## The reaction of *p*-toluenesulfonylhydrazide with 1,2:5,6-di-*O*-isopropylidene-*a*-D-*ribo*-hexofuranos-3-ulose\*

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The transformation of a carbonyl function into a methylene group by reduction of the *p*-toluenesulfonylhydrazone derivative with borohydride has previously been described<sup>1,2</sup>. In attempting to apply this procedure to the synthesis of isotopically labelled 3-deoxy-D-ribo-hexose we have found that condensation of 1,2:5,6di-O-isopropylidene- $\alpha$ -D-ribo-hexofuranos-3-ulose with *p*-toluenesulfonylhydrazine yields a readily isolable carbinolamine (1). The isolation of carinolamines of compounds very susceptible to addition has been reported previously<sup>3-8</sup> but not in the carbohydrate series. The carbinolamine structure was assigned on the following basis.



The molecule of the product contains three protons that can be exchanged with  $D_2O$ . These protons resonate at  $\tau$  1.51, 4.72, and 5.12 and are assigned to the two N-H groups ( $\tau$  1.51 and 5.12) and the OH group ( $\tau$  4.72). These assignments are supported by the observation that the signals of the N-H protons have the same coupling constants, and that they are coupled to one another, whereas the OH signal appears as a singlet. Also, the carbinolamine derivative is readily reduced by sodium borohydride to 1,2:5,6-di-O-isopropylidene- $\alpha$ -D-glucose, clearly demonstrating that it is not simply an intimate mixture of the keto compound and the hydrazine. The starting ketone is reduced by borohydride to the *allo* rather than to the *gluco* isomer<sup>9</sup>. The reduction of 1 provides a convenient route for the synthesis of 1,2:5,6-di-O-isoprop-pylidene- $\alpha$ -D-glucopyranose having deuterium or tritium at C-3.

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The configuration at C-3 of 1 has not been established, but it is probable that the hydroxyl group is above the plane of the ring and the *p*-toluenesulfonylhydrazino group is below it (1b). This assignment is made on the basis that reduction of the carbinolamine derivative yields the *gluco* isomer. It should be noted that all of the protons of 1 resonate at higher field than those of 1,2:5,6-di-*O*-isopropylidene- $\alpha$ -Dglucose. This shift would be expected if the aromatic ring can rotate above or below the plane of the tetrahydrofuran ring system, and does not provide a basis for assigning the configuration at C-3.

The form of the precursor keto sugar seems to be important in determining the ease of condensation with *p*-toluenesulfonylhydrazine. For example, oxidation of di-O-isopropylidene- $\alpha$ -D-glucopyranose by the catalytic ruthenium tetraoxide-sodium metaperiodate method of Parikh and Jones<sup>10</sup> leads to the hydrated ketone. Material prepared in this manner does not condense with *p*-toluenesulfonylhydrazine under the same conditions as does the ketone prepared by oxidation with methyl sulfoxide-acetic anhydride, indicating that a free keto group is required for the condensation reaction. Ferrier has reported the condensation of *p*-toluenesulfonylhydrazine with methyl 4,6-O-benzylidene-2-deoxy- $\alpha$ -D-*erythro*-hexosid-3-ulose<sup>11</sup> but did not give details of the preparation of the keto compound.

The carbinolamine undergoes dehydration readily to give two isomeric hydrazones, which arise because rotation about the carbon-nitrogen double bond is restricted. A tentative assignment of structure may be made for these isomers from the coupling constant between H-4 and H-5. In one isomer  $J_{4,5}$  is 9.6 Hz, indicating<sup>17</sup> an H-4-H-5 dihedral angle of about 180°. With this restriction, the *p*-tolylsulfonyl group is most readily accommodated as shown in structure **2**. In the other isomer  $J_{4,5}$  is 2.0 Hz, indicating a much smaller dihedral angle. This arrangement of the side chain, with the 5,6-isopropylidene group rotated away from C-3, allows the *p*-tolylsulfonyl group to occupy the alternative position, and this isomer has been assigned structure **3**. In both isomers the H-2 and H-4 signals show splittings of approximately 1.4 Hz, attributable to long-range effects. An n.m.r. spectrum of the unfractionated reaction mixture for the formation of the hydrazones showed that isomer **2** accounts for 60% of the product formed.

An attempt to reduce the mixed tosylhydrazones with sodium borohydride to 3-deoxy-1,2:5,6-di-O-isopropylidene- $\alpha$ -D-*ribo*-hexofuranose gave instead a crystalline product that appeared to be 3-deoxy-1,2:5,6-di-O-isopropylidene- $\alpha$ -D-*erythro*-hex-3-enofuranose, an unsaturated sugar. Such elimination reactions are generally considered to be base-catalyzed<sup>11</sup> and it seemed possible that borohydride was serving as a base rather than as a reductant. To test this hypothesis a sample of the hydrazone was treated under reflux in methanolic sodium methylate; however, this treatment failed to produce even a trace of the unsaturated sugar, as judged by t.l.c.

## EXPERIMENTAL

General — N.m.r. spectra were obtained on a Varian A-60 spectrometer; chemical shifts are expressed relative to tetramethylsilane as an internal standard.

Evaporations were carried out at water-aspirator pressure. T.l.c. was carried out on glass plates coated with Silica Gel G (Merck), and 95% benzene-methanol as solvent. Spots were visualized by spraying with 10% sulfuric acid and heating for 5 min at  $110^{\circ}$ .

1, 2:5, 6-Di-O-isopropylidene-3-C-(p-toluenesulfonylhydrazino)- $\alpha$ -D-gluco (allo)hexofuranose (1). — 1,2:5,6-Di-O-isopropylidene- $\alpha$ -D-glucofuranose (13.0 g) was oxidized with methyl sulfoxide-acetic anhydride according to the procedure of Sowa and Thomas<sup>9</sup>. Excess reagents were removed at 45° with a mechanical pump. The residue was dissolved in 100 ml ethanol and 9.3 g p-toluenesulfonylhydrazine added. The reaction mixture was kept overnight and 12.5 g of crude product (58%) was isolated by filtration. Recrystallization of this material by dissolution in ethanol at approximately 50° and cooling to 4° gave a compound that decomposed between 143° and 146°. The rate of heating affected the temperature of decomposition.

N.m.r. data (methyl sulfoxide- $d_6$ ):  $\tau$  8.03, 8.77 and 8.81 (3-proton singlets, CMe<sub>2</sub>), 7.62 (3-proton singlet, ArCH<sub>3</sub>), 5.72 (1-proton doublet,  $J_{1,2}$  3.6 Hz, H-2), 5.12 (1-proton doublet, J 3.4 Hz, CNH), 4.72 (1-proton singlet, OH), 4.25 (1-proton doublet,  $J_{1,2}$  3.6 Hz, H-1), 2.22, 2.62 (4-protons 2 doublets, J 9.0 Hz, ArH), 1.5 (1-proton doublet, J 3.4 Hz, SNH). After exchange with D<sub>2</sub>O the signals at  $\tau$  5.12, 4.72 and 1.5 disappeared.

Anal. Calc. for C<sub>19</sub>H<sub>28</sub>N<sub>2</sub>SO<sub>8</sub> (444.52): C, 51.34; H, 6.35. Found: C, 51.24; H, 6.42.

1,2:5,6-Di-O-isopropylidene- $\alpha$ -D-glucofuranose. — The carbinolamine 1 (1.0 g) in 50 ml of ethanol with 1.0 g of sodium borohydride was heated under reflux for 18 h. The reaction mixture was concentrated to dryness and the residue extracted with ethyl acetate. Removal of solvent gave a crude product that was recrystallized from cyclohexane; yield 0.4 g, m.p. and mixed m.p. 110°. The compound gave the same n.m.r. spectrum as the authentic material.

Isomeric forms of 1,2:5,6-di-O-isopropylidene- $\alpha$ -D-ribo-hexofuranos-3-ulose ptoluenesulfonylhydrazone (**2** and **3**). — A solution of **1** (1 g) in 100 ml of ethanol was heated for 6 h under reflux. T.l.c. indicated the presence of two new major components ( $R_F$  0.32 and 0.48), and a minor component ( $R_F$  0.60). When the reaction mixture was cooled a precipitate formed that consisted of starting material ( $R_F$  0.23) and traces of the components having  $R_F$  0.32 and 0.48. The supernatant solution was concentrated to 25 ml and the compound having  $R_F$  0.32 crystallized as fine needles; yield 0.42 g (43%) that decomposed at 168°; n.m.r. data (CDCl<sub>3</sub>):  $\tau$  8.67 (9 protons, singlet with shoulder, CMe<sub>2</sub>), 8.43 (3-proton singlet, CMe<sub>2</sub>), 7.61 (3-proton singlet, ArCH<sub>3</sub>), 5.48 (1-proton quartet,  $J_{4,5}$  9.6 Hz,  $J_{2,4}$  1.4 Hz, H-4), 5.15 (1-proton quartet,  $J_{1,2}$  4.2 Hz, H-2), 4.25 (1-proton doublet, H-1). 2.22 and 2.75 (2-proton doublets, J 9.0 Hz, ArH); -0.27 (1-proton singlet N-H) This compound was assigned structure **2**.

Anal. Calc. for  $C_{19}H_{26}N_2SO_7$  (426.50) : C, 53 51; H, 6.15. Found: C, 53.56; H, 6.07.

After removal of crystals of the first isomer, concentration of the solution to 15 ml under a stream of nitrogen gave a crop of cotton-like needles; yield, 0.250 g

(25%), m.p. 172–174° decomp. This product consisted primarily of the compound having  $R_F$  0.48, together with traces of the compound having  $R_F$  0.32; n.m.r. data (CDCl<sub>3</sub>):  $\tau$  8.88 (6-proton singlet, CMe<sub>2</sub>), 8.71 and 8.63 (3-proton singlets, CMe<sub>2</sub>), 7.61 (3-proton singlet, ArCH<sub>3</sub>), 5.38 (1-proton quartet,  $J_{2,4}$  1.5 Hz,  $J_{4,5}$  2.0 Hz, H-4), 5.03 (1-proton quartet,  $J_{1,2}$  4.8 Hz, H-2), 4.03 (1-proton doublet, H-1), 2.18 and 2.71 (2-proton doublets, 9.0 Hz, ArH), 1.24 (1-proton singlet N–H). This compound was assigned structure 3.

Anal. Calc. for C<sub>19</sub>H<sub>26</sub>N<sub>2</sub>SO<sub>7</sub> (426.50): C, 53.51; H, 6.15. Found: C, 53.50; H, 5.97.

3-Deoxy-1,2:5,6-di-O-isopropylidene- $\alpha$ -D-erythro-hex-3-enofuranose. — A solution of 5 g of 1,2:5,6-di-O-isopropylidene- $\alpha$ -D-ribo-hexofuranose-3-ulose p-toluenesulfonylhydrazone (2 and 3) in 100 ml of ethyl alcohol was heated with 2.8 g of sodium borohydride for 19 h under reflux. T.l.c. indicated the presence of a major component having  $R_F$  0.60. The reaction mixture was concentrated to dryness and extracted with ethyl acetate. Removal of solvent gave a solid product (1.75 g) which, upon purification by sublimation, gave material having  $R_F$  0.60, m.p. 49.0–50.5° (Weygand and Wolz<sup>13</sup> reported m.p. 51°; Brimacombe et al.<sup>14</sup> reported m.p. 46-48°). The compound showed weak absorption at 1620 cm<sup>-1</sup> (KBr pellet); n.m.r. data (CDCl<sub>3</sub>):  $\tau$  8.59 (3-proton singlet, CMe<sub>2</sub>), 8.49 (9-proton singlet, CMe<sub>2</sub>), 5.92 (2-proton multiplet, H-6), 5.40 (1-proton triplet, H-5), 4.68 (2-proton multiplet, H-2 and H-3), 3.90 (1-proton doublet, J 4.5 Hz, H-1).

## REFERENCES

- 1 L. CAGLIOTO AND P. GRASELLI, Chem. Ind. (London), (1964) 153.
- 2 A. N. DE BELDER AND H. WEIGEL, Chem. Ind. (London), (1964) 1689.
- 3 P. K. CHANG AND T. L. V. ULBRICHT, J. Amer. Chem. Soc., 80 (1958) 976.
- 4 A. HANTZSCH, Ber., 25 (1892) 701.
- 5 A. KLING, Compt. Rend., 148 (1909) 569.
- 6 G. KNÜPFER, Monatsch., 32 (1911) 768.
- 7 E. J. POZIOMELS, D. N. KRAMER, B. W. FROMM, AND W. A. MOSHER, J. Org. Chem., 26 (1961) 432.
- 8 R. CONTOREL AND J. GUENGET, Bull. Soc. Chim. Fr., (1961) 1285.
- 9 W. SOWA AND G. H. S. THOMAS, Can. J. Chem., 44 (1966) 836.
- 10 V. M. PARIKH AND J. K. N. JONES, Can. J. Chem., 43 (1965) 3452.
- 11 R. J. FERRIER, J. Chem. Soc., (1964) 5443.
- 12 M. KARPLUS, J. Chem. Phys., 30 (1959) 11.
- 13 F. WEYGAND AND H. WOLZ, Ber., 85 (1952) 256.
- 14 J. S. BRIMACOMBE, M. E. EVANS, E. J. FORBES, A. B. FOSTER, AND J. M. WEBBER, Carbohyd. Res., 4 (1967) 239.

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