

# Synthesis of Deoxy Sugars I

## New Synthesis of 3-Deoxy-D-glucose and 3-Deoxy-D-mannose

By DANIEL H. MURRAY and J. PROKOP

Condensation of 2-deoxy-D-ribose with nitromethane gave, after deionization, a syrupy mixture of epimeric 1-nitro-1,3-dideoxy-hexitols. Acid hydrolysis under Nef reaction conditions produced a mixture of 3-deoxy-D-glucose and 3-deoxy-D-mannose, separable by cellulose chromatography or fractional crystallization. The glucose compound was characterized *via* the *p*-nitrophenylhydrazine and tetraacetyl derivatives. The 3-deoxy-D-mannose was characterized as the *p*-nitrophenylhydrazine and by conversion to 3-deoxy-D-mannitol and its pentabenzoate.

IN OUR PROGRAM of synthesis of nucleosides carrying an unusual sugar, it has been of interest to prepare a series of 3'-deoxyaldosyl purines. Suitable starting materials for a number of the required 3-deoxy-sugar moieties are the hexoses, 3-deoxy-D-glucose and 3-deoxy-D-mannose. It was anticipated that substantial quantities of these aldoses would be required, and the authors have sought a synthetic route which is conveniently short and amenable to adaptation to fairly large-scale preparation.

Until recently, procedures for the synthesis of 3-deoxyhexoses have been lengthy and have given inconveniently low yields. One of the routes to glycosidic derivatives of 3-deoxyglucose involved reductive opening of 2,3-anhydro intermediates. When methyl-2,3-anhydro-4,6-benzylidene- $\alpha$ -D-allopyranoside was submitted to high-pressure hydrogenation, a mixture containing predominantly methyl-3-deoxyglucoside along with its 4,6-hexahydrobenzylidene derivative resulted (1). This route was re-evaluated by Richtmyer and Pratt (2) and led to the isolation of the desired 3-deoxy-D-glucose in crystalline form but low yield. A similar high pressure reduction of methyl-2,3-anhydro-4,6-benzylidene- $\alpha$ -D-mannoside gave a mixture of 3-deoxymannosides corresponding to that obtained from the 2,3-anhydroalloside (3). When the 2,3-anhydro-mannoside was reduced with lithium aluminum hydride, however, methyl-4,6-benzylidene-3-deoxy- $\alpha$ -D-mannoside was obtained in 85% yield (2, 4). Subsequent acid hydrolysis gave 3-deoxy-D-mannose in an over-all yield of 3% from D-glucose (4).

These routes illustrate the reason for the previous relative inaccessibility of 3-deoxyglucose and 3-deoxymannose. The routes are long, and hence involve both considerable work-

up effort and a low over-all yield. Both factors made such routes unattractive to meet our own practical requirement to accumulate substantial quantities of the two sugars.

One route would seem to have considerable potential as a convenient pathway to the two desired 3-deoxyhexoses. This involves the alkaline conversion of glucose to mixed glucometasaccharinic acids, and these, *via* a subsequent Ruff degradation, give rise to 2-deoxy-D-ribose in over-all yield of 10% from glucose (5). Since the Ruff degradation customarily proceeds in yields of 40-60%, it is evident that alkaline isomerization of glucose leads to metasaccharinic acids in yields of 20% or higher. It was visualized that these might be isolated, lactonized, and reduced to yield the mixed 3-deoxyhexoses. The authors' attempts to accomplish this have thus far been unsuccessful, as have been similar attempts by other workers (6). The route itself remains attractive, and work on successfully developing it continues.

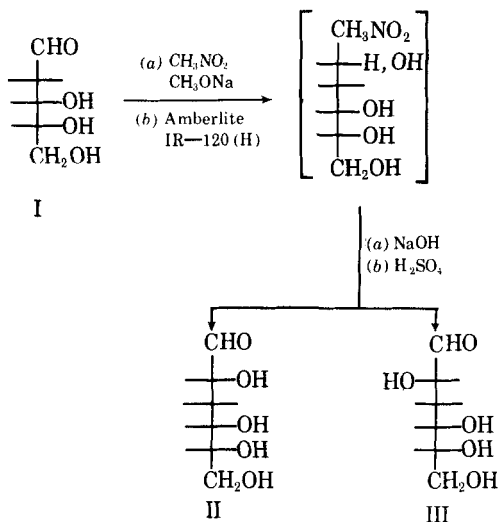
An alternative, though less attractive preparative possibility stems from the foregoing, in that treatment of glucose with alkali, followed by a Ruff degradation, has made 2-deoxyribose a readily accessible material in recent years (5). Chain lengthening of this sugar by one carbon would lead to mixed 3-deoxyhexoses, potentially separable. Wood and Fletcher (6) have condensed 2-deoxy-D-ribose with sodium cyanide to give an epimeric mixture of 3-deoxyhexonic acids. These were separated by fractional crystallization and converted to the corresponding lactones. Reduction of one of these with sodium borohydride led to 3-deoxy-D-glucose in a yield of approximately 20% from 2-deoxyribose. Similarly, reduction of the other lactone with sodium amalgam gave 3-deoxy-D-mannose as a crude syrup which was converted to the crystalline dimethylthioacetal. The yield of the crude sugar from 2-deoxyribose was about 12%.

The authors have developed a somewhat similar route employing a Sowden-Fischer pro-

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cedure. The above Kiliani synthesis involves three steps and separation at the intermediate acid stage, thus necessitating essentially parallel manipulations through the subsequent steps to the two sugars. From the same starting material, 2-deoxy-D-ribose (I), the procedure leads in two steps, condensation with nitromethane followed by acid hydrolysis (Nef reaction conditions), to yield 65% of a mixture of 3-deoxy-D-glucose (II) and 3-deoxy-D-mannose (III). (See Scheme I.) These are separable by cellulose column chromatography or more readily by fractional crystallization from ethanol.

#### EXPERIMENTAL<sup>1</sup>

**Condensation of 2-Deoxy-D-ribose with Nitromethane.**—To a well-stirred suspension of 20.0 Gm. (0.149 mole) of 2-deoxy-D-ribose (7) in 24.0 ml. (0.488 mole) of nitromethane and 100 ml. of anhydrous methanol at 0 to 5° was added dropwise a solution of 10.1 Gm. (0.186 mole) of sodium methoxide in 200 ml. of anhydrous methanol. The sugar dissolved completely in a short time. The reaction was stored at 5° in a stoppered flask for 25 hr., during which time the color of the reaction gradually changed from colorless to yellow-orange. The slightly turbid reaction mixture was diluted with 300 ml. of cold water and passed through a column (4.5 × 45 cm.) of Amberlite IR-120 (H+)<sup>2</sup> ion-exchange resin. After washing the column with an additional 1.5 L. of cold water, the combined eluate and washing, pale green in color, was evaporated to dryness *in vacuo* at 40° to give an amber syrup which was dried further by repeated distillations *in vacuo* at 40° of absolute ethanol (3 × 100 ml.); yield, 34.8 Gm. (120%);  $\nu_{\text{max}}^{\text{min}}$  (cm.<sup>-1</sup>) 3400 (OH), 1555 (NO<sub>2</sub>). This product was not purified further, but was employed directly in the following step.

<sup>1</sup> The melting points recorded here were determined in an oil bath and are uncorrected. Elementary analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

<sup>2</sup> Amberlite is a product of Rohm & Haas Co.

#### 3-Deoxy-D-glucose and 3-Deoxy-D-mannose.—

To a well-stirred solution of 34.8 Gm. of crude nitrohexitols in 145 ml. of water was added dropwise 233 ml. of 2 N sodium hydroxide solution while maintaining the temperature at -2 to 0° (dry ice-acetone bath). The solution was transferred immediately to a chilled dropping funnel and added dropwise with rapid stirring to a solution of 87 ml. of concentrated sulfuric acid in 117 ml. of water, while maintaining the temperature at -20° (about 25 min.). The temperature of the solution was allowed to rise spontaneously to 0° (about 30 min.), during which time a slow evolution of gas was observed. After stirring for an additional hour at 0°, the solution was neutralized by the dropwise addition of 2 N sodium hydroxide solution at 0°, then filtered immediately free of precipitated inorganic salts. The salt cake was washed with 100 ml. of methanol, and the combined filtrate and washing was evaporated to dryness *in vacuo* at 40°. The residue was diluted with 1 L. of absolute methanol, filtered, and the cake washed with additional methanol (4 × 50 ml.). These washings were combined with the filtrate and evaporated to near dryness *in vacuo*. The residual syrup was dissolved in 250 ml. of water and passed through a column containing 270 ml. of Amberlite MB-1<sup>3</sup> ion-exchange resin. After washing the column with 3 L. of water, the combined eluate and washing (colorless) was evaporated to dryness *in vacuo* at 40° to give a syrup. This was adsorbed on 100 Gm. of Whatman powdered cellulose, dried by repeated distillations of absolute ethanol *in vacuo*, and transferred to a cellulose packed column (3 × 42 in.) which had been dried previously with acetone. The column was eluted with 92% aqueous acetone and fractions of 200–250 ml. were collected and analyzed by the periodate-thiobarbiturate procedure (8). A total of four major fractions were obtained which were found to be, in order of elution, an artifact (not characterized), 2-deoxyribose (8%), 3-deoxymannose, and 3-deoxyglucose in combined yield from 2-deoxyribose of 65%. A rechromatography of each of these partially separated 3-deoxyhexoses, under the above conditions, gave the individual sugars in sufficient purity to crystallize spontaneously. The ratio of deoxyglucose to deoxymannose was found to be approximately 3:4. The rechromatographed fractions deposited 4.5 Gm. of deoxyglucose and 5.7 Gm. of deoxymannose from absolute ethanol. Two recrystallizations of 3-deoxy-D-mannose (fraction 3) from 95% ethanol gave the analytical sample, m.p. 143–144°;  $[\alpha]_D^{25} + 52^\circ$  (c 1.03, H<sub>2</sub>O) (at equilibrium). These constants compare favorably with those reported by Rembarz (4), m.p. 141–142°;  $[\alpha]_D + 53.1^\circ$  (H<sub>2</sub>O), for this sugar.

*Anal.*—Calcd. for C<sub>6</sub>H<sub>12</sub>O<sub>5</sub>: C, 43.90; H, 7.37. Found: C, 44.27; H, 7.46.

3-Deoxy-D-glucose (fraction 4) was recrystallized similarly from 95% ethanol and gave the following constants: m.p. 137°;  $[\alpha]_D^{25} + 30.6^\circ$  (c 2.45, H<sub>2</sub>O) (at equilibrium). Anet (9) reports m.p. 137°;  $[\alpha]_D^{25} + 30.4^\circ$  (c 3.55, H<sub>2</sub>O) for the crystalline sugar.

*Anal.*—Calcd. for C<sub>6</sub>H<sub>12</sub>O<sub>5</sub>: C, 43.90; H, 7.37. Found: C, 44.00; H, 7.27.

Once these sugars had been obtained in crystalline form, it was found that they could be isolated from the crude deionized isomeric mixture by fractional

crystallization. This was accomplished by diluting the syrup with five parts of absolute ethanol and seeding the solution with 3-deoxy-D-glucose. After removal of the crystals by filtration, the filtrate is concentrated to about one-half volume by removal of the solvent *in vacuo*, and the resulting solution is seeded with 3-deoxy-D-mannose. This procedure is then reapplied to the deoxymannose filtrate until further crops of crystals are no longer obtained. Ordinarily, one can obtain the two sugars in a crystalline yield of about 50% from 2-deoxyribose by application of this procedure. Two recrystallizations of each crop from ethanol are usually required to obtain the pure sugar.

**3-Deoxy-D-glucose p-Nitrophenylhydrazone.**—To a suspension of 100 mg. (0.61 mmole) of 3-deoxy-D-glucose in 1.2 ml. of 95% ethanol was added 100 mg. (0.65 mmole) of *p*-nitrophenylhydrazine and the mixture heated to boiling (water bath) until a clear solution was obtained (5–6 min.). On cooling to 0°, a yellow crystalline solid separated rapidly. This was collected on a filter, washed with 1 ml. of cold 95% ethanol, and dried *in vacuo* over phosphorous pentoxide; yield, 163 mg. (90%), m.p. 201–202.5° dec. Two recrystallizations from 95% ethanol gave the analytical sample, m.p. 203–204° dec.

*Anal.*—Calcd. for  $C_{12}H_{17}N_3O_6$ : C, 48.16; H, 5.72; N, 14.04. Found: C, 48.25; H, 5.84; N, 13.93.

**3-Deoxy-D-mannose p-Nitrophenylhydrazone.**—This was prepared in a manner similar to that described for the 3-deoxyglucose derivative. From 100 mg. of 3-deoxy-D-mannose, there was obtained 171 mg. (94%) of a yellow crystalline solid, m.p. 198–200° dec. For analysis, a sample was recrystallized twice from absolute ethanol, m.p. 202–203° dec. Mixed melting point with 3-deoxy-D-glucose *p*-nitrophenylhydrazone gave m.p. 188–189° dec.

*Anal.*—Calcd. for  $C_{12}H_{17}N_3O_6$ : C, 48.16; H, 5.72; N, 14.04. Found: C, 48.29; H, 5.79; N, 13.96.

**1,2,4,6-Tetra-O-acetyl-3-deoxy-D-glucopyranose.**—A mixture of 2.20 Gm. (13.4 mmoles) of 3-deoxy-D-glucose, 1.2 Gm. of anhydrous sodium acetate, and 16 ml. of acetic anhydride was heated 100–105° (oil bath) for 2 hr. with continuous stirring. The cooled mixture was poured into 20 ml. of ice water, stirred for 1 hr., and extracted with chloroform (4 × 50 ml.). The combined extract was washed with water (50 ml.), aqueous saturated sodium bicarbonate (50 ml.), and water (50 ml.), dried over magnesium sulfate, filtered, and evaporated *in vacuo* to a syrup. This was crystallized from 10 ml. of absolute ethanol; yield, 2.18 Gm. (49%), m.p. 133.5–134°. Two recrystallizations from ethanol gave the analytical sample, m.p. 134–135°;  $[\alpha]_D^{25} -12^\circ$  [c 1.1, (CH<sub>2</sub>Cl<sub>2</sub>)];  $\bar{\nu}_{max}^{KBr}$  (cm.<sup>-1</sup>) 1740 (acetate C=O), 1380 sh (methyl), 1230 (acetate C—O—C), and no absorption at 3400 (OH). Reported values (10) are m.p. 129–130° and  $[\alpha]_D^{25} -20^\circ$ .

*Anal.*—Calcd. for  $C_{14}H_{20}O_9$ : C, 50.60; H, 6.07. Found: C, 50.68; H, 5.99.

**3-Deoxy-D-mannitol.**—To a stirred solution of 0.70 Gm. (18 mmoles) of sodium borohydride in 20 ml. of water was added dropwise, over a period of 20 min., a solution of 1.00 Gm. (6.1 mmoles) of 3-deoxy-D-mannose in 40 ml. of water. After stirring for an additional 30 min., the solution was passed through a column containing 100 ml. of Amberlite IR-120 (H+) ion-exchange resin (gas evolution). After washing the column with 200 ml. of water, the eluate and washing were combined and evaporated to dryness *in vacuo* at 40° giving a partially crystalline residue. Boric acid was removed by successive evaporations *in vacuo* of methanol (5 × 50 ml.) to give a clear, colorless syrup; yield, 1.02 Gm. (101%);  $[\alpha]_D^{25} -30^\circ$  (c 0.98, H<sub>2</sub>O). Literature (6)  $[\alpha]_D^{25} -27^\circ$  (c 0.9, H<sub>2</sub>O).

**1,2,4,5,6-Penta-O-benzoyl-3-deoxy-D-mannitol.**—To a stirred solution of 0.90 Gm. (6.0 mmoles) of 3-deoxy-D-mannitol in 12 ml. of reagent pyridine at 0° was added dropwise, over a period of 15 min., 5.1 ml. (45 mmoles) of benzoyl chloride. After stirring for 1 additional hr. at 0°, the mixture was stored overnight at 5° in a stoppered flask. The reaction was quenched by the dropwise addition of 5 ml. of water, then poured into 100 ml. of cold water with rapid stirring. The mixture was extracted with chloroform (4 × 25 ml.), and the combined extracts were washed with aqueous saturated sodium bicarbonate (2 × 50 ml.) and water (50 ml.), then dried over magnesium sulfate, filtered, and evaporated to dryness *in vacuo* at 40°. The last traces of pyridine were removed by evaporation of toluene (2 × 10 ml.) at low pressure. The residual syrup was dissolved in 6 ml. of ethyl acetate and 9 ml. of pentane, treated with 500 mg. of activated charcoal, and filtrated. The filtrate was set aside at 5° for several hours, during which time the product separated as a white crystalline solid. This was collected on a filter, washed with pentane-ethyl acetate (4:1), and dried; yield, 1.39 Gm., m.p. 95–103°. A second crop was isolated from the filtrate, 0.71 Gm., m.p. 93–103°. Combined yield, 2.10 Gm. (57%). For analysis, a sample was recrystallized twice from ethyl acetate-pentane (2:3), m.p. 105–107°;  $[\alpha]_D^{25} -32^\circ$  [c 1.2, (CH<sub>2</sub>Cl<sub>2</sub>)];  $\bar{\nu}_{max}^{KBr}$  (cm.<sup>-1</sup>) 1720 (benzoate C=O) 1275 sh (benzoate C—O—C), 705 (monosubstituted phenyl). Literature (6) m.p. 105–106°;  $[\alpha]_D^{25} -34.4^\circ$  (c 0.6, CHCl<sub>3</sub>).

*Anal.*—Calcd. for  $C_{31}H_{34}O_{16}$ : C, 71.71; H, 4.99. Found: C, 71.94; H, 4.89.

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