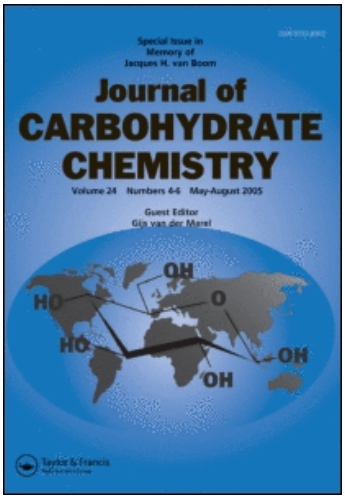

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Benzoyl Group Migrations in Methyl 2,3,6-Trio-*O*-Benzoyl-4-deoxy-4-(*N*-Hydroxyamino)-α-D-*Gluco* and α-D-*Galacto*-Pyranosides

Jean M. J. Tronchet[a]; Nicoletta Bizzozero[a]; Michel Geoffroy[b]
[a] Departments of Pharmaceutical Chemistry, [b] Physical Chemistry, University of Geneva, Geneva 4, Switzerland

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COMMUNICATION

BENZOYL GROUP MIGRATIONS IN METHYL 2,3,6-TRI-*O*-BENZOYL-4-DEOXY-4-(*N*-HYDROXYAMINO)-α-D-*GLUCO* AND α-D-*GALACTO*-PYRANOSIDES

Jean M. J. Tronchet,* Nicoletta Bizzozero* and Michel Geoffroy**

Departments of Pharmaceutical Chemistry* and of Physical Chemistry,** University of Geneva, 1211 Geneva 4 Switzerland

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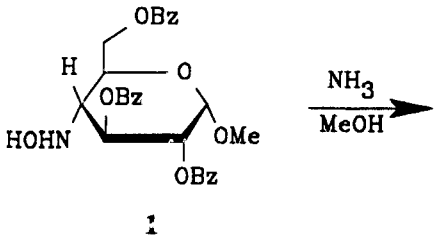
Deoxy-*N*-hydroxyaminosugars constitute a novel family of sugars. The interest in them is mainly due to their close structural similarity to natural sugars, coupled, with their easy oxidation to nitroxide free radicals, enabling their study by ESR spectroscopy.[1] From the point of view of their chemical reactivity, the hydroxyamino group is an ambident nucleophile possessing complex orbital and topographical factors, which direct its reactivity to either of its heteroatoms.

Upon ammonolysis (saturated methanolic solution of ammonia at 0°), both the *gluco* and *galacto* epimers[2] **1** and **2** gave rise to a 3 --> 4 migration of a benzoyl group but following different routes. The *gluco* epimer led mainly to the product of an *O*-3 --> *O*-4 migration **3** (33%), together with the formation of the two mono-di-*O*-benzoylated compounds **4** (8%) and **5** (14%). The structures of **3** - **5** were established by their elementary analysis and their



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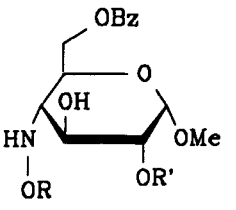
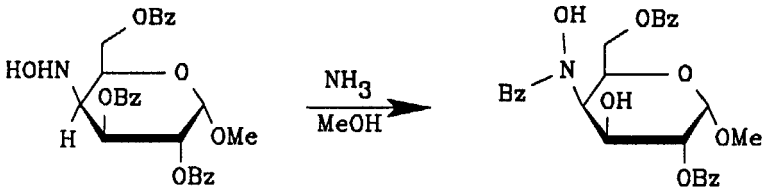


3 R = R' = Bz
4 R = H, R' = Bz
5 R = Bz, R' = H



2 6

spectroscopic data, particularly the chemical shifts in ^{1}H NMR of their H-2, H-3 and H-4 protons (TABLE).

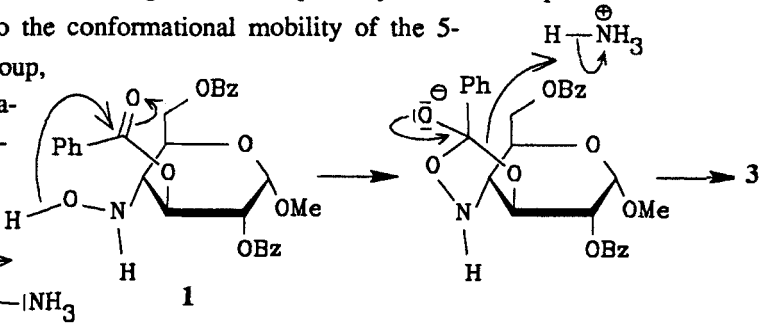
The *galacto* derivative **2** led to the hydroxamic acid **6** (44%) whose ^{1}H NMR at room temperature showed the expected peak broadening provoked by the hindered rotation of the CO-N bond. The chemical shifts of H-3 (5.90 ppm for **2**, *ca.* 4.50 for **6**) and H-4 (3.84 ppm for **2**, *ca.* 4.50 for **6**) were also in accordance with the proposed structure. The definitive confirmation of the structure of **6** was given by the ESR spectrum of the corresponding nitroxide free radical obtained from **6** by spontaneous oxidation in the air : an a_N hyperfine coupling of 7.4 G typical of *N*-acylnitroxides[3] and a small a_H coupling of 0.9 G indicating an almost eclipsed conformation with the C_4-H bond lying in the plane of the nitroxide group. This last hyperfine coupling was more than five times smaller than that of the unacylated radical derived from **2** (4.7 G).[2] This cannot be explained only by the delocalization of the impaired electrons onto the carbonyl group. More probably the increase in size provoked by benzoylation strongly favoured the eclipsed conformer.

Semi-empirical calculations[4] (AM1) on deoxy-*N*-hydroxyaminosugars have shown that the atomic orbital participating the most to the HOMO is a nitrogen orbital. In the

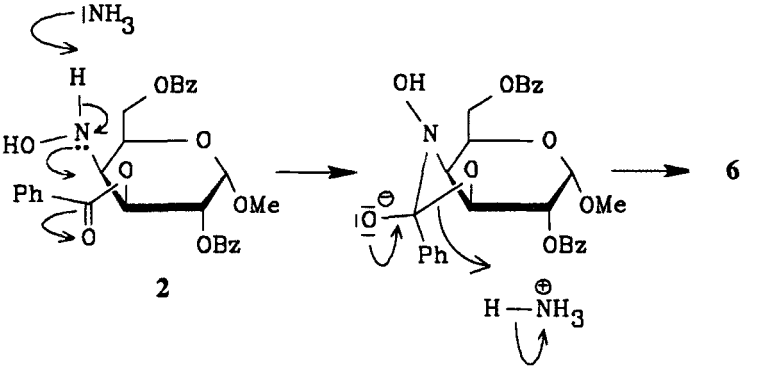
TABLE. Selected ^{1}H NMR Data of Compounds 1, 3, 4 and 5.

Compounds	H-2	H-3	H-4
1	5.40	6.05	2.99
3	5.09	4.33	3.33
4	5.01	4.60	2.88
5	3.65	3.88	3.19

galacto case, an attack through the nitrogen atom can lead to an unstrained *cis*-fused isoxazolidine intermediate leading to **6**. This pathway is, for entropic reasons pertaining to the conformational mobility of the 5-benzoyloxymethyl group, preferred to the formation of the perhydrooxazine corresponding to a transfer of the 6-*O*-benzoyl group.



In the *gluco* case, the *trans*-fused isoxazolidine pathway being impracticable, the reaction proceeded by an oxygen attack of the 3-*O*-benzoyl leading to **3** then probably to **4** and **5**. This reaction is more favourable, again for entropic reasons, than a nitrogen attack on the 6-*O*-benzoyl group. This points to the large flexibility in the reactivity of the hydroxyamino group.



EXPERIMENTAL

General procedures.[5] Optical rotations were measured in chloroform solutions.

Methyl 2,6-Di-*O*-benzoyl-4-(*N*-benzoyloxyamino)-4-deoxy-α-D-glucopyranoside (3). A solution of **1** (190 mg, 0.36 mmol) in methanol saturated with ammmonia (7 mL) was stirred at 0 °C for 1 h, concentrated, then extracted with dichloromethane (2x20 mL). The organic layer was washed (water, 10 mL), dried (magnesium sulfate), and concentrated to give after column chromatography (ethyl acetate/hexane 4:1) 63 mg of **3** (33%), 12 mg of **4** (8%), and 22 mg of **5** (14%): mp 59.7-60.8 °C; $[\alpha]_D^{22}$ +87.8° (*c* 0.8); $\nu_{max}^{CCl_4}$1720 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.05 (*broad s*, 1H, OH), 3.33 (*t*, 1H, $J_{3,4} = J_{4,5} = 10$ Hz, H-4), 3.42

(*s*, 1H, OMe), 4.33 (*m*, 2H, $J_{2,3}$ 10 Hz, $J_{5,6a}$ 7 Hz, $J_{5,6b}$ 3 Hz, H-5,3), 4.82 (*m*, 2H, 2H-6), 5.09 (*dd*, 1H, $J_{1,2}$ 4 Hz, H-2), 5.11 (*d*, 1H, H-1), 7.30-8.10 (*m*, 15H, Arom.), and 8.50 (*s*, 1H, NH). MS: *m/z* 412 (0.3), 369 (0.5), 323 (0.4), 235 (2), 191(4), 174 (6), 155 (7), 122 (32), 105 (100), 77 (41), and 51 (16).

Anal. Calcd for $C_{28}H_{27}NO_9$ (521.53): C, 64.49; H, 5.22; N, 2.69. Found: C, 64.25; H, 5.15; N, 2.70.

Methyl 2,6-Di-*O*-benzoyl-4-deoxy-4-hydroxyamino-α-D-glucopyranoside (4). Obtained as described for **3**: mp 66.1-67.8 °C; $[\alpha]_D^{23}$ +73.3° (*c* 0.15); ν_{max}^{CCl4} 3460 (OH+NH), and 1720 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.88 (*t*, 1H, $J_{3,4} = J_{4,5}$ = 10 Hz, H-4), 3.38 (*s*, 3H, OMe), 4.32 (*ddd*, 1H, $J_{5,6a}$ 5.2 Hz, $J_{5,6b}$ 2 Hz, H-5), 4.58 (*dd*, 1H, $J_{6a,6b}$ 12 Hz, H-6a), 4.60 (*t*, 1H, $J_{2,3}$ 10 Hz, H-3), 4.70 (*broad s*, 3H, OH and NHOH), 4.88 (*dd*, 1H, H-6b), 5.01 (*dd*, 1H, $J_{1,2}$ 3.5 Hz, H-2), 5.08 (*d*, 1H, H-1), and 7.35-8.15 (*m*, 10H, Arom.). MS: *m/z* 385 (1, M^{+} - MeOH), 235 (3), 207 (2), 192 (2), 174 (3), 122 (11), 105 (100), 77 (33), 59 (7), and 51 (9).

Anal. Calcd for $C_{21}H_{23}NO_8$ (417.42): C, 60.43; H, 5.55; N, 3.36. Found: C, 60.33; H, 5.64; N, 3.34.

Methyl 6-*O*-Benzoyl-4-deoxy-4-(*N*-benzoyloxyamino)-α-D-glucopyranoside (5). Obtained as described for **3**: mp 45.3-45.7 °C; $[\alpha]_D^{23}$ +80.6° (*c* 0.5); ν_{max}^{CCl4} 3350 (OH+NH), and 1720 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.19 (*t*, 1H, $J_{3,4} = J_{4,5}$ = 10 Hz, H-4), 3.45 (*s*, 3H, OMe), 3.65 (*dd*, 1H, $J_{2,3}$ 10 Hz, $J_{1,2}$ 3.5 Hz, H-2), 3.88 (*t*, 1H, H-3), 4.20 (*ddd*, 1H, H-5), 4.72 (*dd*, 1H, $J_{6a,6b}$ 12.5 Hz, $J_{5,6a}$ 4 Hz, H-6a), 4.80 (*dd*, 1H, $J_{5,6b}$ 3 Hz, H-6b), 4.83 (*d*, 1H, H-1), 7.20-8.10 (*m*, 10H, Arom), and 8.41 (*s*, 1H, NH). MS: *m/z* 385 (0.3, M^{+} - CH_3OH), 266 (0.4), 246 (0.7), 219 (0.5), 207 (0.3), 193 (1), 177 (0.7), 165 (3), 149 (3), 131 (2), 122 (40), 105 (100), 77 (42), 59 (9), and 51 (15).

Anal. Calcd for $C_{21}H_{23}NO_8$ (417.42): C, 60.43; H, 5.55; N, 3.36. Found: C, 60.29; H, 5.54; N, 3.44.

Methyl 2,6-Di-*O*-benzoyl-4-deoxy-4-(*N*-hydroxybenzamido)-α-D-galactopyranoside (6). A suspension of **2** (160 mg, 0.31 mmol) in methanol saturated with ammonia (5 mL), was stirred at 0 °C for 2 h, then it was concentrated and extracted with dichloromethane (50 mL). The organic layer was washed (water, 50 mL), dried (magnesium sulfate), and concentrated to give after column chromatography (hexane/ethyl acetate 1:1) 70 mg (44%) of **6**: mp 136.3-136.7 °C, $[\alpha]_D^{22}$ +72.4° (*c* 0.8); ν_{max}^{CCl4} 3400 (OH+NH), and 1730 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.08 (*s, exchangeable*, HO-3), 3.42 (*s*, 3H, OMe), 4.37 and 4.65 (*2m*, 5H, H-3,4,5 and 2H-6), 5.20 (*d*, 1H, $J_{1,2}$ 3 Hz, H-1), 5.77 (*dd*, 1H, $J_{2,3}$ 10 Hz, H-2), 7.45 (*m*, 9H, Arom), 8.00 (*m*, 6H, Arom), and 9.00 (*broad s*, 1H, NOH). MS: *m/z* 259 (0.03, M^{+} - 2PhCOOH - H_2O), 244 (0.3), 227 (0.1), 216 (0.2), 200 (0.3), 191 (0.1), 178 (0.6), 172 (0.2), 165 (0.06), 155 (0.4), 146 (0.2), 140 (0.9), 122 (27), 105 (100), 96 (0.06), 85 (0.1), 77 (2), 66 (1), 58 (3), and 51 (15).

Anal. Calcd for $C_{28}H_{27}NO_9$ (521.53): C, 64.49; H, 5.22; N, 2.69. Found: C, 64.47; H, 5.19; N, 2.85.

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