Carbohydrate Research, 78 (1980) 185–189

Note

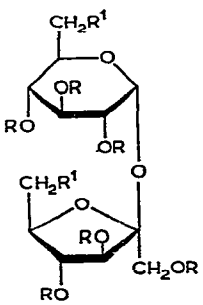
Synthesis of 6,6′-dideoxy-6,6′-dihalosucroses and conversion of 6,6′-dichloro-6,6′-dideoxysucrose hexa-acetate into 6,6′-diamino-6,6′-dideoxysucrose*

RIAZ KHAN, C. LAL BHARDWAJ, KHIZAR S. MUFTI, AND MICHAEL R. JENNER

Tate & Lyle Limited, Group Research and Development, Philip Lyle Memorial Research Laboratory, University of Reading, P.O. Box 68, Reading RG6 2BX (Great Britain)

(Received April 23rd, 1979; accepted for publication, May 1st, 1979)

A direct synthesis of 6,6′-dichloro-6,6′-dideoxysucrose (**2**) is of interest because, in addition to its value as a synthetic intermediate[2], **2** has a reversible contraceptive effect in male rats[3]. The reaction of sucrose with sulphuryl chloride gives[4], after chromatography, the dichloride **2** in 29% yield. Since the completion of our work reported in this communication, two more reagents, namely, tris(dimethylamino)-phosphine–carbon tetrachloride–potassium hexafluorophosphine–tetramethylammonium chloride–*N*,*N*-dimethylformamide[5] and triphenylphosphine–carbon tetrachloride–pyridine[6], have been reported to effect chlorination at C-6 and C-6′ in sucrose.



1 R = Ac, R^1 = Cl
2 R = H, R^1 = Cl
3 R = Ac, R^1 = Br
4 R = H, R^1 = N_3
5 R = H, R^1 = NH_2
6 R = H, R^1 = NHAc
7 R = Ac, R^1 = NHAc

Chlorination reactions. The methanesulphonyl chloride–*N*,*N*-dimethylformamide (reagent *A*) complex effects selective replacement of primary hydroxyl groups in hexopyranoside[7,8], methyl maltoside[8], and sucrose derivatives[9] by chlorine. Under forcing conditions, chlorination at a chiral centre has also been observed[8,9].

Treatment of sucrose with reagent *A* at −20° for 1.5 h and then at 70° for 10 h afforded a mixture of products. In t.l.c., these products moved faster than a standard

*Sucrochemistry: Part XXVIII. For Part XXVII, see Ref. 1.

sample[10] of the dichloride **2**, presumably because of the formation of formic esters during the reaction. Sugars are known[7,9] to give formate derivatives when treated with reagent *A*. Hence, the reaction mixture was first treated with acetic anhydride and pyridine, and the product was isolated by precipitation from ice–water. The residue was then de-esterified, using sodium methoxide in methanol, and re-esterified with acetic anhydride and pyridine, to give the crystalline dichloride hexa-acetate **1** in 51% yield. Conventional de-esterification of **1** gave the dichloride **2** in 98% yield. Despite the fact that the over-all yield of **2** was lower than that (92%) reported by Whistler and co-workers[6], this method has the advantage that the product can be isolated without recourse to column chromatography.

The selective replacement of primary hydroxyl groups in sugars and certain nucleosides by chlorine has been achieved by the use of triphenylphosphine–*N*-chlorosuccinimide–*N*,*N*-dimethylformamide (reagent *B*)[11]. Treatment of sucrose with reagent *B* gave a mixture that contained (t.l.c.) the dichloride **2** as the major carbohydrate product, which could be isolated as **1**, after acetylation and chromatography, in 69% yield.

Bromination reactions. Treatment of sucrose with methanesulphonyl bromide[12,13] and *N*,*N*-dimethylformamide (reagent *C*) at −50° for 1.5 h, then at room temperature for 24 h, and finally at 70° for 4 h gave, after processing as described for **1** with reagent *A*, the dibromide hexa-acetate **3** in 24% yield. The structure of **3** was supported by its ^{1}H-n.m.r. and mass spectra.

Use of triphenylphosphine, *N*-bromosuccinimide, and *N*,*N*-dimethylformamide (reagent *D*) is known[11] to effect bromination at primary hydroxyl groups in monosaccharides and certain nucleosides. Treatment of sucrose with reagent *D* gave, after processing as described for **1** with reagent *B*, the dibromide hexa-acetate **3** in 21% yield.

Conversion of the dichloride hexa-acetate **1** *into the diamine* **5**. Treatment of **1** with sodium azide in hexamethylphosphoric triamide at 85° for 24 h, followed by de-esterification with sodium methoxide in methanol, gave the diazide **4** in 70% yield. Hydrogenation of **4** over palladium-on-charcoal afforded the corresponding diamine **5**, which was treated with acetic anhydride in methanol, to give the di-*N*-acetyl derivative **6**. Conventional acetylation of **6** with acetic anhydride and pyridine afforded the hexa-acetate **7**, the first-order coupling constants ($J_{1,2}$ 3.75, $J_{2,3}$ 10.00, $J_{3,4}$ 10.00, and $J_{4,5}$ 10.00 Hz) of which confirmed the *gluco* configuration and $^4C_1$ conformation.

EXPERIMENTAL

For details of general procedure, see Part XXIV[14].

6,6′-Dichloro-6,6′-dideoxysucrose hexa-acetate (**1**). — (*a*) A solution of sucrose (20 g) in *N*,*N*-dimethylformamide (200 ml) was treated with methanesulphonyl chloride (80 ml) at −20° for 1.5 h. The mixture was brought to room temperature over a period of 2 h and then heated at 70° for 10 h. The mixture was then treated with acetic anhydride (50 ml) and pyridine (200 ml), initially at −5° and then at

room temperature for 16 h. The solution was poured into ice–water, and the precipitate was collected, washed well with water, and taken up in dichloromethane. The solution was dried (Na_2SO_4) and concentrated to give a syrupy residue that was then treated with sodium methoxide in methanol (500 ml) to pH 10. T.l.c. (chloroform–methanol, 8:1) showed a major product which was coincident with an authentic sample[10] of the dichloride **2**. The solution was deionised with Amberlyst-15(H^+) resin and concentrated, and the residue was treated with acetic anhydride (40 ml) and pyridine (200 ml) at room temperature for 8 h. The resulting solution was then concentrated by co-distillation with toluene, and the syrupy residue was crystallised from ether–light petroleum, to give **1** (22.4 g, 50.6%), m.p. 118–119° (lit.[14], m.p. 117–118°), $[\alpha]_D$ +55.8° (*c* 1.4, chloroform). Mass-spectral data [3:1 doublets (1 Cl) due to oxycarbonium ions]: *m/e* 307, 247, 157, and 145. The 100-MHz, ^{1}H-n.m.r. spectrum was identical with that of an authentic[10] sample.

Conventional de-esterification of **1** (1 g), with sodium methoxide in methanol to pH 10, at room temperature for 24 h gave **2** (590 mg, 98%). The physical constants were identical to those reported for an authentic sample[10].

(*b*) A cooled (0–5°) solution of sucrose (10 g) in *N*,*N*-dimethylformamide (320 ml) was treated with *N*-chlorosuccinimide (24 g), and triphenylphosphine (47.2 g) was added during 15 min. The mixture was then stirred at 50–55° for 5 h, after which time t.l.c. (chloroform–methanol, 8:1) showed a fast-moving, major product. The solution was concentrated by co-distillation with toluene, and the resulting syrup was partitioned between chloroform (3 × 250 ml) and water (3 × 100 ml). The aqueous layer was concentrated to dryness, and the residue was acetylated with acetic anhydride (20 ml) and pyridine (200 ml) at room temperature for 24 h. The solution was then concentrated, and a solution of the residue in dichloromethane was washed with 10% aqueous sodium hydrogen carbonate. The organic layer was dried (Na_2SO_4) and concentrated. A solution of the syrupy residue in ether was decolorised (activated charcoal) and concentrated, and the residue was eluted from a column of silica gel (400 g) with ether–light petroleum (4:1), to give **1** (13 g, 68.7%).

6,6'-Dibromo-6,6'-dideoxysucrose hexa-acetate (**3**). — (*a*) A solution of sucrose (2.25 g) in *N*,*N*-dimethylformamide (25 ml) was treated with methanesulphonyl bromide[12,13] at −50° for 1.5 h. The mixture was allowed to attain room temperature slowly, stirred for 24 h, and then heated at 70° for 4 h. The mixture was then worked up, as described for **1** in (*a*), to give **3** (1.12 g, 24%), m.p. 126–127° (from ether), $[\alpha]_D$ +42.2° (*c* 1, chloroform); n.m.r. data ($CDCl_3$): τ 4.43 (d, $J_{1,2}$ 3.5 Hz, H-1), 5.15 (q, $J_{2,3}$ 10.00 Hz, H-2), 4.57 (q, $J_{3,4}$ 10.00 Hz, H-3), 4.96 (t, $J_{4,5}$ 9.5 Hz, H-4), and 7.84–7.99 (6 OAc). Mass-spectral data [3:1 doublets (1 Br) due to oxycarbonium ions]: *m/e* 351, 291, 249, 231, and 189.

Anal. Calc. for $C_{24}H_{32}Br_2O_{15}$: C, 40.0; H, 4.5; Br, 22.2. Found: C, 39.8; H, 4.4; Br, 22.2.

(*b*) A cooled (0–5°) solution of sucrose (3.42 g) in *N*,*N*-dimethylformamide (120 ml) was treated with *N*-bromosuccinimide (8.85 g), and then triphenylphosphine

(13.1 g) was added with stirring over a period of 15 min. The mixture was heated at 50° for 10 h and then worked up, as described for **1** in (*b*), to give a syrup. Elution from a column of silica gel (200 g) with ether–light petroleum (4:1) gave **3** (1.5 g, 20.8%).

6,6'-Diazido-6,6'-dideoxysucrose (**4**). — A solution of **1** (5 g) in hexamethylphosphoric triamide (25 ml) was treated with sodium azide (5 g) at 85° for 24 h. The cooled solution was then poured into ice–water, and the precipitate was filtered off, washed well with water, and dried. The product was treated with sodium methoxide in methanol to pH 10, at room temperature for 8 h, after which the solution was deionised with Amberlyst-15(H^+) resin and concentrated, to give **4** (2.7 g, 70%), $[\alpha]_D$ +78.8° (*c* 1, water); ν_{max} 3420–3180 (OH) and 2100 cm^{-1} (azide).

Anal. Calc. for $C_{12}H_{20}N_6O_9$: C, 36.7; H, 5.1; N, 21.4. Found: C, 36.5; H, 5.1; N, 19.7.

6,6'-Diamino-6,6'-dideoxysucrose (**5**). — A solution of the diazide **5** (1 g) in methanol (30 ml) was hydrogenated in the presence of 5% palladium-on-barium sulphate at 80 p.s.i., for 6 h at 40°. T.l.c. (chloroform–methanol, 2:1) then revealed a slow-moving product which gave a positive reaction with ninhydrin. The catalyst was removed, the filtrate was concentrated, and the residue was partitioned between ethyl acetate and water. The aqueous layer was concentrated to a syrup; trituration with acetone then gave **5** (870 mg, 95%), m.p. 105–110°, $[\alpha]_D$ +51.6° (*c* 1.5, water); ν_{max} 3400–3100 (OH, NH_2) and 1652 cm^{-1}.

Anal. Calc. for $C_{12}H_{24}N_2O_9 \cdot C_6H_{12}O_2$: C, 47.4; H, 7.9; N, 6.1. Found: C, 47.4; H, 7.6; N, 5.8.

6,6'-Diacetamido-6,6'-dideoxysucrose (**6**). — A solution of **5** (1 g) in methanol (100 ml) was treated with acetic anhydride (2.5 ml) for 24 h at room temperature. T.l.c. (chloroform–methanol, 2:1) then showed a fast-moving product. The solution was concentrated to a syrup which was triturated with ether, to give **6** (640 mg, 80%), m.p. 85–88°, $[\alpha]_D$ +44.5° (*c* 0.86, methanol); ν_{max} 3220 (NH), 1650 and 1550 cm^{-1} (amide).

Anal. Calc. for $C_{16}H_{28}N_2O_{11}$: C, 45.3; H, 6.6; N, 5.6. Found: C, 45.2; H, 6.8; N, 5.5.

6,6'-Diacetamido-6,6'-dideoxysucrose hexa-acetate (**7**). — A solution of **5** (1 g) in pyridine (24 ml) was treated with acetic anhydride (2.5 ml) at room temperature for 24 h. T.l.c. (chloroform–methanol 9:1) showed a fast-moving product. The solution was concentrated by co-distillation with toluene, to afford a syrup, which was eluted from a column of silica gel (50 g), using chloroform–acetone (4:1), to give **7** (750 mg, 75%), m.p. 86–89° (from ether), $[\alpha]_D$ +70.5° (*c* 1.1, chloroform); ν_{max} 3440 (NH), 1750 (ester), and 1675 (amide) cm^{-1}; n.m.r. (100 MHz) data: τ 4.4 (d, $J_{1,2}$ 3.75 Hz, H-1), 5.28 (q, $J_{2,3}$ 10.0 Hz, H-2), 4.66 (t, $J_{3,4}$ 10.0 Hz, H-3), 5.23 (t, $J_{4,5}$ 10.0 Hz, H-4), 4.62 (d $J_{3',4'}$ 6.0 Hz, H-3'), 4.8 (t, $J_{4',5'}$ 6.0 Hz), 3.43, 3.63 (2 NH), and 7.7–8.0 (8 OAc).

Anal. Calc. for $C_{34}H_{42}N_2O_{19}$: C, 49.15, H, 5.85; N, 4.1. Found: C, 48.9; H, 6.2; N, 4.0.

ACKNOWLEDGMENTS

We thank Professor A. J. Vlitos, Chief Executive of the Tate & Lyle Research Centre, for his interest and support, and Dr. K. J. Parker for helpful discussions.

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