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Note

Apparent isomerization at C-4 during oxidation of 1,2:5,6-di-*O*-cyclohexylidene-α-D-glucofuranose

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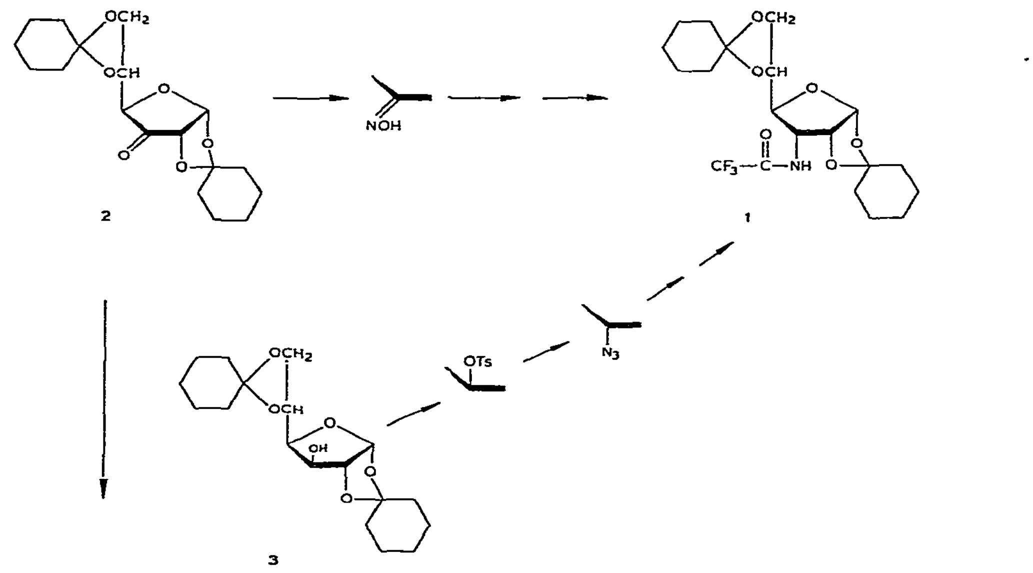
For a projected synthesis, we needed 1,2:5,6-di-*O*-cyclohexylidene-3-deoxy-3-trifluoroacetamido-α-D-allofuranose (**1**). This compound was synthesized from the oxime[1] of 1,2:5,6-di-*O*-cyclohexylidene-α-D-*ribo*-hexos-3-ulofuranose (**2**) by reduction[2] with lithium aluminum hydride followed by acylation. The stereochemistry of the amide **1** was proved by independent synthesis from 1,2:5,6-di-*O*-cyclohexylidene-α-D-glucofuranose (**3**), *via* azide displacement of the *p*-toluenesulfonic ester[3], followed by reduction and subsequent acylation.

In addition to the crystalline *allo*-amine (**4**) obtained by reduction of **2**, a non-crystalline mixture of amines was also obtained. This mixture was also trifluoroacetylated, and chromatography gave more **1**, as well as another trifluoroacetamide (**5**) formed in 6% yield. It seemed unlikely that the latter was the *gluco* isomer, as Onodera *et al.*[4] reported obtaining only the *allo* isomer upon reduction of the di-isopropylidene oxime, and James *et al.*[1] reported only the *allo* alcohol from reduction of the dicyclohexylidene ketone. As Baker *et al.*[5] had obtained a trace (<3%) of the *gluco* alcohol on reduction of the diisopropylidene ketone with lithium aluminum hydride, we synthesized 1,2:5,6-di-*O*-cyclohexylidene-3-deoxy-3-trifluoroacetamido-α-D-glucofuranose (**6**) from the corresponding azide[6] by reduction and subsequent acylation. As **6** and **5** had different melting points and n.m.r. spectra, we turned our attention to another stereochemical possibility for **5**, the *gulo* configuration. 1,2:5,6-Di-*O*-cyclohexylidene-3-deoxy-3-trifluoroacetamido-α-D-gulofuranose was synthesized from **2** by a method analogous to that used in the diisopropylidene series by Meyer zu Reckendorf[7] and Brimacombe *et al.*[8]. In the dicyclohexylidene series, we found that catalytic hydrogenation was very satisfactory for converting the enol acetate (**7**) into the *gulo* acetate (**8**), in a yield of 70%, as compared with 30% by using sodium borohydride in the diisopropylidene series. Hydrolysis of **8** gave the *gulo* diacetal (**9**), which was oxidized to the ketone (**10**). Treatment of **10** with hydroxylamine gave two compounds, **11** and **12**, both of which gave analyses consistent with the oxime structure, but which had different n.m.r. spectra and melting points. We assume that


OCH2
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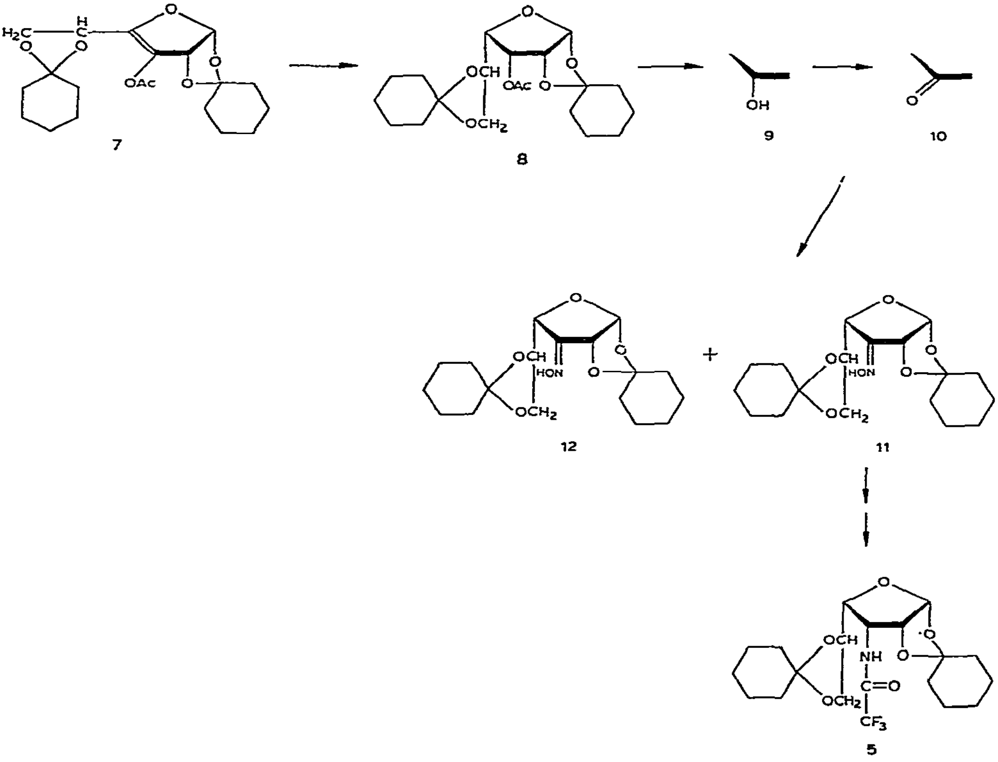
H2C
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7
OCH
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OCH2
8
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OCH
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12
+
OCH
HON
OCH2
11
OCH
NH
C=O
OCH2
CF3
5

these are the *syn* and *anti* forms of the oxime. The n.m.r. spectra suggest that **11** has the OH group toward C-2, and **12**, toward C-4, as the signal for H-2 is downfield in **11** as compared with **12** (5.22 *vs.* 4.87), whereas that for H-4 is downfield in **12** as compared with **11** (4.95 *vs.* ~4.4). An attempt to catalytically reduce **11** gave only partial uptake of hydrogen, and so the reduction was completed with lithium aluminum hydride and the product trifluoroacetylated to give **5**, which had the same m.p. and n.m.r. spectrum as the minor product obtained as just described.

The partial isomerization at C-4 probably occurred during oxidation of **3**, as the product used for formation of the oxime had not been purified by crystallization. Isomerization during this oxidation with dimethyl sulfoxide–phosphorus pentaoxide[4] or during that of the diisopropylidene analog has not been reported before, but Baker and Buss[9] reported isomerizations as great as 86% under the very similar Pfitzner–Moffatt[10] conditions.

The chemical shifts of the anomeric proton in the n.m.r. spectra could be correlated with the configuration at C-4, when C-3 was an sp^3-substituted carbon atom. In the *gluco* and *allo* compounds, the anomeric doublet was centered at δ 5.87–5.95, whereas, in the *gulo* compounds, the doublet was shifted upfield to δ 5.77–5.81. As the difference is small, predictions are most useful when data for two isomers are available.

The differences between the ^{13}C-n.m.r. spectra of **1** and **5** were small, and comparison with the spectrum of **3** gave no useful correlations.

EXPERIMENTAL

3-Amino-1,2:5,6-di-O-cyclohexylidene-3-deoxy-α-D-allofuranose (**4**). — The oxime of **2**, (35.6 g, 0.1 mol) in dry oxolane (0.5 L) was stirred under nitrogen while 15.2 g (0.4 mol) of lithium aluminum hydride was added during 0.5 h. The mixture was stirred for 5.5 h at 65° and allowed to cool. Ethyl acetate (120 mL) was added carefully and the mixture poured into water (2.5 L) with stirring. The mixture was extracted with chloroform and the extracts were washed with water, dried, and evaporated. The residue was dissolved in benzene, the solution filtered, and the filtrate evaporated. This residue was crystallized from hexane to give 8.45 g of **4**, m.p. 80–82° (Found: C, 64.05; H, 8.50; N, 4.32. $C_{18}H_{29}NO_5$ calc.: C, 63.69; H, 8.61; N, 4.13%). In addition, 14.7 g of non-crystalline material was obtained.

1,2:5,6-Di-O-cyclohexylidene-3-deoxy-3-trifluoroacetamido-D-allofuranose (**1**). — The amine **4** (8.29 g, 24 mmol) was dissolved in dichloromethane (35 mL) and pyridine (5.8 g, 73 mmol), and the mixture was stirred under nitrogen at 0° while 5.1 g (24 mmol) of trifluoroacetic anhydride was added during 15 min. The solution was stirred for 2 h and kept overnight at 20°. It was diluted with dichloromethane, washed with aqueous potassium carbonate and water, dried, and evaporated. The residue crystallized after being dissolved in toluene and the solution evaporated. It was recrystallized from heptane to give 7.9 g of **1**, m.p. 111–112° (Found: C, 55.32; H, 6.52; N, 2.89; F, 13.41. $C_{20}H_{28}F_3NO_6$ calc.: C, 55.16; H, 6.48; N, 3.22; F, 13.09%).

The non-crystalline amine (14.7 g) from the foregoing experiment was trifluoroacetylated by the same method. Crystallization of the product gave 5.75 g of **4**. The remaining material (9.8 g) was chromatographed on silica gel. Elution with 7% ethyl acetate–benzene gave first 3.1 g of additional **4**, followed later by another compound (**5**), which was crystallized from hexane to give 1.2 g of product, m.p. 143–144.5° (Found: C, 55.45, 55.22; H, 6.23, 6.42; N, 3.10, 3.40; F, 13.23%).

*3-Azido-1,2:5,6-di-*O*-cyclohexylidene-3-deoxy-α-*D*-allofuranose.* — 1,2:5,6-Di-*O*-cyclohexylidene-3-*O*-*p*-tolylsulfonyl-*α*-D-glucofuranose (5.75 g) was dissolved in hexamethylphosphoric triamide (60 mL), sodium azide (6 g) was added, and the mixture was heated for 18 h at 120°. Part of the solvent was then distilled off under vacuum and water was added to the residue. A solid separated. The aqueous layer was decanted and extracted with dichloromethane. The extracts were washed 3 times with water, combined with the solid, and evaporated. The residue was chromatographed on Woelm silica (250 g) in a low-pressure system using 5% ethyl acetate–benzene. The separation was monitored by t.l.c. and n.m.r. spectroscopy. The residues from 450–690 mL were crystallized from hexane to give 0.95 g of product, m.p. 91–94° (Found: C, 59.25; H, 7.66; N, 11.23. $C_{18}H_{27}N_3O_5$ calc.: C, 59.16; H, 7.45; N, 11.50%).

*1,2:5,6-Di-*O*-cyclohexylidene-3-deoxy-3-trifluoroacetamido-α-*D*-allofuranose* (**1**). — The foregoing azide (0.4 g) was dissolved in dry ether (100 mL) and 0.8 g of lithium aluminum hydride was added. The mixture was boiled under reflux. After 1.5 h, the excess of hydride was decomposed with ethyl acetate. Water was added dropwise until the solid turned white. The mixture was filtered and the filtrate evaporated under nitrogen. The residue was dissolved in dichloromethane (10 mL) and pyridine (5 mL) and cooled to 0°, and trifluoroacetic anhydride (0.4 mL) was added. After 1 h, 20 mL of dichloromethane was added, and the solution was washed with aqueous sodium hydrogencarbonate and water. The dried solution was evaporated under nitrogen and the residue triturated with hexane to yield 0.3 g of **1**, m.p. 112–113°, $[\alpha]_D$ +34° (*c* 0.1, chloroform), whose n.m.r. spectrum was identical with that of **1** obtained by oxime reduction.

*1,2:5,6-Di-*O*-cyclohexylidene-3-deoxy-3-trifluoroacetamido-α-*D*-glucofuranose* (**6**). — 3-Azido-1,2:5,6-di-*O*-cyclohexylidene-3-deoxy-*α*-D-glucofuranose[6] (1.8 g) was reduced and then trifluoroacetylated by the foregoing method to give 1.1 g of **6**, m.p. 113–115°, $[\alpha]_D$ −19° (*c* 0.1, chloroform) (Found: C, 54.96; H, 6.47; N, 3.25. $C_{20}H_{28}F_3NO_6$ calc.: C, 55.16; H, 6.48; N, 3.22%). The n.m.r. spectrum was different from that of the *allo* isomer.

*3-*O*-Acetyl-1,2:5,6-di-*O*-cyclohexylidene-α-*D*-*erythro*-hex-3-enofuranose* (**7**). — The hydrate of ketone **2** was dissolved in pyridine (150 mL) and acetic anhydride (75 mL), and the solution was heated overnight. The solvents were removed under vacuum. The residue solidified when poured onto ice, and it was recrystallized from ether to give 13 g of **7**, m.p. 74–75.5° (Found: C, 63.19; H, 7.42. $C_{20}H_{28}O_7$ calc.: C, 63.14; H, 7.42%).

*3-*O*-Acetyl-1,2:5,6-di-*O*-cyclohexylidene-α-*D*-gulofuranose* (**8**). — The enol acetate **7** (2.0 g) was dissolved in methanol (100 mL) and hydrogenated for 2 h at room temperature and 2 lb.in^{-2} with 0.2 g of palladium-on-carbon. The catalyst was filtered off and the filtrate evaporated. The residue was dissolved in ether and **8** crystallized as the solvent evaporated; yield 1.4 g, m.p. 120–122°, $[\alpha]_D$ +48° (*c* 0.1, chloroform) (Found: C, 62.51; H, 7.83. $C_{20}H_{30}O_7$ calc.: C, 62.81; H, 7.91%).

1,2:5,6-Di-O-cyclohexylidene-α-D-gulofuranose (**9**). — The acetate **8** (1.4 g) was dissolved in methanol (10 mL), a solution of potassium hydroxide (0.3 g) in water (10 mL) was added, and the mixture was warmed. On cooling, crystals of **9** formed; yield 0.85 g, m.p. 151–151.5°, $[\alpha]_D$ 0 (*c* 0.1, chloroform) (Found: C, 63.68; H, 8.37. $C_{18}H_{28}O_6$ calc.: C, 63.51; H, 8.29%).

*1,2:5,6-Di-O-cyclohexylidene-α-D-*xylo*-hexofuranos-3-ulose* (**10**). — The D-*gulo* diacetal **9** (5.0 g) was dissolved in dimethyl sulfoxide (60 mL) and acetic anhydride (40 mL). After 20 h, the solvents were removed under vacuum. The residue was vacuum-dried and crystallized from ether to yield 2.45 g of ketone **10**. A part of the material was recrystallized from ether; m.p. 131.5–132.5°, $[\alpha]_D$ +18° (*c* 0.1, chloroform) (Found: C, 63.84; H, 7.83. $C_{18}H_{26}O_6$ calc.: C, 63.89; H, 7.74%).

*1,2:5,6-Di-O-cyclohexylidene-α-D-*xylo*-hexofuranos-3-ulose oxime*. — The ketone **10** (1 g) was dissolved in ethanol (20 mL) and pyridine (20 mL) containing 2 g of hydroxylamine hydrochloride. The solution was heated for 2 h on a steam bath and then evaporated. The residue was triturated with water, filtered off, and the solid recrystallized from hexane. The first fraction (**11**, 0.45 g) had m.p. 155.5–161°, $[\alpha]_D$ +45.5° (*c* 0.1, chloroform) (Found: C, 61.17; H, 7.66; N, 3.90. $C_{18}H_{27}NO_6$ calc.: C, 61.17; H, 7.70; N, 3.96%). The second fraction was recrystallized from hexane to give **12** (0.3 g), m.p. 126–126.5° (Found: C, 60.84; H, 7.70; N, 3.98%).

1,2:5,6-Di-O-cyclohexylidene-3-deoxy-3-trifluoroacetamido-α-D-gulofuranose (**5**). — One form (**11**) of the oxime (0.4 g) was hydrogenated in 1-butanol (25 mL) at atmospheric pressure and room temperature over platinum oxide (0.2 g). As the uptake of hydrogen stopped after 40% of the theoretical uptake, even after addition of more catalyst, the mixture was filtered and the filtrate concentrated under vacuum. Toluene was added and distilled off. The residue was dissolved in ether (100 mL) and lithium aluminum hydride (1 g) was added. The mixture was swirled occasionally and, after several h, acetone was added, followed by just enough water to turn the grey solid white. The solution in ether was decanted and the solid triturated twice with ether. The combined ethereal solutions were evaporated, and the residue was dissolved in dichloromethane (10 mL) and pyridine (5 mL) and cooled to 0°. Trifluoroacetic anhydride (0.4 mL) was added and, after several h, dichloromethane (20 mL). The solution was washed once with aqueous sodium hydrogencarbonate and twice with water, and evaporated. The residue was triturated with hot hexane. When the triturates were allowed to evaporate, crystals of **5** formed. They were recrystallized from hexane to give 60 mg of product, m.p. 142–145°, whose n.m.r. spectrum was the same as that of the sample of **5** obtained earlier.

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