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Branched-chain Sugars. IX. Reaction of 3,6-Anhydro-1,2-O-isopropylidene-
α-D-ribo-hexofuranos-3-ulose with Nitromethane or Hydrogen Cyanide

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3,6-Anhydro-1,2,6-O-isopropylidene-α-D-ribo-hexofuranos-3-ulose (2) was converted into 5,6-di-O-acetyl-1,2-O-isopropylidene-α-ribo-hexofuranos-3-ulose (5) by the protection of the carbonyl function with hydroxylamine, followed by acetylation and removal of the protecting group with chromium(II) acetate. Nitromethane condensation of 2 and 5 at room temperature gave the corresponding 3-nitromethyl derivatives having α-glucos- and α-allo-configuration, respectively. The difference in the stereoselectivity was explained by the easiness of isomerization of the initial product to thermodynamically stable epimer, because the reaction temperature was essential to control the selectivity in the same reaction of 1,2 : 5,6-di-O-isopropylidene-α-D-ribo-hexofuranos-3-ulose. Reaction of 2 with hydrogen cyanide in dry pyridine followed by acetylation gave the corresponding 3,5,6-tri-O-acetyl-3-cyano derivative of α-allo-type, whereas, the reaction in water gave instantly 3-(hydroxycarbonimidoyl)-1,2-O-isopropylidene-α-allofuranose 3',5-lactone, by the participation of the C4-hydroxyl group.

Up to date, many works have been reported on the nucleophilic reaction of easily available 1,2 : 5,6-di-O-isopropylidene-α-D-ribo-hexofuranos-3-ulose (1),2-4) and we also reported on the stereoselectivities of some reactions.5) This compound decomposes often to 3,6-anhydro-1,2,6-O-isopropylidene-α-D-ribo-hexofuranos-3-ulose (2)8) during the storage, unless kept at lower temperature in pure state. Although 2 is easily obtained by the partial hydrolysis of 1,7) it is unfavorably formed during the preparation of 1 by the dimethyl sulfoxide oxidation of 1,2 : 5,6-di-O-isopropylidene-α-D-glucofuranose, and easily separated from the chloroform solution of the products by extraction with water, sometimes in ca. 30% yield. Intramolecular hemiacetal structure of 29) indicates a diminished reactivity of the carbonyl function, but the hydrogenation6) and p-nitrophenylhydrazone formation5) of 2 were described in literatures.

In order to find useful utilizations of 2 as a starting material for the branched-chain sugar synthesis, 2 was converted into 5,6-di-O-acetyl-1,2-O-isopropylidene-α-D-ribo-hexofuranos-3-ulose, and the addition of nitromethane and hydrogen cyanide to both compounds were carried out in this paper. A new evidence on the stereoselectivity of the former reaction and a participation of a neighboring hydroxyl group in the latter reaction are described.

Results and Discussion

Attempted acetonation of 2 into 1 and the Grignard reaction of 2 gave unsuccessful results, indicating that the intramolecular hemiacetal ring of 2 is fairly stable that of 2-ketoses. Although much stronger nucleophiles such as nitromethanide anion and cyanide ion are deduced to be reactable with 2, conversion of 2 into a more reactive 3-ulose derivative having the naked carbonyl group was tried at first. Condensation of 2 with hydroxylamine in aqueous ethanol gave the cor-
K-nichi-a)

Heteroconjugation was then a reduction to the corresponding n-allo-type epimer in each case. The kinetic difference between the epimers in each case. The kinetic studies will be reported elsewhere.

On the other hand, reaction of 2 with hydrogen cyanide in water at 0 °C for 6 h and successive acetolysis of the reaction mixture with acetic anhydride gave the corresponding 3-cyano-tri-0-acetate (12) in 54% yield. The configuration of 12 was confirmed to be d-allo-type by comparison of the NMR spectrum with that of the authentic sample, prepared from the corresponding 5,6-O-isopropylidene derivative. Besides, the reaction of 2 with potassium cyanide in water at the presence of sodium hydrogencarbonate at 0 °C gave instantly a crystalline product (13) in 66% yield, which shows characteristic IR absorptions at 3300 (C=O) and 1705 (-O-C=NH) cm\(^{-1}\).

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Tem| Reaction conditions | Epimer ratio |
---|---------------------|-------------|
| Solvent | Temp (°C) | Time (min) | Base | Gluco | allo |
| EtOH | -78 | 30 | NaOEt | 0 | 1 |
| EtOH | -78 | 30 | Et4N | 0 | 1 |
| THF | -78 | 30 | Et4N | 0 | 1 |
| Dioxane | -78 | 30 | Et4N | 0 | 1 |
| EtOH | -25 | 3 | NaOEt | 0 | 1 |
| EtOH | -25 | 30 | NaOEt | 1 | 0 |
| THF | -25 | 30 | NaOEt | 1 | 0 |
| Dioxane | -25 | 30 | NaOEt | 1 | 0 |
| THF | -25 | 30 | Et4N | 1 | 0 |
| CH3NO2 | -25 | 30 | NaH | 1 | 0 |
| Glyme | 25 | [24 h] | NaH | 0.8 | 0.2 |
| DMF | 25 | 30 | Et4N | 0.8 | 0.2 |
| HMPA | 25 | 30 | HMPA | 0 | 1 |
| DMSO | 25 | 30 | Et4N | 0 | 1 |

a) The reaction mixture was extracted with chloroform, after neutralization with 60% acetic acid. The configuration and ratio of epimers were estimated from the intensity of H2-proton signals in the NMR spectrum. b) THF = tetrahydrofuran, DMF = N,N-dimethylformamide, HMPA = hexamethylyphosphoramide, DMSO = dimethyl sulfoxide, Glyme = 1,2-dimethoxyethane. c) The amount of bases used were a slightly excess than the equivalent. d) Cited from the literature, A. Rosenthal, K.-S. Ong, and D. Baker, Carbohydr. Res., 13, 113 (1970).
ambiguous at present, but the similar participations are known in carbohydrate chemistry.\textsuperscript{10,17}

**Experimental**

All the melting points are uncorrected. The solution were evaporated under diminished pressure at a bath temperature not exceeding 45 °C. Specific rotations were measured in a 0.5 dm tube, with a Carl Zeiss LEP-AI polarimeter. The IR spectra were recorded with a Hitachi Model EPI-G2 spectrometer, using tetramethyldisilane as an internal standard, in deuterochloroform unless otherwise stated. Chemical shifts and coupling constants were recorded in δ and Hz units, and frequencies in cm\(^{-1}\).

1,2-O-Isopropylidene-a-D-ribo-hexofuranos-3-ulose Oxime (3).

To an aqueous ethanol solution (1 : 1, 100 ml) of hydroxylamine prepared from hydroxyamine hydrochloride (1.8 g, 25.9 mmol) and sodium hydroxide (1.0 g, 27.5 mmol) was added the hemiketal 2 (5 g, 22.9 mmol). After standing the reaction mixture at room temperature for 18 h, the solution was concentrated to a half volume, and then extracted with 1-butanol. Evaporation of the butanol solution gave crystals which were recrystallized from ethanol-hexane.

Yield, 3.95 g (74%); mp 161–164°C; IR: 3430 (OH), 3250 (OH), 1540 (NO\(_2\)). Found: C, 46.35; H, 6.48; N, 6.01%. Calcd for C\(_{13}\)H\(_9\)NO\(_4\): C, 46.35; H, 6.48; N, 6.01%.

3-Acetoxymino-5,6-di-O-acetyl-1,2-O-isopropylidene-a-D-ribo-hexofuranose (4).

A base-catalyzed acetylation of 3 with acetic anhydride in the usual manner gave a sirupy product quantitatively. NMR spectrum of the sirup showed the presence of two kind of isomers (pm- and anti-form) in the ratio of 1 : 1 (H\(_{11}\) : 6.05 and 5.98). This sirup was used for the next conversion without further identification. IR: 1740 (OAc).

5,6-Di-O-acetyl-1,2-O-isopropylidene-a-D-ribo-hexofuranos-3-ulose (5).

A suspension of the above sirup (200 mg, 0.56 mmol) and excess chromium(II) acetate (340 mg, 2.06 mmol) in ethanol (5 ml) at room temperature. After standing the reaction mixture for 30 min, it was neutralized with 60% acetic acid, and then evaporated to give crystals which were recrystallized from ethanol. Yield, 128 mg (95%), mp 122–123°C. IR: 3400, 3210, and 3125 (OH). Found: C, 51.16; H, 6.72; N, 3.60%. Calcd for C\(_{15}\)H\(_{12}\)NO\(_6\): C, 51.16; H, 6.72; N, 3.60%.

5,6-Di-O-acetyl-1,2-O-isopropylidene-a-D-glucofuranos-3-ulose (6).

A solution of 5 (200 mg, 0.56 mmol) in ethanol (5 ml) was added with stirring to a solution of nitromethane (1 ml) and sodium (100 mg, 4.3 mmol) in ethanol (5 ml) at room temperature. After standing the reaction mixture for 30 min, it was neutralized with 60% acetic acid, and then evaporated to give crystals which were recrystallized from ethanol-hexane. Yield, 154 mg (71%), mp 130–132°C; [\(\alpha\)]\(_{D}\) = +42.4° (c 0.9, CHCl\(_3\)). IR: 3420 (OH), 1740 (OAc), 1505 (NO\(_2\)); 5.79 (H\(_{11}\) : d, J\(_{11},\alpha\) = 4.3, J\(_{11},\beta\) = 12.4); 4.77 (H\(_{7}\) : d, J\(_{7},\alpha\) = 4.4, J\(_{7},\beta\) = 12.5); 4.03 (H\(_{9}\) : d, J\(_{9},\alpha\) = 8.2); 3.30 (OH); 2.10 and 2.06 (2\(\times\)OAc, NAc), 1.51 and 1.32 (2\(\times\)C-CH\(_2\)). Found: C, 51.16; H, 6.72; N, 3.60%. Calcd for C\(_{15}\)H\(_{12}\)NO\(_6\): C, 51.19; H, 6.71; N, 3.73%.

5,6-Di-O-acetyl-1,2-O-isopropylidene-3-(nitromethyl)-a-D-allofuranose (7).

i) From 5. A solution of 5 (200 mg, 0.56 mmol) in ethanol (5 ml) was added with stirring to a solution of nitromethane (1 ml) and sodium (100 mg, 4.3 mmol) in ethanol (5 ml) at room temperature. After standing the reaction mixture for 30 min, it was neutralized with 60% acetic acid, and then evaporated to give crystals which were recrystallized from ethanol-hexane. Yield, 154 mg (71%), mp 130–132°C; [\(\alpha\)]\(_{D}\) = +42.4° (c 0.9, CHCl\(_3\)). IR: 3420 (OH), 1740 (OAc), 1505 (NO\(_2\)); 5.79 (H\(_{11}\) : d, J\(_{11},\alpha\) = 4.3, J\(_{11},\beta\) = 12.4); 4.77 (H\(_{7}\) : d, J\(_{7},\alpha\) = 4.4, J\(_{7},\beta\) = 12.5); 4.03 (H\(_{9}\) : d, J\(_{9},\alpha\) = 8.2); 3.30 (OH); 2.10 and 2.06 (2\(\times\)OAc, NAc), 1.51 and 1.32 (2\(\times\)C-CH\(_2\)). Found: C, 51.16; H, 6.72; N, 3.60%. Calcd for C\(_{15}\)H\(_{12}\)NO\(_6\): C, 51.19; H, 6.71; N, 3.73%.

5,6-Di-O-acetyl-1,2-O-isopropylidene-3-(nitromethyl)-a-D-allofuranose (11).

ii) From 1,2:5,6-di-O-isopropylidene-3-(nitromethyl)-a-D-allofuranose. A solution of the starting material (500 mg) in acetic acid (70%) (20 ml) was kept at room temperature for 24 h, and then evaporated to give a glassy solid [1,2-O-isopropylidene-3-(nitromethyl)-a-D-allofuranose (11)] quantitatively, which could not be crystallized. [\(\alpha\)]\(_{D}\) = +18.5° (c 3.6 mmol) and anhydrous copper(II) sulfate (3.0 g) in dry acetonitrile (50 ml) was stirred at 50°C for 24 h, filtered through active carbon, and the filtrate was evaporated. A chloroform solution of the residue was washed with water and evaporated to give crystals which were recrystallized from ethanol. Yield, 0.82 g (71.4%), mp 139–140°C; [\(\alpha\)]\(_{D}\) = +22.3° (c 1.0, CHCl\(_3\)); 1\(\times\) [lit.\(\alpha\)]\(_{D}\) = +22.8° (CHCl\(_3\)). This specimen showed no depression of mp by admixture with an authentic sample.
0.7, MeOH), IR: 1560 (NO₂).

Found: C, 42.55; H, 6.12; N, 4.60%. Caled for C₈H₄O₂N₂: C, 43.01; H, 6.14; N, 5.02%.

Acetylation of 11 (200 mg) with acetic anhydride (3 ml) in pyridine (5 ml) in the usual manner gave 10 quantitatively which was identical with the above mentioned sample.

3,5,6-Tri-O-acetyl-3-cyanyl-1,2-O-isopropylidene-α-D-allofuranose (12). To a solution of 2 (1 g, 4.6 mmol) and hydrogen cyanide (0.3 ml) in pyridine (10 ml) which was stirred at 0°C for 6 h was added acetic anhydride (3 ml), the mixture was kept at room temperature for 15 h, and the excess hydrogen cyanide was poured into water, and the resulting solution was extracted with methylene dichloride. The extracted solution was washed with water and evaporated to give a syrup which was crystallized and recrystallized from ethanol-hexane. Yield, 0.92 g, (54%), mp 140-142°C,

Found: C, 51.00; H, 5.49%. Caled for C₁₀H₁₅O₅: C, 50.91; H, 5.49%.

IR and NMR spectra were identical with those of the authentic sample. U = 105, 1978 (1972).

Acetylation of 3 (125 mg, 1.0 mmol) and sodium hydrogen carbonate (84 mg, 1.0 mmol) in methanol (5 ml) was refluxed for 12 h, evaporated, and the residue was crystallized from ethanol-hexane to give needles quantitatively. Yield, 0.74 mg, (66%), mp 166-168°C,

Found: C, 41.91; H, 5.42%. Caled for C₁₀H₁₂O₃Na: C, 41.96; H, 5.28%.

References