (**18**) [8] was treated with piperidine in ether for 3 days at rt, compounds **8** and **9** were obtained (Table 1). This fact revealed that two consecutive benzoyl migrations had taken place during the reaction: a migration

Table 4
^{1}H NMR chemical-shift correlations for compounds **8**–**14**

$\Delta\delta$ (ppm)[a] for indicated compounds	Atom						
	H-1	H-2	H-3	H-4	H-5	H-6[b]	H-6′[b]
10–**8**	+0.12	+0.11	+0.45	+1.78[c]	+0.32	−0.26[d]	−0.02[d]
11–**8**	+0.05	+0.05	+0.26	+1.56[c]	+0.19	−0.30[d]	−0.05[d]
10–**9**	+0.14	+0.27	+1.79[c]	+0.28	+0.12	+0.06	0.00
14–**12**	+0.12	+1.47[c]	+0.10	+0.04	−0.01	+0.01	+0.03
14–**13**	+0.04	+0.07	+0.19	+1.51[c]	+0.18	−0.19[d]	−0.19[d]

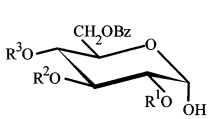
[a] Chemical-shift values from Table 2.
[b] The assignments of H-6 and H-6′ are shown in Fig. 1.
[c] Typical downfield shift of the signal from the proton of the α-carbon atom on *O*-acylation [6].
[d] Upfield shift upon *O*-acylation of C-4, attributable to a diamagnetic anisotropic shielding effect exerted by the introduced carbonyl group on H-6 in rotamers a_1 and a_3, and on H-6′ in rotamer a_3 (Fig. 1).

Table 5
^{13}C NMR chemical-shift correlations for compounds **8**–**11**

$\Delta\delta$ (ppm)[a] for indicated compounds	Atom					
	C-1	C-2	C-3	C-4	C-5	C-6
10–**8**	+0.35	+0.30	−3.57[b]	+0.23	−2.37[b]	−0.29
11–**8**	+0.30	+0.22	−3.32[b]	−0.61	−2.51[b]	−0.63
10–**9**	+0.32	−2.71[b]	−0.87	−2.64[b]	+0.15	−0.24

[a] Chemical-shift values from Table 3.
[b] Typical upfield shift of the signal from the β-carbon atom on *O*-acylation [7].

from O-3 to O-2 to give the 2,4,6-tribenzoate, followed by a migration from O-4 to O-3 to give the 2,3,6-tribenzoate. These migrations must accompany or follow the formation of the glucosylamine linkage, since in D-glucopyranose derivatives acyl migrations generally proceed away from C-1 and towards C-6. It has been reported [13] that in the monoacetates of methyl 6-*O*-trityl-α-D-glucopyranoside, acetyl migration under mild alkaline conditions takes place in the direction O-2 → O-3 → O-4.



	R^1	R^2	R^3
15	Bz	Bz	H
16	Bz	H	Bz
17	Bz	Bz	Bz
18	H	Bz	Bz

The mechanism of the reaction of **1** with piperidine was studied by employing five 1,2,3,4,6-penta-*O*-benzoyl-D-glucopyranoses containing ^{14}C-labeled benzoyloxy groups attached to different carbon atoms (**2**–**6**). In each case, compound **8**, *N*-benzoylpiperidine, and benzoic acid were isolated from the reaction mixture. From the activity data of substrates and products, the moles of labeled benzoyl groups per mol in the products were calculated (Table 6). The contributions of each benzoyl group of 1,2,3,4,6-penta-*O*-benzoyl-D-glucopyranose to the formation of **8**, *N*-benzoylpiperidine, and piperidinium benzoate are indicated in Table 7. These results indicate that benzoyloxy-C-1 of the substrate is removed mostly as *N*-benzoylpiperidine, piperidinium benzoate is formed mainly at the expense of benzoyloxy-C-2, and the benzoyloxy groups originally attached to C-3, C-4, and C-6 are entirely recovered in the major product **8**. This is a clear proof that the first compound formed in the reaction should be *N*-(3,4,6-tri-*O*-benzoyl-β-D-glucopyranosyl)pi-

Table 6
Moles of labeled benzoyl groups per mol[a] in the products isolated from the reaction of labeled 1,2,3,4,6-penta-*O*-benzoyl-D-glucopyranoses with piperidine

Substrate	Carbon atoms with labeled benzoyloxy groups	Products		
		8	*N*-Benzoylpiperidine	Benzoic acid
2	C-1	0.02[b]	0.86	0.04
3	C-4	1.00	0.01[b]	0.10
4	C-6	0.99	0.06	0.01[b]
5	C-1, C-2, C-3	1.00	0.93	0.89
6	C-1, C-3, C-4	2.00	0.88	0.25

[a] Calculated as: activity of the product/activity per labeled benzoyl group of the substrate.
[b] Values within the error of the method employed.

Table 7
Contributions of benzoyl groups of 1,2,3,4,6-penta-*O*-benzoyl-D-glucopyranose to the formation of **8**, *N*-benzoylpiperidine, and piperidinium benzoate[a]

Location of the benzoyloxy group in the substrate	**8**	*N*-benzoylpiperidine	Piperidinium benzoate
C-1	0.02[b]	0.86	0.04
C-2	0.00[c]	0.06[c]	0.74[c]
C-3	0.98[d]	0.01[b,d]	0.11[d]
C-4	1.00	0.01[b]	0.10
C-6	0.99	0.06	0.01[b]

[a] Expressed in moles of benzoyl group per mol of product.
[b] Values within the error of the method employed.
[c] Values calculated by subtracting the individual contributions of benzoyloxy-C-1 and benzoyloxy-C-3 from the total contribution of the benzoyloxy groups attached to C-1, C-2, and C-3.
[d] Values calculated by subtracting the individual contribution of benzoyloxy-C-1 and benzoyloxy-C-4 from the total contribution of the benzoyloxy groups attached to C-1, C-3, and C-4.

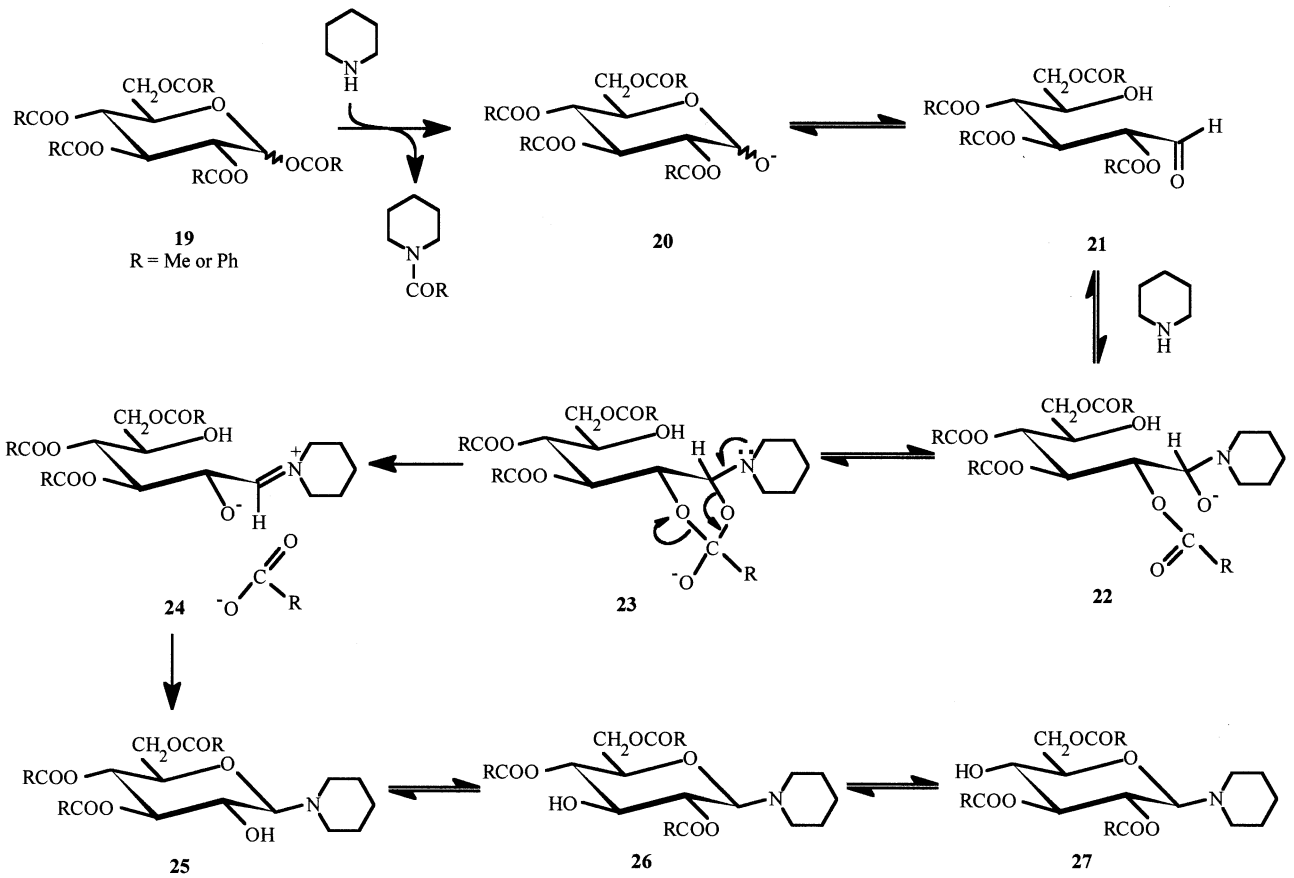
peridine, which could not be isolated because it undergoes two consecutive benzoyl migrations: a migration from O-3 to O-2 to give **9**, followed by a migration from O-4 to O-3 to give **8**. These migrations of benzoyl groups in a direction towards C-1 in *N*-β-D-glucopyranosylpiperidine derivatives are apparent exceptions to the generalization [14] that in partially acylated monosaccharides, acyl migrations take place away from the anomeric center. It is known that the intramolecular O → O acyl transfer is a reversible base-catalyzed reaction which proceeds through a cyclic anionic addition intermediate [13]. The position of the equilibrium is strongly dependent on the 'acidity' of the hydroxyl groups involved in the acyl transfer, as in intermolecular acyl-transfer processes. It has been reported [15], that as the acidity of the acceptor hydroxyl group decreases, the rate of acyl transfer increases. In D-glucopyranose derivatives, the anomeric carbon bears two electron-withdrawing oxygen atoms; consequently, the acidity of hydroxyl groups increases in a direction towards C-1, favoring the acyl migrations away from the anomeric center. In *N*-D-glucopyranosylpiperidine derivatives, the observed acyl migrations in a direction towards C-1 might be a consequence of the replacement of an oxygen atom at C-1 by a less electronegative nitrogen atom, thus reducing the electron-withdrawing effect of the anomeric center.

In order to rationalize the different results obtained [2] in the analogous reaction of penta-*O*-acetyl-β-D-glucopyranose (**7**) with piperidine, this reaction was repeated in the same conditions described by Hodge and Rist. From the reaction mixture, *N*-(3,4,6-tri-*O*-acetyl - β - D - glucopyranosyl)piperidine (**12**)

slowly crystallized; chromatography of the mother liquor from the crystallization of **12** afforded *N*-(2,3,6-tri-*O*-acetyl-β-D-glucopyranosyl)piperidine (**13**) and *N*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)piperidine (**14**). (Table 1). In the reaction of **7** with piperidine, the product primarily formed by O-deacetylation at C-1 and C-2 of the substrate could be isolated because it is scarcely soluble in the reaction medium and crystallizes spontaneously. The high yield of **12** is not necessarily a consequence of the greater stability of **12** compared to **13**, since external factors such as solubility can influence the equilibrium [16].

When the reaction of **7** with piperidine was performed under homogeneous conditions, only compounds **13** and **14** could be isolated in low yield by chromatography. Compound **12** was not detected in the reaction mixture because it undergoes two consecutive acetyl migrations in a direction towards C-1 to give **13**. The low yield of **13** (4.1%) contrasts with the yield obtained for **8** in the similar reaction of **1** with piperidine (44.1%). The difference might be explained considering that acetoxy groups of **13** undergo aminolysis by piperidine at a greater rate than benzoyloxy groups of **8**. This was corroborated by studying the stability of these compounds in piperidine–ether after a reaction period of 6 days. Starting from **12**, **13**, or **14**, *N*-acetylpiperidine was an important component of the reaction mixtures. On the contrary, starting from **8**, **9**, or **10**, *N*-benzoylpiperidine could not be detected in the reaction media.

The *N*-(2,3,6-tri-*O*-acyl-β-D-glucopyranosyl)piperidine could presumably have been formed from a penta-*O*-acyl-D-glucopyranose (**19**) by the reaction pathway depicted in Scheme 1. In a first step, the acyloxy-C-1 of the substrate, which is aminolyzed at a greater rate than the remaining acyloxy groups, is removed as *N*-acylpiperidine. Calculations [17] showed that in the resulting 2,3,4,6-tetra-*O*-acyl-D-glucopyranose (**20**) the HO–C-1 is highly ionized in an aprotic reaction medium. This was corroborated in the present work by the isolation, at the beginning of the reaction,



Scheme 1.

of a 1:1 salt-like adduct of 2,3,4,6-tetra-*O*-benzoyl-D-glucopyranose and piperidine. The ionization of the hemiacetal facilitates the opening of the pyranoid ring that generates the carbonyl group (**21**). Nucleophilic addition of piperidine leads to the carbinolamine **22**, highly ionized in aprotic media [17]. Intramolecular attack of the oxyanion from C-1 on the carbonyl group of acyloxy-C-2 results in the formation of intermediate **23**, which subsequently decomposes expelling a carboxylate anion to give the iminium cation **24**. Nucleophilic attack of O-5 leads to a *N*-(3,4,6-tri-*O*-acyl-β-D-glucopyranosyl)piperidine (**25**), which could be isolated only in the reaction of **7** with piperidine under crystallizing conditions. A first O-3 → O-2 acyl migration produces the 2,4,6-tri-*O*-acyl derivative **26**, that was isolated as a minor product in the reaction of **1** with piperidine. A subsequent O-4 → O-3 acyl migration produces the 2,3,6-tri-*O*-acyl derivative **27**, that was the major product isolated in the reaction of **1** with piperidine, and in the reaction of **7** with piperidine under homogeneous conditions.

3. Experimental

General methods.—Melting points were determined with a Fisher–Johns apparatus and are uncorrected. Optical rotations were measured with a Perkin–Elmer 141 polarimeter. Solvents were distilled prior to use. Ligroin had bp 100–120 °C. Evaporations were conducted below 40 °C under diminished pressure. Samples for analysis were dried under vacuum over P_2O_5. Column chromatography was performed on Alumina Woelm neutral, activity grade I. TLC on alumina was conducted on glass plates (10 × 20 cm) coated with Aluminium oxide G, type E (E. Merck; 0.25-mm thickness). Detection was effected with iodine vapor. TLC on silica gel was done on aluminium sheets precoated with Silica Gel 60 F (E. Merck; 0.2-mm thickness). Detection was effected by charring with 10% H_2SO_4 (v/v) in EtOH. The following mixtures of hexane–EtOAc (v/v) were used as developing solvents: A, 4:1; B, 7:3; C, 3:2. NMR spectra were recorded for solutions in $CDCl_3$ on a

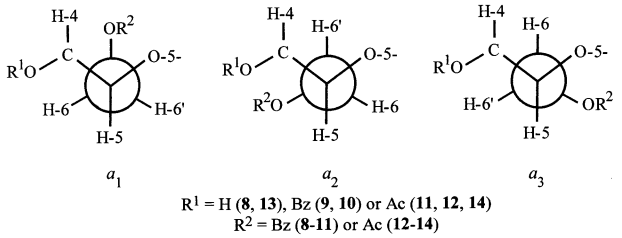


Fig. 1. The staggered rotamers of the C-5–C-6 fragment in *N*-(β-D-glucopyranosyl)piperidine derivatives. Rotamer a_2 (H-5 trans-coplanar to H-6′) can be excluded as a significant contributor to the conformational population because of the low values of $J_{5,6'}$ (Table 2); this exclusion would be expected as this rotamer has a destabilizing 1,3-parallel interaction between O-4 and O-6. The intermediate values of $J_{5,6}$ (Table 2) accord with an equilibrium in which rotamers a_1 (H-5 gauche to H-6) and a_3 (H-5 trans-coplanar to H-6) both contribute significantly.

Bruker AC-200 spectrometer operating at 200 MHz for ^1H and 50.2 MHz for ^{13}C. Me_4Si was employed as the internal reference-standard. Signal multiplicities are indicated by: bs, broad singlet; d, doublet; dd, double doublet; m, multiplet; s, singlet; t, triplet. The two magnetic nonequivalent geminal protons at C-6 are denoted H-6 and H-6′ as shown in Fig. 1. The geminal coupling constant $J_{6,6'}$ was assumed to be negative, in analogy to the data on geminal coupling constants for other saturated carbohydrates [18]. Hydroxyl protons were exchanged for deuterium by adding D_2O. The two-dimensional $^1H-^1H$ and $^{13}C-^1H$ chemical-shift correlated spectra were obtained with the standard COSY and HETCOR pulse sequences. Benzoyl [*carbonyl*-^{14}C]-chloride was prepared from benzoic [*carboxyl*-^{14}C]acid and unlabeled benzoic acid, according to Schmid and Banholzer [19]. The activity of the product was determined by hydrolysis to benzoic acid. Labeled 1,2,3,4,6-penta-*O*-benzoyl-D-glucopyranoses were recrystallized to constant specific activity. Activities were measured with a Rackbeta Wallack 1214 liquid scintillation counter. The scintillation solution contained 400 mg of 2,5-diphenyloxazole (PPO) and 10 mg of 1,4-bis-2-(4-methyl-5-phenyloxazolyl)-benzene (di-methyl POPOP) per 100 mL of toluene. Activities are expressed as disintegrations per min per mmol (dpm/mmol).

Preparation of 1,2,3,4,6-penta-O-*benzoyl-β*-D-*glucopyranose* (**1**).—Compound **1** was pre-

pared from D-glucose by following the method described by Ness et al. [20] for the β anomer. The crude product was successively recrystallized from glacial HOAc, 5:1 acetone–water and 3:1 MeOH–acetone; a pure product was obtained having mp 158–160 °C, $[\alpha]_D + 23.9°$ (*c* 1, $CHCl_3$), in agreement with the values reported in the literature [20,21].

Reaction of **1** *with piperidine.*—Compound **1** (17.5 g, 25 mmol) was suspended in dry Et_2O (250 mL) and piperidine (15 mL, 150 mmol) was added. The mixture was stirred for 6 days at rt, solution being attained after about 5 days. The solution was evaporated to a thick dark-yellow syrup (27.1 g), that was dissolved in Et_2O (250 mL) and extracted with water (4 × 50 mL). The aq extract containing piperidinium benzoate was acidified with concd HCl and cooled to 0 °C; 2.75 g of benzoic acid were obtained, mp 121–122 °C, identical with an authentic sample.

The ether layer was evaporated to a syrup (19.35 g). Examination by TLC on alumina (solvent A) showed four spots, R_f 0.70, 0.48, 0.34, and 0.24. The syrup was chromatographed on a dry-column of alumina (1200 g); elutions were performed by using hexane with increasing concentrations of EtOAc. Fractions (400 mL each) were collected, and monitored by TLC. Elution with 9:1 hexane–EtOAc afforded the products having R_f 0.70 (fractions 17–19) and R_f 0.48 (fractions 20–25), while a 4:1 mixture of the same solvents eluted the components having R_f 0.34 (fractions 39–41) and R_f 0.24 (fractions 42–60).

Evaporation of fractions 17–19 gave a syrupy residue (83 mg, 0.5%) that crystallized from 1:1 Et_2O–ligroin yielding **10**: mp 146–147 °C (d); $[\alpha]_D + 36.3°$ (*c* 0.4, $CHCl_3$); R_f 0.70 (alumina, solvent A), identical with an authentic sample prepared on benzoylation of **8**.

Fractions 20–25 were evaporated to a syrup (4.82 g) that crystallized on standing in a refrigerator: mp 45–50 °C; R_f 0.48 (alumina, solvent A). It was identified as *N*-benzoylpiperidine by comparison with an authentic sample; lit mp 48 °C [22].

N-*(2,4,6-Tri*-O-*benzoyl-β*-D-*glucopyranosyl)-piperidine* (**9**).—Evaporation of fractions 39–41 gave a partially crystalline residue (285 mg) which was dissolved in Et_2O (15 mL) and precipitated by adding ligroin (15 mL); crystals were obtained (209 mg, 1.5%); R_f 0.34 (alumina, solvent A). A further recrystallization from the same solvent mixture gave **9**: mp 180–181 °C (d); $[\alpha]_D + 33.5°$ (*c* 0.4, $CHCl_3$); for ^1H and ^{13}C NMR data see Tables 2 and 3. Anal Calcd for $C_{32}H_{33}NO_8$: C, 68.68; H, 5.94; N, 2.50. Found: C, 68.90; H, 5.84; N, 2.65.

2,4,6-Tri-O-*benzoyl-α*-D-*glucopyranose* (**16**).—To a solution of **9** (60 mg, 0.107 mmol) in 3:1 acetone–water (4.8 mL) was added Amberlite IR-120 (H^+) resin (240 mg). The suspension was stirred at rt for 24 h, filtered and the filtrate evaporated to dryness. The amorphous residue crystallized (51 mg, 96.6%) from toluene; examination by TLC on silica gel (solvent C) showed two spots having R_f 0.48 and 0.42. The relative intensities of the C-1 resonance signals in the ^{13}C NMR spectrum indicated that this product was a 7:2 mixture of α and β anomers. Two recrystallizations from benzene gave **16**: mp 122–124 °C, lit 124–126 °C [8]; $[\alpha]_D + 78.9°$ (*c* 0.3, EtOH), lit $+81.6°$ [8]; R_f 0.48 (silica gel, solvent C); ^1H NMR data: δ 5.63 (d, $J_{1,2}$ 3.5 Hz, H-1), 5.13 (dd, $J_{2,3}$ 9.9 Hz, H-2), 4.51 (t, $J_{3,4}$ 9.5 Hz, H-3), 5.42 (t, $J_{4,5}$ 9.5 Hz, H-4), 4.61 (m, H-5), 4.42 (dd, $J_{5,6}$ 4.0, $J_{6,6'}$ −11.5 Hz, H-6), 4.65 (dd, $J_{5,6'}$ 2.6 Hz, H-6′), 7.25–8.11 (15 H, Ph), 2.60 and 3.05 (2 bs, 2 OH, disappeared on deuteration); ^{13}C NMR data: δ 90.53 (C-1), 74.23 (C-2), 69.97 (C-3), 72.21 (C-4), 67.57 (C-5), 63.09 (C-6), 128.34–133.62 (Ph), 166.21 (× 2), 166.32 (3 *C*OPh).

N-*(2,3,6-Tri*-O-*benzoyl-β*-D-*glucopyranosyl)-piperidine* (**8**).—Evaporation of fractions 42–60 afforded a crystalline residue (8.36 g) which was dissolved in Et_2O (140 mL) and precipitated by adding ligroin (140 mL); crystals were obtained (6.16 g, 44.1%); R_f 0.24 (alumina, solvent A). A further recrystallization from the same solvent mixture gave **8**: mp 151–152 °C (d); $[\alpha]_D + 67.3°$ (*c* 0.5, $CHCl_3$); for ^1H and ^{13}C NMR data see Tables 2 and 3. Anal Calcd for $C_{32}H_{33}NO_8$: C, 68.68; H, 5.94; N, 2.50. Found: C, 68.59; H, 5.76; N, 2.72.

2,3,6-Tri-O-*benzoyl-α*-D-*glucopyranose* (**15**).—To a solution of **8** (600 mg, 1.07 mmol) in 3:1 acetone–water (48 mL) was added Amberlite IR-120 (H^+) resin (2.4 g). The suspension was stirred at rt for 24 h, filtered and the

filtrate evaporated to dryness. The amorphous residue crystallized (501 mg, 95%) from toluene; examination by TLC on silica gel (solvent C) showed two spots having R_f 0.44 and 0.38. The relative intensities of the C-1 resonance signals in the ^{13}C NMR spectrum of the product revealed that it was a 7:3 mixture of α and β anomers. Four recrystallizations from 1:1 Et_2O–ligroin gave **15**, mp 165–166 °C; $[\alpha]_D + 141.3°$ (*c* 0.5, $CHCl_3$); R_f 0.44 (silica gel, solvent C); ^1H NMR data: δ 5.66 (d, $J_{1,2}$ 3.5 Hz, H-1), 5.27 (dd, $J_{2,3}$ 10.1 Hz, H-2), 5.89 (t, $J_{3,4}$ 9.7 Hz, H-3), 3.91 (m, $J_{4,5}$ 9.9, $J_{4,OH}$ 4.3 Hz, H-4; triplet on deuteration), 4.39 (m, H-5), 4.77 (dd, $J_{5,6}$ 3.7, $J_{6,6'}$ −12.1 Hz, H-6), 4.63 (dd, $J_{5,6'}$ 1.9 Hz, H-6′), 7.25–8.09 (15 H, Ph), 3.53 and 3.80 (2 bs, 2 OH, disappeared on deuteration); ^{13}C NMR data: δ 90.57 (C-1), 71.76 (C-2), 73.46 (C-3), 69.63 (C-4), 70.23 (C-5), 63.43 (C-6), 128.40–133.36 (Ph), 165.96, 167.02, 167.35 (3 *C*OPh). Anal. Calcd for $C_{27}H_{24}O_9$: C, 65.85; H, 4.91. Found: C, 66.08; H, 5.15.

N-*(4-O-Acetyl-2,3,6-tri-O-benzoyl-β-D-glucopyranosyl)piperidine* (**11**).—Compound **8** (300 mg, 0.54 mmol) was dissolved in pyridine (0.6 mL) and treated with Ac_2O (0.3 mL, 3.18 mmol) at 0 °C. The solution was kept for 3 days in a refrigerator and then evaporated in vacuo over H_2SO_4 and KOH. The resulting crystalline residue was recrystallized from MeOH to give **11** (194 mg, 60%): mp 181–182 °C (d); $[\alpha]_D + 95.1°$ (*c* 0.5, $CHCl_3$); for ^1H and ^{13}C NMR data see Tables 2 and 3. Anal. Calcd for $C_{34}H_{35}NO_9$: C, 67.89; H, 5.82; N, 2.33. Found: C, 67.69; H, 6.00; N, 2.50.

N-*(2,3,4,6-Tetra-O-benzoyl-β-D-glucopyranosyl)piperidine* (**10**).—A solution of **8** (3.5 g, 6.26 mmol) in pyridine (14 mL) was cooled to 0 °C and benzoyl chloride (2.1 mL, 18.09 mmol) was slowly added. The mixture was kept for 3 days in a refrigerator and then poured into ice-cold 5% aq $NaHCO_3$ (70 mL). After being kept for 1 h with occasional shaking until evolution of gas ceased, the mixture was extracted with $CHCl_3$ (3 × 70 mL). The organic extract was washed with water (2 × 70 mL), dried (Na_2SO_4), and evaporated to a syrup that failed to crystallize. Examination by TLC (alumina, solvent A), revealed the presence of a major component, R_f 0.70. Chromatographic purification on a dry-column of alumina with 17:3 hexane–EtOAc as the eluent gave **10** (2.99 g, 72%), which crystallized from 1:1 Et_2O–ligroin: mp 148–149 °C (d); $[\alpha]_D + 36.7°$ (*c* 0.5, $CHCl_3$); for ^1H and ^{13}C NMR data see Tables 2 and 3. Anal. Calcd for $C_{39}H_{37}NO_9$: C, 71.00; H, 5.04; N, 2.12. Found: C, 70.97; H, 5.33; N, 2.01.

Preparation of 2,3,4,6-tetra-O-benzoyl-α-D-glucopyranose (**17**).—Compound **10** (2.4 g, 3.62 mmol) was suspended in 2:1 acetone–water (80 mL) and Amberlite IR-120 (H^+) resin (10 g) was added. The mixture was stirred at 50 °C for 1 h and then at rt for 24 h. The suspension was filtered and the filtrate evaporated to dryness. The amorphous residue crystallized (2.1 g, 97%) from 1:1 Et_2O–ligroin; examination by TLC on silica gel (solvent B) showed two spots having R_f 0.40 and 0.33. Integration of the ^1H NMR spectrum in the region of the H-3 resonance signals revealed that the product was a 4:1 mixture of α and β anomers. Recrystallization from ligroin gave **17** (1.38 g, 64%): mp 118–120 °C, lit 117–120 °C [9]; $[\alpha]_D + 74.9°$ (*c* 0.5, $CHCl_3$), lit + 72.4° [9]; R_f 0.40 (silica gel, solvent B); ^1H NMR data: δ 5.72 (d, $J_{1,2}$ 3.5 Hz, H-1), 5.30 (dd, $J_{2,3}$ 10.2 Hz, H-2), 6.28 (t, $J_{3,4}$ 9.9 Hz, H-3), 5.72 (t, $J_{4,5}$ 9.8 Hz, H-4), 4.69 (m, H-5), 4.48 (dd, $J_{5,6}$ 4.5, $J_{6,6'}$ −12.1 Hz, H-6), 4.63 (dd, $J_{5,6'}$ 3.1 Hz, H-6′), 7.25–8.08 (20 H, Ph), 3.90 (bs, OH, disappeared on deuteration); ^{13}C NMR data: δ 90.53 (C-1), 72.44 (C-2), 70.44 (C-3), 69.69 (C-4), 67.76 (C-5), 63.03 (C-6), 128.38-133.38 (Ph), 165.25, 165.89 (× 2), 166.37 (4 *C*OPh).

Reaction of **17** *with piperidine. Adduct of 2,3,4,6-tetra-O-benzoyl-D-glucopyranose and piperidine*.—Compound **17** (596 mg, 1 mmol) was suspended in dry Et_2O (10 mL) and piperidine (0.6 mL, 6 mmol) was added. The resulting solution was kept at rt; after a few minutes crystallization began. The reaction mixture was cooled to 0 °C and the crystals deposited were filtered off (595 mg, 87.4%): mp 101–103 °C (d); $[\alpha]_D + 56.7°$ (*c* 0.5, $CHCl_3$). The ^1H NMR spectrum revealed that the product was a 1:1 adduct of 2,3,4,6-tetra-*O*-benzoyl-D-glucopyranose and piperidine; integration of the H-3 signals showed that the tetrabenzoate was present in the adduct as a

4:1 mixture of α and β anomers. The N–H signal of piperidine was shifted in the adduct from δ 1.40 to 3.90 and appeared as a broad singlet superimposed with the HO–C-1 signal of the tetrabenzoate. Anal. Calcd for $C_{39}H_{39}NO_{10}$: C, 68.72; H, 5.73; N, 2.06. Found: C, 68.57; H, 6.01; N, 1.80.

The reaction was repeated under the same conditions with a further amount (596 mg) of **17**. The crystalline precipitate formed was not separated, and the reaction mixture was kept with stirring for 6 days at rt, solution being attained after about 4 days. Evaporation of the solution afforded a thick dark yellow syrup (823 mg); it was dissolved in Et_2O (10 mL) and extracted with water (4 × 2 mL). On acidifying the aq extract with concd HCl and cooling to 0 °C, 109 mg of benzoic acid were obtained: mp 122–123 °C.

The organic layer was evaporated to a syrup (527 mg). Examination by TLC on alumina (solvent A) showed the presence of compounds **8** (R_f 0.24), **9** (R_f 0.34), **10** (R_f 0.70), and traces of *N*-benzoylpiperidine (R_f 0.48). Chromatographic separation of the syrup was performed as described for the analogous reaction of **1** with piperidine. Crystallization of the products isolated from 1:1 Et_2O–ligroin gave **8** (300 mg, 53.7%), mp 152–153 °C (d), **9** (13 mg, 2.3%), mp 178–180 °C (d), and **10** (8 mg, 1.2%), mp 147–148 °C (d). They were identified by comparison with authentic samples.

Treatment of **8**, **9**, *and* **10** *with piperidine–ether.*—Samples (10 mg) of each compound were separately dissolved in 1:9 (v/v) piperidine–Et_2O (0.5 mL). The solutions were stored at rt for 6 days and then evaporated in vacuo. The resulting residues were examined by TLC on alumina (solvent A). Starting from **8** or **9** indistinctly, the reaction mixture showed two spots: a main spot having R_f 0.24 (compound **8**) and a minor one having R_f 0.34 (compound **9**). Starting from **10**, the reaction mixture showed only one spot having R_f 0.70 (compound **10**).

Reaction of 3,4,6-tri-O-*benzoyl*-α-D-*glucopyranose* (**18**) *with piperidine.*—Compound **18** (197 mg, 0.2 mmol), mp 165–167 °C, $[\alpha]_D + 55°$ (*c* 0.5, EtOH) [8] was dissolved in dry Et_2O (4 mL) and piperidine (0.24 mL, 2.4 mmol) was added. The reaction mixture was stirred for a few minutes until dissolution of the crystalline precipitate initially formed. The solution was stored for 3 days at rt and then evaporated to a dark-yellow syrup (224 mg). Examination by TLC on alumina (solvent A) revealed the presence of compounds **8** (R_f 0.24) and **9** (R_f 0.34). Chromatographic separation of the syrup on a dry-column of alumina using 4:1 hexane–EtOAc as the eluent, followed by crystallization from 1:1 Et_2O–ligroin gave **8** (118 mg, 52.7%), mp 150–152 °C (d), and **9** (4 mg, 1.8%), mp 176–178 °C (d). They were identified by comparison with authentic samples.

Preparation of labeled 1,2,3,4,6-penta-O-*benzoyl*-D-*glucopyranoses*

2,3,4,6-tetra-O-*benzoyl-1*-O-*[*carbonyl-^{14}*C]-benzoyl*-α-D-*glucopyranose* (**2**). A solution of **17** (2 g, 3.36 mmol) in pyridine (8 mL) was cooled to −20 °C and Ph[^{14}C]COCl (1.2 mL, 10.34 mmol; activity 1.71×10^5 dpm/mmol) was slowly added. The mixture was kept for 3 days in a refrigerator and then poured into ice-cold 5% aq $NaHCO_3$. After standing overnight in the refrigerator, the solid deposited was pulverized, filtered off, washed with water, soaked in MeOH and dried. After three recrystallizations from 3:1 MeOH–acetone a pure product was obtained having mp 191–192 °C; $[\alpha]_D + 137.4°$ (*c* 0.5, $CHCl_3$), in agreement with the values reported in the lit for the α anomer [20]; activity 1.67×10^5 dpm/mmol.

1,2,3,6-Tetra-O-*benzoyl-4*-O-*[*carbonyl-^{14}*C]-benzoyl*-β-D-*glucopyranose* (**3**), *1,2,3,4-tetra*-O-*benzoyl-6*-O-*[*carbonyl-^{14}*C]benzoyl*-β-D-*glucopyranose* (**4**), *and 4,6-di*-O-*benzoyl-1,2,3-tri*-O-*[*carbonyl-^{14}*C]benzoyl*-β-D-*glucopyranose* (**5**). Compounds **3**, **4**, and **5** were prepared as described by Gros et al. [23]. Compound **3** had mp 165–167 °C; $[\alpha]_D + 23.3°$ (*c* 0.5, $CHCl_3$); activity 4.15×10^6 dpm/mmol; calcd activity after isotopic dilution with **1**, 6.63×10^5 dpm/mmol. Compound **4** had mp 161–163 °C; $[\alpha]_D + 21.8°$ (*c* 0.5, $CHCl_3$); activity 4.30×10^6 dpm/mmol; calcd activity after isotopic dilution with **1**, 8.59×10^5 dpm/mmol. Compound **5** had mp 166–168 °C; $[\alpha]_D + 20.2°$ (*c* 0.5, $CHCl_3$); activity 3.99×10^6 dpm/mmol; activity per labeled benzoyl group 1.33×10^6 dpm/mmol.

2,6-Di-O-benzoyl-1,3,4-tri-O-[carbonyl-^{14}C]-benzoyl-α-D-glucopyranose (**6**). Compound **6** was prepared from 2,6-di-*O*-benzoyl-α-D-glucopyranose [24] (2 g, 5.15 mmol) by benzoylation with Ph[^{14}C]COCl (4.5 mL, 38.76 mmol; activity 1.10×10^6 dpm/mmol) and pyridine (10 mL), in the same conditions employed for the preparation of **2**. The product obtained had mp 190–191 °C; $[\alpha]_D + 135.2°$ (*c* 0.5, $CH\text{-}Cl_3$); activity 3.30×10^6 dpm/mmol; activity per labeled benzoyl group 1.10×10^6 dpm/mmol.

Reaction of **2**, **3**, **4**, **5**, *and* **6** *with piperidine.*—The labeled compound (350 mg, 0.5 mmol) was suspended in dry Et_2O (5 mL) and piperidine (0.5 mL, 3 mmol) was added. The mixture was stirred for 6 days at rt; the isolation of **8**, *N*-benzoylpiperidine, and benzoic acid was carried out as described for the reaction of **1** with piperidine. The yields of the labeled products were in all cases similar to those reported for the unlabeled ones. Compound **8** and benzoic acid were recrystallized to constant specific activity. *N*-benzoylpiperidine failed to crystallize; further purification was accomplished by dry-column chromatography on alumina with 9:1 hexane–EtOAc as the eluent. The resulting chromatographically homogeneous syrup, R_f 0.48 (alumina, solvent A), was dried at rt/0.13 Pa before measuring the activity.

Compound **2** gave **8**, activity 0.03×10^5 dpm/mmol; *N*-benzoylpiperidine, activity 1.43×10^5 dpm/mmol; benzoic acid, activity 0.07×10^5 dpm/mmol. Compound **3** gave **8**, activity 6.62×10^5 dpm/mmol; *N*-benzoylpiperidine, activity 0.09×10^5 dpm/mmol; benzoic acid, activity 0.69×10^5 dpm/mmol. Compound **4** gave **8**, activity 8.54×10^5 dpm/mmol; *N*-benzoylpiperidine, activity 0.51×10^5 dpm/mmol; benzoic acid, activity 0.11×10^5 dpm/mmol. Compound **5** gave **8**, activity 1.33×10^6 dpm/mmol; *N*-benzoylpiperidine, activity 1.23×10^6 dpm/mmol; benzoic acid, activity 1.18×10^6 dpm/mmol. Compound **6** gave **8**, activity 2.20×10^6 dpm/mmol; *N*-benzoylpiperidine, activity 0.97×10^6 dpm/mmol; benzoic acid, activity 0.28×10^6 dpm/mmol.

Reaction of 1,2,3,4,6-penta-O-acetyl-β-D-glucopyranose (**7**) *with piperidine under crystallizing conditions.* N-*(3,4,6-tri-O-acetyl-β-D-glucopyranosyl)piperidine* (**12**).—Compound **7** (10 g, 25 mmol) was suspended in dry Et_2O (25 mL) and piperidine (10 mL, 100 mmol) was added. The mixture was stirred for 20 min at rt until complete dissolution of **7**. Hexane (15 mL) was added, and the homogeneous mixture was kept in a refrigerator overnight. The crystalline precipitate that slowly formed was filtered off, washed by stirring it with absolute EtOH (40 mL) and dried to give **12** (3.10 g, 33.2%): mp 136–137 °C (d) (browning from 130 °C), lit 125 °C (d) [2]; $[\alpha]_D + 34.6°$ (*c* 0.5, $CHCl_3$), lit $+31.6°$ [2]; R_f 0.23 (alumina, solvent B); for ^{1}H NMR data see Table 2.

The filtrate and washings were combined and evaporated to a dark-yellow liquid residue (12.98 g). Examination by TLC on alumina (solvent B) showed four spots, R_f 0.83, 0.52, 0.32, and 0.07. The residue was dissolved in Et_2O (100 mL) and extracted with water (5×20 mL); piperidinium acetate (R_f 0.07) and most of the *N*-acetylpiperidine (R_f 0.52) were thus removed. The ether layer was evaporated to a syrup (5.02 g); TLC of the residue showed the presence of a major component (R_f 0.32), a minor one (R_f 0.83), and traces of *N*-acetylpiperidine (R_f 0.52). The syrup was chromatographed on a dry-column of alumina (300 g); elutions were performed by using hexane with increasing concentrations of EtOAc. Fractions (100 mL each) were collected, and monitored by TLC. Elution with 3:1 hexane–EtOAc afforded the product having R_f 0.83 (fractions 12–14), and a 13:7 mixture of the same solvents eluted the component having R_f 0.32 (fractions 29–36).

N-*(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)piperidine* (**14**).—Evaporation of fractions 12–14 gave a solid residue (52 mg, 0.5%), which crystallized from 1:1 Et_2O–ligroin yielding **14**: mp 122–123 °C, lit 123 °C [25]; $[\alpha]_D - 3.5°$ (*c* 0.5, $CHCl_3$), lit $-3.5°$ [25]; R_f 0.83 (alumina, solvent B); for ^{1}H NMR data see Table 2.

N-*(2,3,6-Tri-O-acetyl-β-D-glucopyranosyl)-piperidine* (**13**).—Evaporation of fractions 29–36 afforded a colorless amorphous solid

(168 mg, 1.8%), R_f 0.32 (alumina, solvent B); by dissolving it in Et_2O (2.5 mL) and adding ligroin (2.5 mL) crystals of **13** were obtained: mp 127–128 °C (d) (browning from 125 °C); $[\alpha]_D - 24.8°$ (*c* 0.5, $CHCl_3$); for ^1H NMR data see Table 2. Anal. Calcd for $C_{17}H_{27}NO_8$: C, 54.69; H, 7.24; N, 3.75. Found: C, 54.72; H, 7.38; N, 3.74.

The rest of the chromatographed material was retained in the column and could not be eluted even with EtOAc, presumably due to alteration when brought into contact with the adsorbent.

Reaction of **7** *with piperidine under homogeneous conditions.*—Compound **7** (4 g, 10 mmol) was suspended in dry Et_2O (100 mL) and piperidine (4 mL, 40 mmol) was added. The mixture was stirred until complete dissolution of **7** and kept at rt for 5 days. It was then evaporated to a dark-yellow liquid residue (6.4 g), which on examination by TLC (alumina, solvent B) revealed the presence of compounds **13** (R_f 0.32), **14** (R_f 0.83), *N*-acetylpiperidine (R_f 0.52), and piperidinium acetate (R_f 0.07). The residue was processed and chromatographed as described for the previous reaction of **7** with piperidine. Crystallization of the products isolated from 1:1 Et_2O–ligroin gave **13** (152 mg, 4.1%), mp 126–127 °C (d), and **14** (12 mg, 0.3%), mp 121–122 °C, identical with authentic samples.

Treatment of **12**, **13**, *and* **14** *with piperidine–ether.*—Samples (10 mg) of each compound were separately treated with 1:9 (v/v) piperidine–Et_2O (0.5 mL). As compound **12** remained insoluble, the reaction mixture was stirred for 2 days until complete dissolution of **12**. The solutions were stored at rt for 6 days and then evaporated in vacuo. The resulting residues were examined by TLC on alumina (solvent B). Starting from **12** or **13** indistinctly, the reaction mixture showed spots having R_f 0.32 (compound **13**), R_f 0.52 (*N*-acetylpiperidine), and $R_f \approx 0$. Starting from **14**, the reaction mixture showed spots having R_f 0.83 (compound **14**), R_f 0.52 (*N*-acetylpiperidine), and $R_f \approx 0$. The spots with $R_f \approx 0$ were not investigated.

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References

[1] H. Vogel, *Ber. Dtsch. Chem. Ges.*, 70 (1937) 1193–1202.
[2] J.E. Hodge, C.E. Rist, *J. Am. Chem. Soc.*, 74 (1952) 1498–1500.
[3] B. Lindberg, O. Theander, M.S. Feather, *Acta Chem. Scand.*, 20 (1966) 206–210.
[4] R.M. Rowell, M.S. Feather, *Carbohydr. Res.*, 4 (1967) 486–491.
[5] A. Klemer, G. Drolshagen, H. Lukowski, *Ber. Dtsch. Chem. Ges.*, 96 (1963) 634–635.
[6] Z. Smiatacz, *Carbohydr. Res.*, 38 (1974) 117–123.
[7] K. Bock, C. Pedersen, *Adv. Carbohydr. Chem. Biochem.*, 41 (1983) 27–66.
[8] A.E. Salinas, J.F. Sproviero, V. Deulofeu, *Carbohydr. Res.*, 170 (1987) 71–99.
[9] J.G. Douglas, J. Honeyman, *J. Chem. Soc.*, (1955) 3674–3681.
[10] M. Vincendon, *Bull. Soc. Chim. Fr.*, (1973) 3501–3511.
[11] S.J. Angyal, Conformations of sugars, in W. Pigman, D. Horton (Eds.), *The Carbohydrates, Chemistry and Biochemistry*, Vol. 1A, 2nd ed., Academic Press, New York, 1972, pp. 204–205.
[12] B. Helferich, W. Portz, *Bericht*, 86 (1953) 604–612.
[13] C.G. Casinovi, M. Framondino, G. Randazzo, F. Siani, *Carbohydr. Res.*, 36 (1974) 67–73.
[14] F. Brown, L. Hough, J.K.N. Jones, *J. Chem. Soc.*, (1950) 1125–1127.
[15] J. Gerstein, W.P. Jencks, *J. Am. Chem. Soc.*, 86 (1964) 4655–4663.
[16] G.J.F. Chittenden, J.G. Buchanan, *Carbohydr. Res.*, 11 (1969) 379–385.
[17] A.E. Salinas, Tesis, Facultad de Ciencias Exactas y Naturales, Universidad de Buenos Aires, 1983.
[18] L.D. Hall, J.F. Manville, *Carbohydr. Res.*, 4 (1967) 271–273.
[19] H. Schmid, K. Banholzer, *Helv. Chim. Acta*, 37 (1954) 1706–1716.
[20] R.K. Ness, H.G. Fletcher Jr., C.S. Hudson, *J. Am. Chem. Soc.*, 72 (1950) 2200–2203.
[21] P.A. Levene, G.M. Meyer, *J. Biol. Chem.*, 76 (1928) 513–519.
[22] C. Schotten, *Ber. Dtsch. Chem. Ges.*, 21 (1888) 2235–2254.
[23] E.G. Gros, M.A. Ondetti, J.F. Sproviero, V. Deulofeu, J.O. Deferrari, *J. Org. Chem.*, 27 (1962) 924–929.
[24] P. Brigl, H. Grüner, *Justus Liebigs Ann. Chem.*, 495 (1932) 60–83.
[25] J.E. Hodge, C.E. Rist, *J. Am. Chem. Soc.*, 74 (1952) 1494–1497.