HYDROFORMYLATION OF 5,6-ANHYDRO-1,2-*O*-ISOPROPYLIDENE-α-D-GLUCOFURANOSE. UTILIZATION OF THE PRODUCT IN NUCLEOSIDE SYNTHESIS

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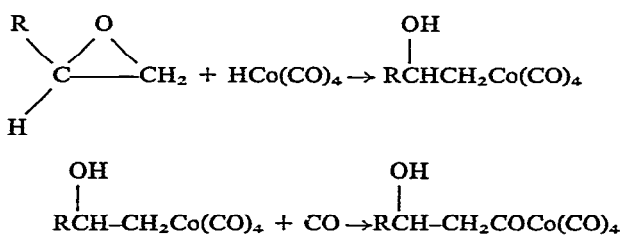
ABSTRACT

Hydroformylation of 5,6-anhydro-1,2-*O*-isopropylidene-α-D-glucofuranose (**1**) with carbon monoxide and hydrogen in the presence of dicobalt octacarbonyl for 1.5 h at 105° gave 6-deoxy-1,2-*O*-isopropylidene-α-D-*gluco*-heptodialdo-1,4-furanose-7,3-pyranose (**5**) and 6-deoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranos-5-ulose (**3**) in 78 and 7% yields, respectively. The dialdose **5** was acetylated to afford the diacetate **6**, which was fused with 5,6-dimethylbenzimidazole in the presence of monochloroacetic acid to afford an anomeric mixture of nucleosides **7a** and **7b**.

DISCUSSION

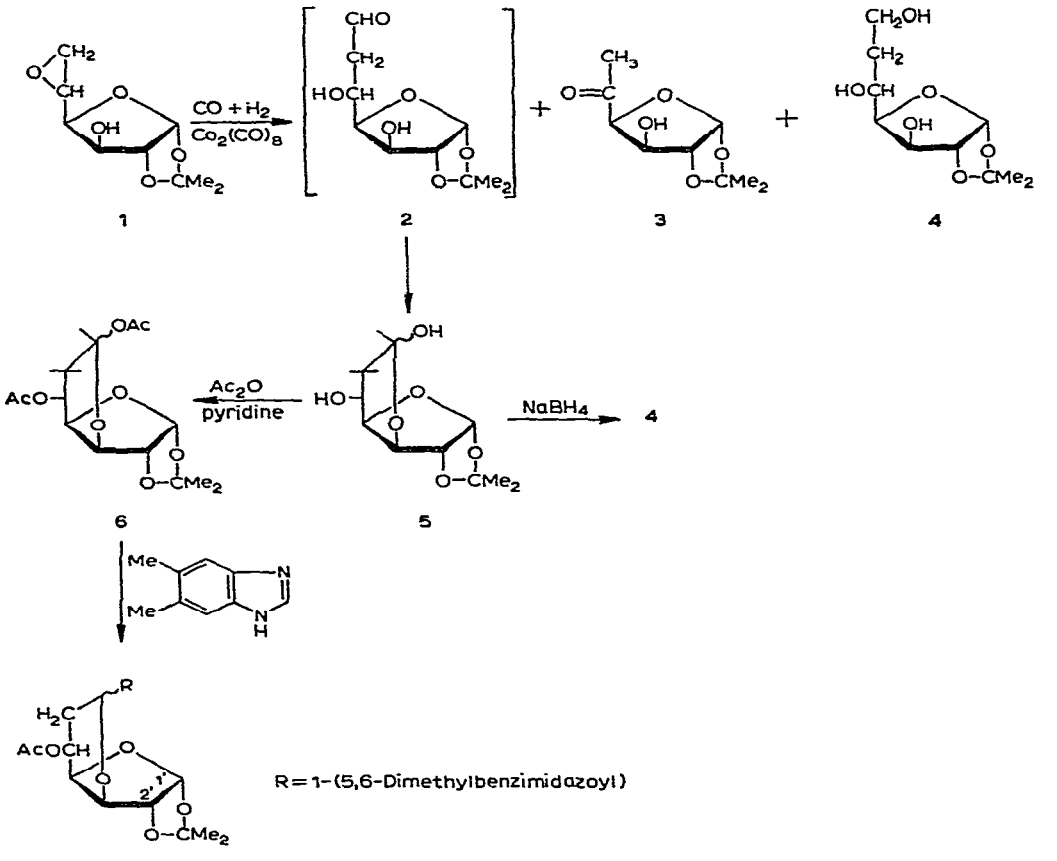
Although the hydroformylation of ethylene oxide has presented tremendous difficulties and the yield of the expected product, namely 3-hydroxypropionaldehyde, has been very low (~15%), the homologues of ethylene oxide undergo hydroformylation to give fair yields of isomeric aldehydes and alcohols (carbonylation and reduction products), and, in addition, part of the starting material rearranged to ketones[1]. Orchin and coworkers successfully hydroformylated cyclohexene oxide to yield the expected *trans*-2-hydroxycyclohexanecarboxaldehyde, which was isolated in a cyclic, dimeric form[2]. When preformed cobalt hydrotetracarbonyl (this is assumed to be formed in the hydroformylation reaction) was used as the catalyst, and the reaction temperature was 0°, epoxides were readily carbonylated to give high yields of unstable (2-hydroxyalkyl)cobalt tetracarbonyls, which were readily carbonylated to afford 3-hydroxyacylcobalt tetracarbonyls[3], as illustrated below.



Because the anhydro sugars having an ethylene oxide ring are well known it seemed of interest to extend the hydroformylation reaction to a readily available

anhydro sugar derivative with the hope of preparing a dialdose derivative. In this paper we report complete experimental details[4] of the hydroformylation of 5,6-anhydro-1,2-*O*-isopropylidene-α-D-glucofuranose and the subsequent utilization of the dialdose derivative as an intermediate in the synthesis of novel nucleoside analogs.

When 5,6-anhydro-1,2-*O*-isopropylidene-α-D-glucofuranose (**1**) was allowed to react at 2200 p.s.i. with an equimolar mixture of carbon monoxide and hydrogen in the presence of preformed dicobalt octacarbonyl for 1.5 h at 100–105°, a mixture of three compounds was obtained. The major component (**5**), isolated in 78% yield, crystallized from the reaction product. The n.m.r. spectrum of **5**, when compared with



7a,7b (epimeric at C-7')

the spectrum of 5-deoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranose[5], conclusively shows that the formyl group is attached to position 6 of **1**. The two deoxy protons on **5** gave a multiplet at τ 7.6–7.9 integrating as two hydrogen atoms. If the hydroformylation had proceeded in such a manner as to add the formal group at C-5, then there would have appeared a single methine-proton resonance at lower field than τ 7.6. The n.m.r. spectrum of **5** showed the absence of a formyl hydrogen atom and

showed the presence of two hemiacetal hydrogen atoms, resonating at τ 4.25 and 4.82 and assigned to H-7e and H-7a, respectively. Irradiation of the signals at τ 7.7 altered both of the latter signals. Presumably, the free aldehyde group of the main hydroformylation product **2** immediately cyclized with the free hydroxyl group on C-3 to give an α,β-mixture of anomers possessing the tricyclic structure **5**. Further proof that **5** was an anomeric mixture was provided by the fact that **2** mutarotated rapidly. Reduction of **5** with sodium borohydride afforded a single aldose derivative **4**. This new aldose had the same R_F value as one of the minor components present in the hydroformylation product-mixture. Presumably, the dialdose **2** underwent partial reduction during the hydroformylation reaction.

The second component, present in 7% yield, had m.p. 99–100°, identical with that reported for 6-deoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranos-5-ulose[6]. In addition, its p.m.r. spectrum unambiguously supported the 5-ketone structure **3**. Rearrangements of epoxides to ketones when dicobalt octacarbonyl is used as the catalyst at temperatures above 100°, or when cobalt hydrocarbonyl is used at lower temperatures, are well known[1,3].

The dialdose derivative **5** was used as an intermediate in the synthesis by well known procedures of nucleoside analogs. Acetylation of **5** gave an anomeric mixture of 5,7-di-*O*-acetyl-6-deoxy-1,2-*O*-isopropylidene-α,β-D-*gluco*-heptodialdo-1,4-furanose-7,3-pyranose (**6**). Fusion of the latter with 5,6-dimethylbenzimidazole, with monochloroacetic acid as the catalyst according to the procedure of Whittle and Robins[7], afforded an anomeric mixture of nucleosides (**7a** and **7b**). The latter were separated by preparative t.l.c. on silica gel. Although the analyses were not in accord with pure compounds, both blocked nucleosides were crystalline and each gave a 100-MHz n.m.r. spectrum that supported the structure proposed. The nucleoside **7a** exhibited a poorly resolved quartet for the anomeric proton centered at τ 4.6 having a width of 10 Hz, whereas the nucleoside **7b** exhibited a poorly resolved quartet for the anomeric proton centered at τ 4.2 having a width of 4 Hz. On the basis of the fact that an axially oriented anomeric hydrogen of a 2′-deoxypyranosyl nucleoside was found to resonate at higher field than an equatorially oriented, anomeric proton[8], compound **7a** was tentatively assigned as the β-nucleoside and **7b** as the α-nucleoside. Assignment of anomeric configuration to deoxyglycosylamines on the basis of rotatory data are of little value, since other workers[9] have reported that optical rotations of anomeric 2′-deoxynucleosides were opposite to those expected on the basis of Hudson's rules of isorotation[10].

EXPERIMENTAL

General. — These conditions have been described previously[11].

Hydroformylation of 5,6-anhydro-1,2-O-isopropylidene-α-D-glucofuranose (**1**) *to yield 6-deoxy-1,2-O-isopropylidene-α-D-gluco-heptodialdo-1,4-furanose-7,3-pyranose*(**5**), *6-deoxy-1,2-O-isopropylidene-α-D-xylo-hexofuranos-5-ulose* (**3**), *and 6-deoxy-1,2-O-isopropylidene-α-D-gluco-heptoaldo-1,4-furanose* (**4**). — A solution of compound[12] (**1**) (2.4 g) and dicobalt octacarbonyl (0.3 g) in dry, purified benzene (50 ml) was shaken

with carbon monoxide (1100 p.s.i.) and hydrogen (1100 p.s.i.) in a high-pressure autoclave for 1.5 h at a temperature of 100–105° and then kept for 1 day at room temperature. After the gases had been vented off the crystalline fraction **5** (2.16 g, 78%) was removed by filtration and washed with petroleum ether (b.p. 35–60°). The mother liquor and filtrate were evaporated to dryness to yield a syrup (0.203 g), which was separated by preparative t.l.c. on Silica Gel G with butanone–water azeotrope as developer. Five zones were obtained, two of which contained about 5 mg each. The main zones contained compound **5** (42 mg), compound **3** (91 mg, 7%), and compound **4** (42 mg).

Characterization of compound **5**. — Compound **5** was recrystallized from ethanol–ethyl acetate; m.p. 159–160°, $[\alpha]_D^{22}$ +60° (*c* 2, water). Crude **5** had an initial $[\alpha]_D^{22}$ +39°, and mutarotated to +60° after 3 h; τ^{D_2O} (100 MHz), 3.55 (q, H-1), 4.25 (q, H, H-7e), 4.82 (q, H-7a), 4.95 (DOH), 5.2-5.6 (m), 7.6-7.9 (m, equal to 2H, H-6, 8.2, 8.35 (CMe_2). Irradiation at τ 7.8 altered the signals at τ 4.25 and 4.82.

Anal. Calc. for $C_{10}H_{16}O_6$: C, 51.8; H, 6.9; mol. wt. 232. Found: C, 51.6; 6.7; *m/e* 217 (M^+ −15 due to loss of CH_3).

*6-Deoxy-1,2-*O*-isopropylidene-α-*D*-gluco-heptodialdo-1,4-furanose semicarbazone monohydrate.* — To a solution of compound **5** (0.13 g) in 1 drop of water was added a solution of semicarbazide hydrochloride (0.04 g) and sodium acetate (0.04 g) in 3 drops of water. The reaction mixture was heated for 5 min on a steam bath and then kept at room temperature to give 126 mg of the title compound, m.p. 190–191°, $[\alpha]_D^{20}$ −9° (*c* 1, water).

Anal. Calc. for $C_{11}H_{16}N_3O_5 \cdot H_2O$: C, 43.00; H, 6.84; N, 13.68. Found: C, 43.00; H, 6.66; N, 14.00.

*6-Deoxy-1,2-*O*-isopropylidene-α-*D*-gluco-heptodialdo-1,4-furanose phenylhydrazone.* — To a solution of compound **5** (30 mg) was added 4 drops of a solution of phenylhydrazine hydrochloride (0.10 g), and sodium acetate (0.150 g) in 2 ml of water. The reaction mixture was heated for 1 min on a steam bath and then cooled in ice to deposit 32 mg (78%) of crystals, m.p. 134–135°, $[\alpha]_D^{22}$ −33° (*c* 2, chloroform).

Anal. Calc. for $C_{16}H_{22}N_2O_5$: C, 59.62; H, 6.83; N, 8.69. Found: C, 59.52; H, 6.97; N, 8.83.

*5,7-Di-*O*-acetyl-6-deoxy-1,2-*O*-isopropylidene-α-*D*-gluco-heptodialdo-1,4-furanose-7,3-pyranose* (**6**). — Compound **5** was acetylated in the usual way by using acetic anhydride and pyridine for 48 h at 0° to afford **6** in quantitative yield. Compound **6** was recrystallized several times from ethyl acetate; m.p. 176–177°, $[\alpha]_D^{22}$ +42° (*c* 2, chloroform); τ^{CDCl_3} (100 MHz), 4.1 (d, H-1, $J_{1,2}$ 4 Hz), 4.36 (m, H-7), 4.85 (m, H-5), 5.5 (d, H-2, $J_{1,2}$ 4 Hz), 5.7 (q, H-4), 5.9 (d, H-3), 7.9, 7.93 (acetyl groups), 8 (m, H-6), 8.5, 8.7 (CMe_2).

Anal. Calc. for $C_{14}H_{20}O_8$: C, 53.20; H, 6.20. Found: C, 53.12; H, 6.11.

The mother liquor from the above recrystallization was chromatographed on t.l.c. places by using butanone–water azeotrope to afford the α-anomer as a syrup; $[\alpha]_D^{24}$ +209° (*c* 2, chloroform); τ^{CDCl_3} 4.36 (H-7).

*5,7-Di-*O*-benzoyl-6-deoxy-1,2-*O*-isopropylidene-β-*D*-gluco-heptodialdo-1,4-fura-*

nose-7,3-pyranose. — Compound **5** (101 mg) was treated with freshly distilled benzoyl chloride (0.5 ml) in pyridine (2 ml) for 42 h at room temperature. The product was chromatographed on silica gel by using ethyl ether as developer to yield the dibenzoate (106 mg, 69%), which was crystallized from petroleum ether; b.p. 80–110°; m.p. 118–121°, $[\alpha]_D^{24}$ +7 (*c* 1, chloroform).

Anal. Calc. for $C_{24}H_{24}O_8$: C, 65.4; H, 5.46. Found: C, 65.0; H, 5.20.

Characterization of 6-deoxy-1,2-O-isopropylidene-α-D-xylo-hexofuranos-5-ulose (**3**). — Compound **3** was recrystallized from benzene–petroleum ether (b.p. 60–90°), m.p. 99–100°, $[\alpha]_D^{22}$ −47° (*c* 1, chloroform) (lit.[6] m.p. 99–100°, $[\alpha]_D^{18}$ −107°); τ^{CDCl_3} (60 MHz) 3.9 (d, H-1, $J_{1,2}$ 4 Hz), 5.3–5.6 (m), 7.7 (s, CH_3), 8.5–8.65 (CMe_2). It was converted in the usual way into its phenylhydrazone; m.p. 200–204°; $[\alpha]_D^{24}$ −12° (*c* 1, chloroform).

Anal. Calc. for $C_{15}H_{20}N_2O_4$: C, 61.60; H, 6.85. Found: C, 61.54; H, 6.78.

Characterization of compound **4**. — Compound **5** was reduced with sodium borohydride in methanol to afford a syrup, R_F 0.53; $[\alpha]_D^{24}$ +16° (*c* 2, ethanol); τ^{D_2O} (60 MHz), 4.0 (d, H-1, $J_{1,2}$ 3.5 Hz), 5.3 (d, H-2), 5.65 (q), 5.9–6.4 (m), 6.65 (d), 7.9–8.3 (two C-6 hydrogens), 8.5, 8.65 (CMe_2). This substance **4** had the same physical constants as those possessed by the third product **4** of the hydroformylation mixture.

Fusion of 5,7-di-O-acetyl-6-deoxy-1,2-O-isopropylidene-β-D-gluco-heptodialdo-1,4-furanose-7,3-pyranose (**6**) *with 5,6-dimethylbenzimidazole.* —Compound **6** (1.22 g), 5,6-dimethylbenzimidazole (0.97 g), and monochloroacetic acid (0.026 g) were dissolved in methanol and then the methanol was evaporated off at 80° under high vacuum. The mixture was fused for 24 min at 170–175° under high vacuum[7]. The product was separated by preparative t.l.c. on Silica Gel G impregnated with 1% of G. E. Phosphor (General Electric Co., U. S. A.) with 1:1 (v/v) methanol–benzene as developer. Five zones were obtained, two of which were nucleosides. The presumed β-nucleoside (compound **7a**) (0.2 g, about 10%) had m.p. 168–170°, $[\alpha]_D^{24}$ +120° (*c* 1, chloroform); τ^{CDCl_3} 2.2 (H-2), 2.5 and 2.8 (H-4 and H-7), 4.0 (H-1, $J_{1,2}$ 4 Hz), 4.6 (m, having a width of 10 Hz, H-7a), 4.7 (m, H-5′), 5.4 (d, H-2′, $J_{1',2'}$ 4 Hz), 5.6 (m, H-4′), 5.8 (H-3′), 7.3 (m, H-6′), 7.7, 7.72 (5,6-dimethyl protons), 7.9 (acetyl CH_3), 8.5, 8.7 (CMe_2).

Anal. Calc. for $C_{21}H_{26}N_2O_6 \cdot 1.5H_2O$: C, 58.95; H, 6.78; N, 6.55. Found: C, 58.60; H, 6.80; N, 6.11. The p.m.r. spectrum of **7a** showed the presence of water.

The presumed α-nucleoside (compound **7b**) (0.16 g) had m.p. 108–109°, $[\alpha]_D^{24}$ +70° (*c* 1, chloroform); τ^{CDCl_3} 1.8 (H-2), 2.5, 2.65 (H-4 and H-7), 4.0 (H-1′, $J_{1',2'}$ 4 Hz), 4.2 (m, having a width of 4 Hz, H-7e), 4.6 (m, H-5′), 5.4 (d, H-2′, $J_{1',2'}$ 4 Hz), 5.7 (m, H-4′), 6.2 (H-3′), 7.4 (m, H-6′), 7.70 (5,6-dimethyl proton), 7.9 (acetyl CH_3), 8.6, 8.75 (CMe_2).

Anal. Calc. for $C_{21}H_{26}N_2O_6$: N, 6.96. Found: N, 6.85.

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