Dioxolanylium Ions Derived from Carbohydrates. X. Nucleophilic *trans* Opening with the Trichloroacetimidoyl Neighbouring Group

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Oxidation of 3,4-*O*-benzylidene-galactosan substituted with a trichloroacetimidoyl group at 0–2 gives a 3,4-fused 1,3-dioxolanylium ion which rearranges to a 2,3-fused 1,3-oxazoline of the *gulo* configuration, thus bringing about substitution with a nitrogen nucleophile at C-3. Hydrolysis of the resulting relatively stable cyclic trichloroacetimidate under different conditions is shown to give access to a number of selectively protected aminosugar derivatives as well as the free and peracylated compounds.

In a previous paper[1] in this series, it was demonstrated that an iminoester group situated in a *trans* vicinal position to a carbohydrate benzoxonium ion could participate in a rearrangement with the benzoxonium ion to give an oxazoline fused to the carbohydrate, and that the oxazoline could subsequently be hydrolyzed to an aminosugar derivative. Since the starting material was prepared by acylation of a benzylidene derivative of the carbohydrate with an imidoyl chloride, this approach was limited by the availability of stable imidoyl halides, i.e. to *N*-substituted derivatives, leading to the corresponding *N*-substituted aminosugars on hydrolysis. In view of the interest in the preparation of simple aminosugars, a way was sought to circumvent this limitation in the generality of the reaction.

The traditional iminoester synthesis, treatment of a nitrile with a concentrated solution of hydrogen halide in alcohol, is not directly applicable to carbohydrate benzylidene acetals because the long reaction time under strongly acidic conditions causes other reactions to take place within the carbohydrate moiety. In order to be able to use milder reaction conditions, a suitably reactive nitrile must be found which, in this context, means finding a nitrile with a sufficiently electronegative substituent to increase the polarity of the nitrile bond.

The first nitrile examined was cyanamide since it is known[2] that, in methanol solution, it can be converted into methyl isourea hydrochloride with a small excess of hydrogen chloride to that consumed by the cyanamide. However, all attempts at making cyanamide react with 1,6-anhydro-3,4-*O*-benzylidene-β-D-galactopyranose to give a 2-isourea derivative failed in spite of the great variety of conditions employed, including excess of cyanamide, catalysts (*p*-toluenesulfonic acid, hydrogen chloride, trifluoroacetic acid, copper(I) chloride,[3] sodium hydride), solvents (chloroform, tetrahydrofuran, dimethyl sulfoxide) and various temperatures (20–180 °C). The next nitrile examined was trichloroacetonitrile. Attachment of this compound to carbohydrates in the form of the 1-*O*-trichloroimidate has already been demonstrated by Schmidt and Michel,[4] and their procedure, which consists of treating the sodium salt of a hydroxy compound with trichloroacetonitrile, has been adopted with minor modifications. When 1,6-anhydro-3,4-*O*-benzylidene-β-D-galactopyranose and trichloroacetonitrile in tetrahydrofuran are treated with sodium hydride in the presence of a catalytic amount of imidazole, the

excess of trichloroacetonitrile can be reduced considerably, compared to Schmidt and Michel's 3–4-fold excess. The amount of sodium hydride can be reduced from a stoichiometric to a catalytic amount. This has the advantage that the formation of trichloroacetamide during the aqueous work-up is suppressed sufficiently to avoid contamination of the 1,6-anhydro-3,4-*O*-benzylidene-2-*O*-trichloroacetimidoyl-β-D-galactopyranose (*1*) with the highly crystalline trichloroactamide. This procedure gave an isolated yield of 82 % of *1*, but NMR spectrocopy indicated that the reaction was quantitative.

Oxidation of the iminoester *1* with trityl tetrafluoroborate in acetonitrile, in the manner previously used with success on other benzylidene-galactosan derivatives[1], proceeded rather slowly and gave complicated mixtures. When the oxidation was carried out, however, with *N*-bromosuccinimide using Hanessian-Hullar reaction conditions[5] a rapid reaction took place producing the oxazoline *5c* in 61 % yield. Since the only by-products formed in the reaction were hydroxybenzoates *3d* and *3e*, resulting from hydrolysis of the initially formed benzoxonium ion *2*, the yield was improved to 77 % by substitution of pyridine for barium carbonate to neutralize the hydrogen bromide generated, thus avoiding the formation of water during the reaction.

The easy isolation of the oxazoline *5c* by crystallization in this case is fortuitous. An alternative and more general procedure involves hydrolysis with aqueous base and isolation of the aminosugar as the peracetate *4b* or the hydrochloride *6*, although proceeding well, results in somewhat lower yields, 51 % and 49 %, respectively. Isolation of the iminoester *5c* by chromatography is possible but not very attractive because partial hydrolysis takes place even though the electronegative substitution makes this type of iminoester much more stable toward water than the benzimidates previously encountered.[1]

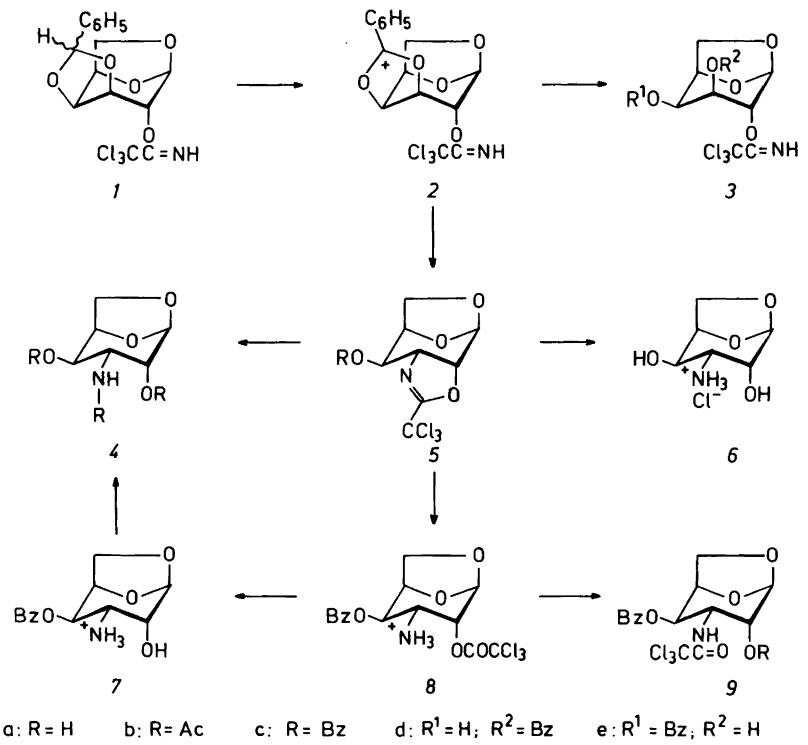
The comparative stability of the oxazoline *5c* makes it a useful type of derivative since it allows manipulations giving selective access to the two oxygen functionalities flanking the introduced nitrogen atom. Thus, treatment of *5c* with sodium methoxide in methanol gave the debenzoylated iminoester *5a*, while careful treatment with trifluoroacetic acid and water in chloroform solution yielded the ammonium salt *8*, which on neutralization during work-up, rearranged to the hydroxyamide *9a* isolated as the crystalline benzoate *9c*. When the hydroxyamide *9a* was treated with trifluoroacetic acid in deuteriochloroform, no reversion to the ammonium salt *8* was observed in the NMR spectrum after two weeks at room temperature. Prolonged hydrolysis of the oxazoline *5c* in trifluoroacetic acid/water gave the monobenzoate *7*, isolated as the crystalline tribenzoate *4c*.

Application of the reactions described above to other carbohydrate derivatives are discussed below; moreover, while this work was in progress, reports have appeared on the use of a trichloroacetimidoyl neighbouring group in other contexts, *e.g.* in epoxide-opening reactions[6] and in iodocyclization reactions.[7–11]

Experimental

Thin layer chromatography (TLC) was performed on silica gel PF_{254} (Merck). For preparative work, 1 mm layers were used on 20×40 cm plates. Melting points were uncorrected. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. ^1H NMR spectra were recorded on a Bruker HXE 90 instrument and ^{13}C NMR spectra on a Bruker WH 90 instrument. All NMR spectra were measured in deuteriochloroform unless otherwise specified. IR spectra were recorded in KBr on a Perkin-Elmer 421 grating spectrometer.

*1,6-Anhydro-3,4-*O*-benzylidene-2-*O*-trichloroacetimidoyl-β-D-galactopyranose* (1). To 1,6-anhydro-3,4-*O*-benzylidene-β-D-galactopyranose[7] (epimeric mixture, *exo*/*endo*-H ~9:1, 10.0 g) suspended in THF (100 ml), was added trichloroacetonitrile (5.0 ml) and imidazole (68 mg). The suspension was cooled to 0 °C, at 50 % sodium hydride suspension in mineral oil (200 mg) was added and the reaction mixture stirred for 5 min at 0 °C and 5 min at 20 °C, during which period, the benzylidene galactosan gave a solution which subsequently deposited a white precipitate. The reaction mixture was poured into 200 ml of $CHCl_3$, 500 ml of ice water and a small amount of sodium hydrogen carbonate. The organic layer was separated, washed with water, dried (Na_2SO_4) and evaporated to give 15.8 g of crude *1*, m.p. 158–170 °C. Recrystallization from ethyl acetate (80 ml) gave 13.0 g (82 %) of *1*, m.p. 161–170 °C, anal. $C_{15}H_{16}NO_5Cl_3$: C,H,N,Cl. ^1H



NMR: δ 5.61 (H1), 5.21 (H2), 4.31 (H3), 4.6–4.7 (H4,H5), 4.17 (H6), 3.57 (H6'), 5.87 (ArCH), 8.62 (NH); J_{12}, J_{23}, $J_{56} < 1$ Hz, $J_{66'} = 7.6$. ^{13}C NMR: δ 98.1 (C1), 75.0 (C3), 74.7, 72.0 (C2,C5), 69.2 (C4), 63.3 (C6), 161.2 (C=NH), 90.6 (CCl_3), 102.9 (ArCH). IR: 1660 cm^{-1} (C=NH).

3-Amino-1,6-anhydro-4-O-benzoyl-3-deoxy-β-D-*gulopyranose 2O,3N-trichloroacetimidate* (5c).

NBS + $BaCO_3$ method: From 10 g of barium carbonate suspended in 70 ml of tetrachloromethane, were distilled 20 ml of the solvent to remove traces of water. The iminoester *1* (1.00 g) was added, followed by *N*-bromosuccinimide (NBS, 542 mg) and the reaction mixture was refluxed for 15 min under vigorous stirring, filtered while hot, and the residue washed twice with chloroform. The combined filtrates were evaporated to dryness, and redissolved in water and ether. The organic phase was separated, washed with water, dried (Na_2SO_4), evaporated to dryness and crystallized from ether/pentane to give 603 mg of *5c*, m.p. 164–165 °C. Recrystallization from ethyl acetate/hexane raised the m.p. to 166–167 °C, anal. $C_{15}H_{12}NO_5Cl_3$: C,H,N,Cl, $[\alpha]_D^{20}$ + 113° (*c* 3.3, $CHCl_3$). ^1H NMR: δ 5.80 (H1), 4.74 (H2), 4.63 (H3), 5.18 (H4), 4.96 (H5), 4.11 (H6), 3.78 (H6'); $J_{12} < 1$ Hz, $J_{23} = 9.1$, $J_{34} = 4.2$, $J_{45} = 6.0$, $J_{56} = 1.2$, $J_{56'} = 5.1$, $J_{66'} = 8.1$. ^{13}C NMR: δ 97.6 (C1), 81.4 (C2), 65.3 (C3), 72.1 (C4), 70.0 (C5) 62.9 (C6), 85.9 (CCl_3). IR: 1653 cm^{-1} (C=N), 1712 (C=O). Preparative TLC (ether/pentane 1:1) of the original mother liquors gave recovered *1* (59 mg) followed by *5c* (26 mg) and a much slower moving fraction (134 mg), presumably containing the hydroxybenzoates *3d* and *3e* (resulting from hydrolysis of the initially formed benzoxonium ion *2*) since reflux with sodium hydroxide (80 mg) in methanol/water (1 ml), for 2 h and evaporation to dryness gave 1,6-anhydrogaloctopyranose and sodium benzoate as seen from a ^{13}C NMR spectrum.

NBS + pyridine method: To finely powdered *1* (5.00 g) and pyridine (1.22 ml) in dry tetrachloromethane (250 ml) was added NBS (2.71 g). The reaction mixture was refluxed for 1 h under vigorous stirring, evaporated to dryness, dissolved

in chloroform, and washed with water containing a small amount of sodium hydrogen carbonate and sodium sulfite, dried ($MgSO_4$), evaporated to dryness, and crystallized from ether (30 ml)/pentane (30 ml) to give 3.86 g (77 %) of *5c*, m.p. 163–166 °C. Recrystallization from ethyl acetate (20 ml)/hexane (30 ml) gave 3.12 g of *5c*, m.p. 165–166 °C.

*1,6-Anhydro-2,4-di-*O*-benzoyl-3-deoxy-3-trichloroacetamido-β-*D*-gulopyranose* (9c).

From the imidate: 5c (500 mg) was dissolved in chloroform (10 ml) and stirred for 5 min at room temperature with 1 ml of trifluoroacetic acid/water (1:1). Addition of saturated aqueous sodium hydrogen carbonate, extraction with chloroform, drying over magnesium sulfate and evaporation to dryness gave 495 mg of crude 1,6-anhydro-4-*O*-benzoyl-3-deoxy-3-trichloroacetamido-β-D-gulopyranose (*9a*). ^{1}H NMR: δ 5.55 (H1), 3.93 (H2), 4.54 (H3), 5.34 (H4), 4.78 (H5), 4.32 (H6), 3.83 (H6′); J_{12} = 2.5 Hz, J_{23} = 4.1, J_{34} = 10.3, J_{45} = 3.9, $J_{56} < 1$, $J_{56'}$ = 5.0, $J_{66'}$ = 8.5, J_{3NH} = 8.6. ^{13}C NMR: δ 101.1 (C1), 72.2, 70.5, 69.6 (C2,C4,C5), 64.1 (C6), 49.9 (C3). Benzoylation with benzoyl chloride in pyridine gave 584 mg of *9c*, m.p. 188–193 °C. Preparative TLC (chloroform) and recrystallization from toluene gave 427 mg of *9c*, m.p. 193–194 °C, $[\alpha]_D^{20}$ + 167° (*c* 1.3, $CHCl_3$), anal. $C_{22}H_{18}NCl_3O$: C,H,N,Cl. ^{1}H NMR: δ 5.74 (H1), 5.39 (H2), 4.79 (H3), 5.53 (H4), 4.82 (H5), 4.37 (H6), 3.91 (H6′), 7.0 (NH); J_{12} = 2.2 Hz, J_{23} = 4.6, J_{34} = 10.5, J_{45} = 3.9, $J_{56} < 1$, $J_{56'}$ = 4.8, $J_{66'}$ = 8.2, J_{3NH} = 8.4. ^{13}C NMR: δ 98.8 (C), 72.6, 70.8, 70.0 (C2,C4,C5), 64.4 (C6), 48.9 (C3).

From the benzylidene compound: 1 (500 mg) was converted to the imidate *5c* with NBS and pyridine as described above. The crude syrup was hydrolysed and benzoylated as described in the preceding paragraph to give 630 mg of crude *9c*. Crystallization from ether gave 452 mg of *9c*, m.p. 188–192 °C, which on recrystallization from ethyl acetate/hexane gave 296 mg of *9c*, m.p. 191–193 °C.

*1,6-Anhydro-3-benzamido-2,4-di-*O*-benzoyl-3-deoxy-β-*D*-gulopyranose* (4c).

From the imidate: 5c (500 mg) was dissolved in trifluoroacetic acid (5 ml). Water (2.5 ml) was added and the solution left at room temperature overnight. Evaporation twice with 25 ml of water, redissolution in chloroform and drying with potassium carbonate gave after evaporation 225 mg of crude 3-amino-1,6-anhydro-4-*O*-benzoyl-3-deoxy-β-D-gulopyranose (*7*) as a glass. ^{1}H NMR: δ 5.53 (H1), 3.81 (H2), 3.25 (H3), 5.12 (H4), 4.66 (H5), 4.12 (H6), 3.73 (H6′); J_{12} = 2.1 Hz, J_{23} = 4.4, J_{34} = 9.7, J_{45} = 3.9, $J_{56} < 1$, $J_{56'}$ = 4.9, $J_{66'}$ = 7.8. ^{13}C NMR: δ 101.8 (C1), 74.0, 72.0, 70.7 (C2,C4,C5), 63.9 (C6), 49.3 (C3). Benzoylation with benzoyl chloride (0.5 ml) in pyridine (5 ml) gave 383 mg of *4c*. Crystallization from ethanol gave 286 mg of *4c*, m.p. 217–218 °C, $[\alpha]_D^{20}$ + 262° (*c* 1.1, $CHCl_3$), anal. $C_{27}H_{23}O_7N$: C,H,N. ^{1}H NMR: δ 5.74 (H1), 5.43 (H2), 5.13 (H3), 5.58 (H4), 4.81 (H5), 4.44 (H6), 3.90 (H6′), 6.41 (NH); J_{12} = 2.1 Hz, J_{23} = 4.4, J_{34} = 10.4, J_{45} = 3.8, $J_{56} < 1$, $J_{56'}$ = 4.8, $J_{66'}$ = 8.1, J_{3NH} = 8.6. ^{13}C NMR ($CDCl_3$–DMSO 4:1): δ 98.2 (C1), 71.4, 70.5, 69.0 (C2,C4,C5), 63.4 (C6), 45.8 (C3).

From the benzylidene compound: 1 (500 mg) was converted to the imidate *5c* as described above. The crude syrup was hydrolyzed and benzoylated as described in the preceding paragraph to give 288 mg of *4c*, which, on crystallization from ethanol, gave 191 mg of *4c*, m.p. 217–218 °C.

*1,6-Anhydro-3-acetamido-2,4-di-*O*-acetyl-3-deoxy-β-*D*-gulopyranose* (4b). The iminoester *5c* (500 mg) was refluxed with sodium hydroxide (250 mg) in methanol (10 ml)/water (10 ml) for 2 h, neutralized with hydrochloric acid (phenolphthalein), evaporated to dryness and twice evaporated with pyridine. Acetylation with acetic anhydride (2.5 ml) in pyridine (5 ml) gave 314 mg of crude *4b*. Crystallization from ethyl acetate/hexane gave 188 mg (51 %) of *4b*, m.p. 168–170 °C, $[\alpha]_D^{25}$ + 48° (*c* 1.3, $CHCl_3$), anal. $C_{12}H_{17}NO_7$: C,H,N. ^{1}H NMR: δ 5.53 (H1), 4.89 (H2), 4.59 (H3), 5.12 (H4), 4.48 (H5), 4.22 (H6), 3.76 (H6′), 5.69 (NH), 2.14, 2.08, 1.94 (OAc); J_{12} = 2.1 Hz, J_{23} = 4.5, J_{34} = 10.4, J_{45} = 3.9, J_{56} <1, $J_{56'}$ = 4.6, $J_{66'}$ = 8.1, J_{3NH} = 9.0. ^{1}C NMR: δ 98.5 (C1), 72.5, 71.3, 69.2 (C2, C4, C5), 64.2 (C6), 46.0 (C3).

*3-Amino-1,6-anhydro-3-deoxy-β-*D*-gulopyranose 2*O*,3*N*-trichloroacetimidate* (5a). *5c* (301 mg) was treated with sodium methoxide (10 drops, 1 M) in methanol (10 ml) for 3 h at 25 °C. The reaction mixture was diluted with water and extracted with chloroform (3×). The organic phases were washed with water, dried ($MgSO_4$) and evapor-

ated to dryness to give 193 mg of *5b*. Crystallization from ether gave 90 mg of *5b*, m.p. 167–170 °C (dec.), $[\alpha]_D^{25}$ + 57° (*c* 0.5, $CHCl_3$), anal. $C_8H_8NO_4Cl_3$: C,H,N,Cl. ^{1}H NMR: δ 5.70 (H1), 4.61 (H2), 4.27 (H3), 3.82 (H4), 4.48 (H5), 4.12 (H6), 3.76 (H6′); $J_{12} < 1$ Hz, $J_{23} = 9.1$, $J_{34} = 5.3$, J_{45}, $J_{56'} \sim 5.5$, $J_{56} = 1.0$, $J_{66'} = 8.1$.

3-Amino-1,6-anhydro-3-deoxy-β-D-gulopyranose hydrochloride (6). The iminoester *5c* (1.00 g) was refluxed with sodium hydroxide (500 mg) in methanol (20 ml)/water (20 ml) for 2 h. To the reaction mixture, was added ion exchange resin IR 120 (H^+) (10 ml). After stirring for 15 min, the slurry was poured onto a column containing a further 20 ml of the same resin. The column was eluted with water (200 ml) until neutral, then with 2.5 % aqueous ammonia (200 ml). The last eluate was evaporated to dryness, dissolved in water, treated with activated charcoal, acidified with hydrochloric acid (methyl red), and evaporated to dryness yielding 460 mg of crude *6*. Crystallization from water (1 ml)/ethanol (25 ml) gave 245 mg (49 %) of *6*, m.p. 230 °C (dec.), $[\alpha]_D^{25}$ + 49° (*c* 1.6, H_2O), anal. $C_6H_{12}NO_4Cl$: C,H,N,Cl. ^{1}H NMR (D_2O): δ 5.45 (H1), 3.99 (H2), 3.38 (H3), 4.05 (H4), 4.58 (H5), 4.10 (H6), 3.72 (H6′); $J_{12} = 2.4$ Hz, $J_{23} = 4.5$, $J_{34} = 10.2$, $J_{45} = 4.5$, $J_{56} < 1$, $J_{56'} = 4.9$, $J_{66'} = 8.4$. ^{13}C NMR (D_2O): δ 101.2 (C1), 75.3, 67.6, 66.4 (C2,C4,C5), 64.0 (C6), 52.3 (C3).

3-Amino-1,6-anhydro-4-O-benzoyl-3-deoxy-2-O-trichloroacetyl-β-D-gulopyranose salt with trifluoroacetic acid (8). *5c* (20 mg) was dissolved in deuteriochloroform (0.5 ml). Addition of trifluoroacetic acid (3 dr) caused only very slight changes in the ^{1}H NMR spectrum of *5c*, but on addition of deuterium oxide (1 dr) instantaneous hydrolysis to *8* took place. ^{1}H NMR: δ 5.84 (H1), 5.40 (H2), 4.38 (H3), 5.68 (H4), 4.92 (H5), 4.38 (H6), 3.94 (H6′); $J_{12} = 2.0$ Hz, $J_{23} = 4.6$, $J_{34} = 10.1$, $J_{45} = 4.0$, $J_{56} < 1$, $J_{56'} = 4.5$, $J_{66'} = 8.7$. Addition of sodium hydrogen carbonate caused rearrangement to *9a* as seen from the ^{1}H NMR spectrum. Isolation of *9a*, redissolution in deuteriochloroform and addition of trifluoroacetic acid did not cause reversion to *8*. The ^{1}H NMR spectrum of *9a* remained unchanged for several days.

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References

1. Jacobsen, S. and Mols, O. *Acta Chem. Scand. B35* (1981) 521.
2. Kurzer, F. and Lawson, A. *Org. Syn.* Coll. Vol. IV, 645.
3. Tsutsumi, I. and Ishido, Y. *Carbohyd. Res. 111* (1982) 75.
4. Schmidt, R. R. and Michel, J. *Angew. Chem. 92* (1980) 763.
5. Hanessian, S. and Plessas, N. R. *J. Org. Chem. 34* (1969) 1035.
6. Bernet, B. and Vasella, A. *Tetrahedron Lett.* (1983) 5491.
7. Cardillo, G., Orena, M., Porzi, G. and Sandri, S. *J. Chem. Soc. Chem. Commun.* (1982) 1308.
8. Cardillo, C., Orena, M., Sandri, S. and Tomasini, C. *J. Org. Chem. 49* (1984) 3951.
9. Pauls, H. W. and Fraser-Reid, B. *J. Chem. Soc. Chem. Commun.* (1983) 1031.
10. Pauls, H. W. and Fraser-Reid, B. *J. Org. Chem. 48* (1983) 1392.
11. Sammers, P. G. and Thetford, D. *J. Chem. Soc. Chem. Commun.* (1985) 352.
12. Hoffmeyer, L., Jacobsen, S. and Pedersen, C. *Acta Chem. Scand. B33* (1979) 175.

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