Arylation of Quinoline Reissert Compound

As described above for the isoquinoline Reissert compound, equimolar quantities of 1-benzoyl-1,2-dihydroquinaldonitrile, *p*-nitrofluorobenzene, and sodium hydride in dimethylformamide gave after dry column chromatography on alumina with benzene and recrystallization from ethanol a 47% yield of **6**, m.p. 253–255°. Mass spectra 275 (100%), 259 (2%), 245 (8%), 229 (42%), 228 (28%), 216 (11%), 203 (5%), 202 (27%), 201 (23%), 176 (17%), 175 (13%), 151 (12%), 149 (4%).

Anal. Calcd. for $C_{16}H_9N_3O_2$: C, 69.81; H, 3.30; N, 15.27. Found: C, 69.57; H, 3.38; N, 15.17.

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Branched-chain sugar nucleosides. II. 9-(3-Deoxy-3-*C*-hydroxymethyl-β-D-glucopyranosyl)-adenine[1]

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Application of the oxo reaction to 1,2,4,6-tetra-*O*-acetyl-3-deoxy-α-D-*erythro*-hex-2-enopyranose (**1**), followed by acetylation of the oxo products, gave crystalline 1,2,3′,4,6-penta-*O*-acetyl-3-deoxy-3-*C*-(hydroxymethyl)-α-D-glucopyranose (**2**) in about 30% yield. Conversion of **2** into the branched-chain sugar bromide, followed by condensation of the latter with 6-benzamidochloromercuripurine afforded a blocked branched-chain sugar nucleoside (**5**) in 67% yield based on **2**. The nucleoside (**5**) was deblocked with methanolic sodium methoxide to afford 9-(3-deoxy-3-*C*-hydroxymethyl-β-D-glucopyranosyl)-adenine (**6**) in 75% yield.

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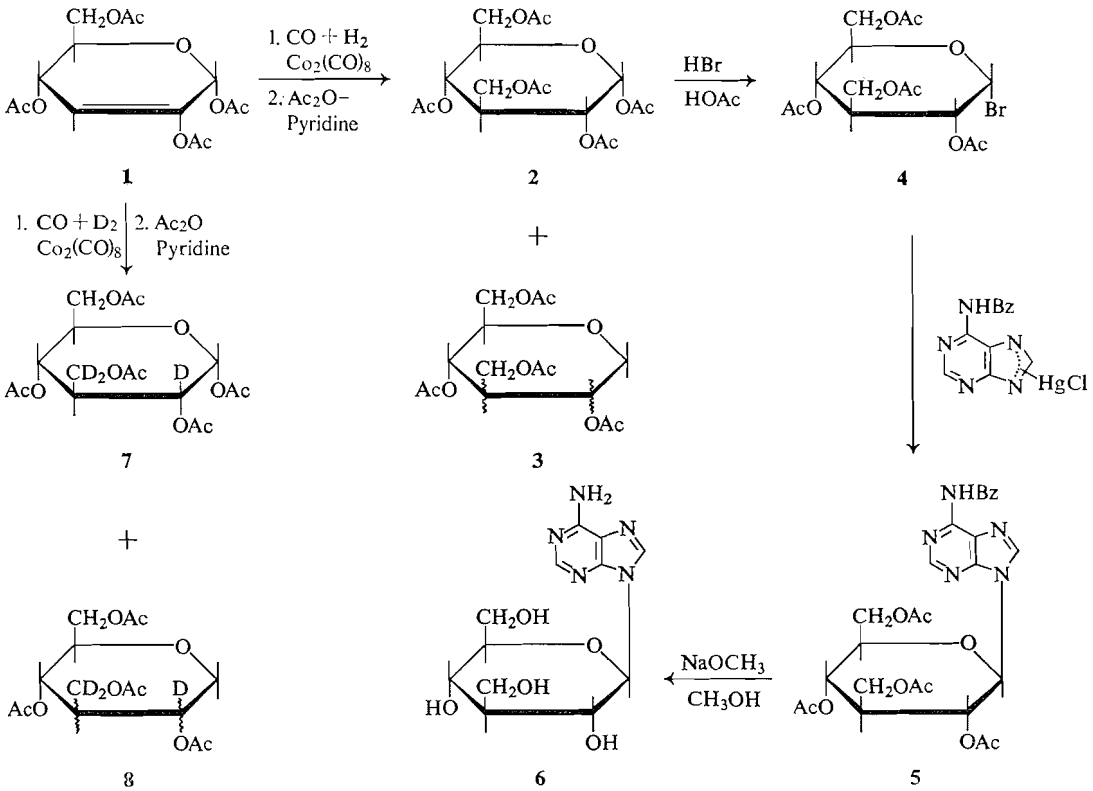
From 1966 to the present a number of reports have appeared (1–8) dealing with branched-chain sugar nucleosides. Most of these unusual nucleosides contain the furanosyl moiety (1–5), but a few have the pyranosyl ring system (6–8). The fact that some of the synthetic branched-chain sugar nucleosides (1–3) have been found to exhibit biological activity has helped to focus further attention on these interesting compounds. In this communication we wish to report complete details of a facile synthesis of the branched-chain deoxy sugar 3-deoxy-3-*C*-hydroxymethyl-D-glucopyranose and its conversion into the branched-chain deoxy sugar nucleoside (8).

When 1,2,4,6-tetra-*O*-acetyl-3-deoxy-α-D-*erythro*-hex-2-enopyranose (**1**) (9) was allowed to react with a mixture of carbon monoxide and hydrogen (oxo synthesis) in the presence of preformed dicobalt octacarbonyl at 150–160° for 2 h, a mixture of oxo products was obtained (8). After the products were freed from catalyst, they were fully acetylated using acetic anhydride and pyridine. An attempt to separate the mixture by column chromatography using alumina as adsorbent and ether as developer gave a partial separation of the products. Preparative vapor phase chromatography (v.p.c.) of the mixture of acetates gave compound (**2**) (having the longest retention time), in about 30% yield. A suggested mechanism of the reaction has already been discussed (8). A parallel reaction of **1** with carbon monoxide and deuterium followed by acetylation gave the partially deuterated analogue, namely, 1,2,3′,4,6-penta-*O*-acetyl-3-deoxy-3-*C*-(hydroxymethyl)-α-D-glucopyranose-2,3′,3′,-$^2H_3$ (*cis*) (**7**). The structures of **2** and **7** were readily ascertained from their nuclear magnetic resonance (n.m.r.) spectra and have already been described (8).

The branched-chain sugar (**2**) was converted into 2,3′,4,6-tetra-*O*-acetyl-3-deoxy-3-*C*-(hydroxymethyl)-D-glucopyranosyl bromide (**4**) by the usual method (not isolated because of instability) and immediately condensed with 6-benzamidochloromercuripurine in the presence of cadmium carbonate to afford the crystalline blocked branched-chain sugar nucleoside (**5**) in 67% yield based on the acetate (**2**). Although a

[1]For part I, see reference 13.



trace of impurity could not be removed from the blocked nucleoside, its analysis (by nitrogen and n.m.r. data) was compatible with the suggested structure. The trace of impurity was readily removed on unblocking **5** using methanolic sodium methoxide to afford the unsubstituted branched-chain sugar nucleoside (**6**) in 75% yield.

The assignment of the structure of **6** was based on the following: (*a*) ultraviolet (u.v.) absorption data of **6** substantiate the site of glycosylation at N-9 (10), (*b*) the *trans* rule (11) indicates that **6** has a β-configuration, (*c*) n.m.r. evidence (H-1′ gave a doublet with $J_{1',2'} = 9$ Hz) clearly corroborates the β-anomeric configuration of **6**.

Experimental

General Considerations

The oxo reaction (8) was performed in an Aminco autoclave. Dicobalt octacarbonyl was purchased from Alfa Inorganics, Inc., Beverley, Massachusetts. Nuclear magnetic resonance spectra were performed on a 100-HMz HA spectrometer, using tetramethylsilane (unless otherwise stated) as the internal standard set at $\tau = 10$. Mass spectra were measured with an A.E.I. M.S.9 spectrometer. Vapor phase chromatography was performed on a Varian Aerograph model 1525 instrument operated at 280° using a 12 ft column of Chromosorb W carrying 10% (by weight) silicone gum rubber SE-52. Detection of nucleosides was performed using a short wave u.v. filter (mineralicht) lamp.

*Reaction of 1,2,4,6-Tetra-O-acetyl-3-deoxy-α-D-erythro-hex-2-enopyranose (**1**) with Carbon Monoxide and Hydrogen to Yield 1,2,3′,4,6-Penta-O-acetyl-3-deoxy-3-C-(hydroxymethyl)-α-D-glucopyranose (**2**)*

A solution of 1,2,4,6-tetra-*O*-acetyl-3-deoxy-α-D-*erythro*-hex-2-enopyranose (8 g) (9) and dicobalt octacarbonyl (3 g) in dry purified benzene (35 ml) was shaken with carbon monoxide (800 p.s.i.) and hydrogen (1400 p.s.i.) in a high-pressure autoclave at a temperature of 150–160° for 2 h. After the gases were vented, 100 ml of petroleum ether (b.p. 35–60°) was added to the reaction mixture. The brown syrup which precipitated was separated from the solution and dissolved in benzene. The benzene solution was decolorized with activated charcoal, filtered, and evaporated under reduced pressure to yield an amber colored syrup (7.7 g). The syrup was acetylated using pyridine (50 ml) and acetic anhydride (50 ml). The acetylation mixture was evaporated to dryness and dissolved in chloroform. The chloroform solution was washed with aqueous sodium bicarbonate followed by water. The dried organic layer was evaporated

under reduced pressure to yield a syrup (8.8 g). Preparative v.p.c. of the product (in 200 ml of toluene) at 280° gave two major zones, A and B, and traces of five minor zones. The loss due to aerosol formation was considerable. One of the major zones (A) (0.530 g), which had the longest retention time (15.4 min), was readily recrystallized from ethyl ether – light petroleum ether (b.p. 30–60°); m.p. 100°, $[\alpha]_D^{22}$ +58° (*c*, 4 in benzene). The n.m.r. of **2** has been reported previously (8).

Anal. Calcd. for $C_{17}H_{24}O_{11}$ (mol. wt. 404): C, 50.47; H, 5.98. Found (mol. wt. 404 (added 43 to parent peak) (*m/e* 361, loss of CH_3CO)): C, 50.41; H, 5.98.

The second major zone (B) (compound **3**) (1.6 g) was a syrup and had a retention time of 11 min. The v.p.c. rerun of zone B at 180° showed the presence of two zones (never separated in 100% purity); τ ($CDCl_3$) 4.9–5.5 (overlapping multiplets, equal to 2 hydrogens attributed to H-2 and H-4), 5.6 to 6.6 (overlapping multiplets equal to 5 hydrogens, assigned to 2H-6, 1H-5, and 2H-3′) 7.55 (t, assigned to a single H-3a methine hydrogen, with J_{3-4} = 12 Hz), 7.36 (m, assigned to H-3e, 8 (12 acetyl H)). There was no signal that corresponded to the H-1 anomeric proton.

Two mobile zones (retention time 5 min) isolated in low yield (about 5%) were directly compared by v.p.c. with products obtained by carrying out a platinum-catalyzed hydrogenation in ethanol of **1**, whereby two main zones (exhibiting no anomeric hydrogens in their n.m.r. spectra) were obtained with retention times identical with those of the two fast moving minor components in the fully acetylated oxo product of **1**.

*Reaction of **1** with Carbon Monoxide and Deuterium to Yield 1,2,3′,4,6-Penta-O-acetyl-3-deoxy-3-C-(hydroxymethyl)-α-D-glucopyranose-2,3′,3′-$^2H_3$ (cis) (7)*

The unsaturated sugar (**1**) was allowed to react with carbon monoxide and deuterium and the product worked up as described above.

Anal. Calcd. for $C_{17}H_{21}D_3O_{11}$ (mol. wt. 407): C, 50.10; H and D, 6.68. Found (mol. wt. 407 (added 43 to parent peak) (*m/e* 364, loss of CH_3CO)): C, 50.26; H and D, 6.56. The nuclear magnetic resonance spectrum of 7 has been shown previously (8).

The branched-chain anhydroalditols (**8**) were not characterized.

3-Deoxy-3-C-(hydroxymethyl)-α(β)-D-glucopyranose-2,3′,3′-$^2H_3$(cis)

Compound (7) was deacetylated with sodium methoxide in methanol and the product worked up in the usual way. Recrystallization of the product from aqueous methanol gave crystalline 3-deoxy-3-*C*-(hydroxymethyl)-α(β)-D-glucopyranose-2,3′,3′-$^2H_3$(*cis*); m.p. 169–170°, $[\alpha]_D^{22}$ +44° (*c*, 1 in water), R_{G1} 1.65 (ethyl acetate, pyridine, water 5:2:7). Too little compound was available for reliable chemical analysis.

Anal. Calcd. for $C_7H_{11}D_3O_6$: C, 42.64; H, 8.63. Found: C, 41.68; H, 7.24.

6-Benzamido-9-(2,3′,4,6-tetra-O-acetyl-3-deoxy-3-C-hydroxymethyl-α-D-glucopyranosyl)-purine (5)

1,2,3′,4,6-Penta-*O*-acetyl-3-deoxy-3-*C*-hydroxymethyl-α-D-glucopyranose (0.146 g, 0.36 mmole) was allowed to react with 18% hydrogen bromide in glacial acetic acid (1 ml) at room temperature for 2 h under anhydrous conditions. After the solvent was removed under reduced pressure (anhydrous conditions), the residue was treated thrice with 3 ml of freshly distilled anhydrous xylene and the solvent then distilled to remove the hydrogen bromide. To a mixture of 0.24 g of 6-benzamidochloromercuripurine (12), 0.24 g of Celite, and 0.10 g of cadmium carbonate in 15 ml of anhydrous xylene (first dried by distilling off 5 ml under anhydrous conditions and normal pressure) was added a solution of the sugar bromide (0.140 g) in xylene (3 ml). The reaction mixture was heated at 60° for 0.5 h and then refluxed for 5 h. The hot reaction mixture was then filtered, and the precipitate washed with 20 ml of chloroform. After the solvent was removed under reduced pressure, the residue was extracted with 20 ml of chloroform. The chloroform solution was washed with 7 ml of 30% potassium iodide and with 7 ml of water. Concentration of the dried ($MgSO_4$) chloroform layer gave 0.20 g of product which was extracted with 10 ml of petroleum ether (b.p. 60–90°) to remove non-nucleoside material. The remaining solid residue in 5 ml of methanol was decolorized with charcoal, filtered, and the solvent removed under reduced pressure; yield, 0.14 g (67%); the crystalline product was recrystallized from methanol; m.p. 102–104°; $[\alpha]_D^{22}$ +18° (*c*, 2 in chloroform). The substance contained a trace of impurity which could not be removed by thin layer chromatography on silica gel using ethyl acetate–benzene (2:1); R_f = 0.25. τ ($CDCl_3$) 7.9 (12 acetyl hydrogens), 7.65 (H-3′, $J_{3',2'}$ = 12 Hz, $J_{3',4'}$ = 12 Hz), 5.6–6.3 (m, assigned to branched-chain CH_2 and to 2H-6′, H-5′), 4.4–4.9 (m, assigned to H-2′ and H-4′), 4.06 (d, H-1′, $J_{1',2'}$ = 9.0 Hz), 2.5 and 2.0 assigned to phenyl, 1.75 and 1.2 assigned to H-2 and H-8.

Anal. Calcd. for $C_{27}H_{29}N_5O_{10}$: N, 11.98. Found: N, 11.62.

9-(3-Deoxy-3-C-hydroxymethyl-β-D-glucopyranosyl)-adenine (6)

The blocked nucleoside (**5**) (0.53 g) (first dried by azeotroping with anhydrous benzene) was allowed to react with 0.05 *N* methanolic sodium methoxide (5 ml) at 50° for 2 h. The cooled solution was added to a column (1 cm diameter) containing 5 ml of freshly activated Rexyn 102 (H^+) resin and the resin then eluted with 10 ml water. The combined eluate was evaporated to dryness and the residue extracted with ether. The resin was further eluted with 50 ml of 0.7 *N* ammonium hydroxide and the eluate evaporated under reduced pressure. The resulting residue was combined with the residue remaining after the ether extraction (total yield, 0.041 g), and separated by paper chromatography using 1-butanol–ethanol–water (40:19:11) as developer; yield of **6**, 0.021 g (75%) amorphous substance which could not be crystallized from methanol or water. The solid nucleoside appeared to lose water at about 100° and decomposed at 230–235°, $[\alpha]_D^{22}$ +7° (*c*, 2 in water); $\lambda_{max}(H_2O)$ (mμ) 258 (ε 12 600); R_f 0.31; τ (D_2O) (DDS as internal standard) 8.2 (H-3′ signal overlapping with DSS signal), 6.15–6.4 (m, 2H-6′, H-5′, H-4′), 6.05 (d, branched-chain CH_2, *J* = 3 Hz), 5.75 (two d, assigned to H-2′, $J_{2',1'}$ = 9 Hz and $J_{2',3'}$ = 9 Hz), 5.3 (DOH), 4.42 (d, H-1′, $J_{1',2'}$ = 9.0 Hz), 1.9 (s, H-8), 1.75

(s, H-2). Irradiation at τ 8.3 changed the doublet at τ 6.05 to a singlet and altered the multiplet at τ 6.15–6.4. Irradiation at τ 4.4 altered the H-2′ signal.

For analysis compound (**6**) was dried at 60° under reduced pressure for 1 h.

Anal. Calcd. for $C_{12}H_{17}N_5O_5 \cdot H_2O$: C, 43.70; H, 5.75; H, 21.20. Found: C, 43.40; H, 5.60; N, 21.41.

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Ring enlargement through acyloin condensation of cycloalkane-1,2-dicarboxylic esters

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Cycloalkane-1,2-dicarboxylic esters of 11-, 12-, and 13-membered rings were prepared from cyclododecanone. Acyloin condensation of these esters in the presence of trimethylchlorosilane followed by acidic hydrolysis afforded 13-, 14-, and 15-membered cycloalkane-1,2-diones in 71–74% yields. The diketones were reduced by treatment with triethyl phosphite and alkali hydroxide into corresponding acyloins.

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Acyloin condensation in the presence of trimethylchlorosilane was first reported by Schräpler and Rühlmann (1) and later extended to the preparation of four membered cyclic acyloins by Rühlmann (2) and Bloomfield (3). Bloomfield further discussed thermal ring-opening of intermediary cyclobutene-1,2-diol disilyl ethers being controlled by the Woodward–Hoffmann rule.[1]

We now wish to report that this procedure, when applied to large ring cycloalkane-1,2-dicarboxylic esters, constitutes a convenient method for ring enlargement affording cycloalkane-1,2-diones under the incorporation of two side-chain carbons into the rings.[2,3]

Experiments were conducted with 11-, 12-, and 13-membered cycloalkane-1,2-dicarboxylic esters (**6***a–c*), all of which were hitherto unknown compounds and prepared from cyclododecanone (**1**) as a common starting material as shown in Scheme 1. The 11-membered unsaturated ester **2** (7) and the 12-membered unsaturated nitrile **3** (8*b*) have already been obtained from cyclo-

[1]For the valence-isomerization of cyclobutenes, see ref. 4.

[2]Brannock *et al.* (5) and Scharf *et al.* (6) reported similar ring enlargements through thermal ring-opening of bicyclic cyclobutene derivatives.

[3]Dr. Bloomfield kindly suggested to us that the application of this procedure to the diester available from cycloalkanone enamine and dimethyl acetylenedicarboxylate (5) can add four carbon atoms into the starting ring.