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Formylation of primary hydroxyl groups in sugars

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ABSTRACT

Application of 99% formic acid at 25° formylates primary hydroxyl groups as shown by the easy formation of 6-*O*-formyl-D-glucopyranose and 6-*O*-formyl-D-fructofuranose, isolated as their tetra-acetates in yields of 77% and 31%, respectively. Likewise, D-glucitol gave the 2,3,4,5-tetra-*O*-acetyl-1,6-di-*O*-formyl derivative (84%) and methyl α-D-glucopyranoside gave the 6-formate (74%) characterized as the crystalline triacetate. On storage of the triacetate in methanol at 25°, the formyl group was lost and the 2,3,6-triacetate was formed, whereas the corresponding tribenzoate was deformylated in acidic methanol without migration of the benzoyl groups.

INTRODUCTION

Formic acid (98–99%) had been used to esterify cholic acid[1] and starch[2–4] where it gives an approximate monoformate with nearly all the ester groups at position 6.

Having a need to protect primary alcohol groups in sugars at moderate temperatures, the use of 99% formic acid at 25° to block the primary hydroxyl groups of D-glucitol (**1**), D-glucose (**4**), D-fructose (**8**), methyl α-D-glucopyranoside (**12**), and sucrose have been examined. Thus, **12** gave 74% of the 6-formate, **1** and **4** gave mixtures from which the primary formates (**2** and **5**) could be isolated as the acetylated derivatives **3** (84%) and **6** (77%), and **8** gave 30% of 1,2,3,4-tetra-*O*-acetyl-6-*O*-formyl-D-fructofuranose derivative (**10**). The times of reaction varied from 2 to 4 h to reach maximum yield and $<10\%$ unformylated sugar was then present (t.l.c.). The starting materials dissolved slowly and ~ 1 h was required for complete dissolution. Only methyl 6-*O*-formyl-α-D-glucopyranoside triacetate (**14**) and tribenzoate (**16**) were crystalline.

Sucrose formates were not obtained. Sucrose dissolved slowly during the formylation reaction and complete dissolution occurred after 1–5 h. T.l.c. then revealed D-glucose and D-fructose and their 6-formates. The ratio of formate to free sugar was $\sim 2{:}3$. Thus, in the short reaction period used, extensive cleavage of the sucrose occurred, possibly either by hydrolysis or by displacement with formate ion to produce a labile glycosyl formate.

The formyl groups in formylated nucleosides can be removed[5] by treatment with

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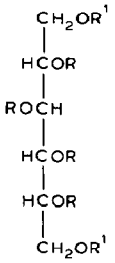

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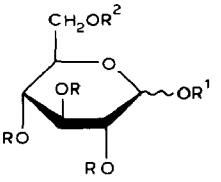
2 R = H, R' = HCO
3 R = Ac, R' = HCO



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6 R = R' = Ac, R² = HCO
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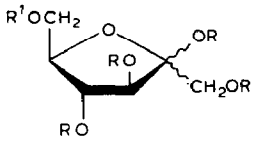
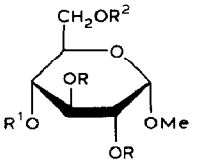


8 R = R' = H
9 R = H, R' = HCO
10 R = Ac, R' = HCO
11 R = R' = Ac



12 R = R' = R² = H
13 R = R' = H, R² = HCO
14 R = R' = Ac, R² = HCO
15 R = R² = Ac, R' = H
16 R = R' = Bz, R² = HCO
17 R = R' = Bz, R² = H

boiling methanol without loss of acetyl groups. On methanolysis of **14** at 25°, deformylation was essentially complete in 3 days but acetyl migration occurred to give the 2,3,6-triacetate **15**. The low stability of **14** is suggested further by the observation that **13**, on storage for a year, contained crystals of methyl α-D-glucopyranoside (**12**). On the other hand, 2,3,4-tribenzoate **16** was resistant to methanolysis even at reflux temperature for 24 h, thereby illustrating the variable stability of formates as observed also in nucleoside derivatives[5]. When a small amount of methanolic hydrogen chloride was added to the solution of **16** in methanol, formate removal occurred within 24 h at 25° producing methyl 2,3,4-tri-*O*-benzoyl-α-D-glucopyranoside (**17**).

EXPERIMENTAL

General methods. — Melting points were determined with a Fisher–Johns apparatus and are uncorrected. Optical rotations were measured with a Perkin–Elmer 241 Polarimeter. Column chromatography employed Merck silica gel (230–400 mesh) at 25°. T.l.c. was performed at 25° on Silica Gel 60 or 60 F_{254} (Merck) with detection by charring with sulfuric acid or by short-wavelength u.v. light. The ^1H- and ^{13}C-n.m.r. spectra (internal Me_4Si) were recorded with a Nicolet NT 200 spectrometer, and the

^{13}C-n.m.r. data are given in Table I. P.c. was performed on Whatman No. 1 paper with *n*-BuOH–EtOH–H_2O (4:1:5, upper layer) at 25°, with detection[8] by *p*-anisidine phosphate in ethanol.

2,3,4,5-Tetra-O-acetyl-1,6-di-O-formyl-D-glucitol (**3**). – A mixture of **1** (1.82 g, 10 mmol) and formic acid (5 mL) was stirred at 25° for 2 h, then concentrated at 25° under reduced pressure. To the syrupy residue was added pyridine (10.0 mL) and acetic anhydride (5.0 mL), and the mixture was shaken to effect dissolution, stirred at 25° for 4 h, poured into ice and water, and extracted with ether. The extract was washed successively with water, aqueous 5% cupric sulfate, and water, dried ($MgSO_4$), and concentrated under reduced pressure. Column chromatography [ethyl acetate–light petroleum (3:17) then benzene–acetone (9:1)] gave **3** (3.43 g, 84%), isolated as a colorless syrup, $[\alpha]_D^{25}$ +17° (*c* 1.2, chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 8.06 (s, 2 H, 2 HCOO), 5.45 (m, 2 H, H-3,4), 5.25 (m, 1 H, H-2), 5.10 (m, 1 H, H-5), 4.44 (m, 2 H, H-1,1'), 4.21 (m, 2 H, H-6,6'), 2.17 (s, 3 H, Ac), 2.08 (s, 9 H, 3 Ac).

Anal. Calc. for $C_{16}H_{22}O_{12}\cdot 0.5H_2O$: C, 46.26; H, 5.54. Found: C, 46.54; H, 5.80.

1,2,3,4-Tetra-O-acetyl-6-O-formyl-D-glucopyranose (**6**). — A mixture of **4** (2.70 g, 15 mmol) and 99% formic acid (7 mL) was stirred at 25° for 3 h, then concentrated at 25° under reduced pressure. The syrupy residue was acetylated as described above. Column chromatography (chloroform–acetone–light petroleum, 4:1:10) of the product gave $\alpha\beta$-**6** as a hygroscopic glass (4.35 g, 77%), $[\alpha]_D^{25}$ +57° (*c* 2.1, chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 8.06 (s, 1 H, HCOO), 6.33 (d, ~5.45 H, $J_{1,2}$ 3.3 Hz, H-1α), 5.73 (d, ~0.55 Hz, $J_{1,2}$ 8.0 Hz, H-1β), 5.06–5.60 (m, 3 H, H-2,3,4), 3.87–4.28 (m, 3 H, H-5,6,6'), 2.02–2.19 (m, 12 H, 4 Ac).

Anal. Calc. for $C_{15}H_{20}O_{11}$: C, 47.87; H, 5.32. Found: C, 47.66; H, 5.71.

TABLE I

^{13}C-N.m.r. chemical shifts (δ, p.p.m.)[a]

Compound	*C-1*	*C-2*	*C-3*	*C-4*	*C-5*	*C-6*	*CH_3O*	*HCOO*
3	60.05	69.0	68.0	68.7	68.2	60.3		160.0
								159.2
6 ($\alpha\beta$)	88.5	69.2	69.3	67.6	68.7	60.6		160.1
	91.2	69.8	72.2	67.5	71.9	60.6		160.1
7 (α)[6]	89	69	69	68	69	61		
7 (β)[6]	91	70	72	67	72	61		
10 ($\alpha\beta$)	62.1	108.6	79.5	81.6	77.0	62.1		160.7
	63.0	105.8	79.5	81.4	76.9	63.6		160.7
11 (α)[7]	61.8	107.9	78.4	80.6	76.1	62.8		
11 (β)[7]	63.7	104.9	75.7	79.5	75.6	63.9		
13[b]	100.8	73.2	74.9	70.4	71.3	63.9	55.3	162.2
14	96.7	70.7	70.0	68.6	66.9	61.5	55.7	160.4
15	96.9	70.6	72.8	69.2	69.7	62.9	55.3	
16	97.0	69.2	70.0	67.4	71.9	61.8	55.7	160.4

[a]All chemical shifts are relative to internal Me_4Si taken as 0 p.p.m. When a secondary reference standard was used, the shifts are converted to the Me_4Si scale; for $CDCl_3$ taken as 77.0 p.p.m. Shifts for acetyl and benzoyl groups are not listed. [b] Using acetone-d_6 as solvent, all others using $CDCl_3$.

1,2,3,4-Tetra-O-acetyl-6-O-formyl-D-fructose (**10**). — A mixture of **8** (1.80 g, 1.0 mmol) and 99% formic acid (5.0 mL) was stirred at 25° for 4 h, then concentrated at 25° under reduced pressure. To the syrupy residue (**9**) was added pyridine (10.0 mL), 4-dimethylaminopyridine (100 mg), and acetic anhydride (5.0 mL), and the mixture was shaken until clear. After storage for 12 h at 25°, the mixture was poured into ice and water, and worked-up as described in the preparation of **6** to give *αβ*-**10** (1.15 g, 31%), isolated as a syrup, $[\alpha]_D^{25}$ +45° (*c* 1.1, chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 8.08 (s, 1 H, HCOO), 5.88 (m, 0.8 Hz, H-3α), 5.61 (m, 0.4 H, H-3,4*β*), 5.17 (m, 0.5 H, H-4α), 4.12–4.70 (m, 5 H, H-1,1′,5,6,6′), 2.11–2.17 (4 s, each 3 H, 4 Ac).

Anal. Calc. for $C_{15}H_{20}O_{11}$: C, 47.87; H, 5.32. Found: C, 48.14; H, 5.66.

Methyl 6-O-formyl-α-D-glucopyranoside (**13**). — A mixture of **12** (1.94 g, 10 mmol) and 99% formic acid (5 mL) was stirred for 3 h at 25°, then concentrated at 25° under reduced pressure. Column chromatography (chloroform–acetone, 2:1) of the syrupy residue gave **13** (1.65 g, 74%), isolated as a colorless glass, $[\alpha]_D^{25}$ +146° (*c* 1.1, methanol and ethanol). ^{1}H-N.m.r. data [$(CD_3)_2CO$]: δ 8.19 (s, 1 H, HCOO), 4.67 (d, 1 H, $J_{1,2}$ 3.0 Hz, H-1), 4.48 (ddd, 1 H, $J_{6,6'}$ 11.7 Hz, H-6), 4.45 (ddd, 1 H, $J_{5,6'}$ 2.2 Hz, H-6′), 4.28 (dd, 1 H, $J_{5,6}$ 6.1 Hz, H-5), 3.74 (t, 1 H, $J_{3,4}$ 9.5 Hz, H-3), 3.65 (t, 1 H, $J_{4,5}$ 9.5 Hz, H-4), 3.40 (dd, 1 H, $J_{2,3}$ 9.5 Hz, H-2), 3.37 (s, 3 H, OMe). See Table I for the ^{13}C-n.m.r. data.

Anal. Calc. for $C_8H_{14}O_7$: C, 43.24; H, 6.36. Found: C, 43.50; H, 6.79.

Methyl 2,3,4-tri-O-acetyl-6-O-formyl-α-D-glucopyranoside (**14**). — A solution of **13** (660 mg, 2.97 mmol) and acetic anhydride (1 mL) in pyridine (2 mL) was stirred for 5 h at 25°, then worked-up as described above. Column chromatography (chloroform–acetone–light petroleum, 4:1:5) of the product (0.8 g) gave **14** (770 mg, 75%), m.p. 85–86° (from EtOH), $[\alpha]_D^{25}$ +136° (*c* 1.4, chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 8.08 (s, 1 H, HCOO), 5.49 (dd, 1 H, $J_{3,4}$ 9.6 Hz, H-3), 5.06 (dd, 1 H, $J_{4,5}$ 9.8 Hz, H-4), 4.96 (d, 1 H, $J_{1,2}$ 3.0 Hz, H-1), 4.90 (dd, 1 H, $J_{2,3}$ 10.0 Hz, H-2), 4.23 (m, 2 H, H-6,6′), 4.04 (dd, 1 H, $J_{5,6}$ 6.1, $J_{5,6'}$ 2.2 Hz, H-5), 3.42 (s, 3 H, OMe), 2.08, 2.04, 2.01 (3 s, each 3 H, 3 Ac).

Anal. Calc. for $C_{14}H_{20}O_{10}$: C, 48.28; H, 5.79. Found: C, 48.37; H, 6.08.

Methyl 2,3,6-tri-O-acetyl-α-D-glucopyranoside (**15**). – A solution of **14** (30 mg, 0.086 mmol) in methanol (2 mL) was stirred for 3 days at 25°, then concentrated under reduced pressure. Column chromatography (toluene–ethyl acetate, 3:2) of the residue gave **15** (16.6 mg, 60%), isolated as a colorless syrup, $[\alpha]_D^{25}$ +96° (*c* 0.95, chloroform); lit.[9] $[\alpha]_D^{20}$ +101° (chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 5.31 (dd, 1 H, $J_{3,4}$ 10.0 Hz, H-3), 4.91 (d, 1 H, $J_{1,2}$ 3.5 Hz, H-1), 4.85 (dd, 1 H, $J_{2,3}$ 10 Hz, H-2), 4.44 (dd, 1 H, $J_{6,6'}$ 12.0 Hz, H-6), 4.33 (dd, 1 H, $J_{5,6'}$ 2.1 Hz, H-6′), 3.84 (ddd, 1 H, $J_{5,6'}$ 4.5 Hz, H-5), 3.58 (dd, 1 H, $J_{4,5}$ 10.0 Hz, H-4), 3.41 (s, 3 H, OMe), 2.09, 2.10, 2.13 (3 s, each 3 H, 3 Ac).

Methyl 2,3,4-tri-O-benzoyl-6-O-formyl-α-D-glucopyranoside (**16**). — To a solution of **13** (1.65 g, 7.43 mmol) in pyridine (10 mL) was added benzoyl chloride (3.14 g, 22.3 mmol) dropwise with cooling (ice–water). After stirring for 5 h at 25°, the mixture was poured into ice–water and extracted with ether–ethyl acetate (1:1), and the extract was washed successively with water, aqueous 50% cupric sulfate, and water, dried (Na_2SO_4), and concentrated under reduced pressure. Column chromatography (chloroform–acetone–light petroleum, 4:1:5) of the product (3.84 g) gave **16** (2.78 g, 70%),

isolated as a colorless glass, $[\alpha]_D^{25}$ +59° (*c* 4.1, chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 8.11 (s, 1 H, HCOO), 7.84–8.04 and 7.23–7.54 (2 m, 15 H, 3 Ph), (t, 1 H, $J_{3,4}$ 9.5 Hz, H-3), 5.60 (t, 1 H, $J_{4,5}$ 9.5 Hz, H-4), 5.25–5.31 (m, 2 H, H-1,2), 4.29–4.39 (m, 3 H, H-5,6,6'), 3.48 (s, 3 H, OMe).

Anal. Calc. for $C_{29}H_{26}O_{10}\cdot H_2O$: C, 63.04; H, 5.07. Found: C, 63.06; H, 4.83.

*Methyl 2,3,4-tri-*O*-benzoyl-*α*-*D*-glucopyranoside* (**17**). — To a solution of **16** (534 mg, 1 mmol) in methanol (50 mL) was added one drop of methanolic 2.7M hydrogen chloride, and the mixture was stirred for 24 h at 25°, then concentrated at 25° under reduced pressure. Column chromatography (chloroform–acetone–light petroleum, 4:1:10) of the residue gave **17** (350 mg, 69%), isolated as a colorless glass, $[\alpha]_D^{25}$ +53.5° (*c* 1.5, chloroform); lit.[10] $[\alpha]_D^{20}$ +49° (chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 7.86–8.06 and 7.26–8.62 (2 m, 15 H, 3 Ph), 6.24 (t, 1 H, $J_{3,4}$ 9.6 Hz, H-3), 5.51 (t, 1 H, $J_{4,5}$ 9.6 Hz, H-4), 5.24–5.33 (m, 2 H, H-1,2), 4.24 (m, 1 H, H-5), 3.77–3.89 (m, 2 H, H-6,6'), 3.48 (s, 3 H, OMe), 2.70 (bs, 1 H, OH). The chemical shifts of H-6 and H-6' were in agreement with those reported[10].

Anal. Calc. for $C_{28}H_{26}O_9$: C, 66.40; H, 5.14. Found: C, 66.51; H, 5.50.

Reaction of sucrose with formic acid. — Finely powdered sucrose (3.42 g, 10.0 mmol) was reacted with 99% formic acid (5 mL) at 25° for 90 min and the solution was then concentrated at 25°. Column chromatography (chloroform–ethanol, 7:3; then chloroform–ethanol–water, 12:8:1) gave mixtures A and B. Mixture A was not resolved in t.l.c. but, after acetylation, the n.m.r. spectra showed the presence of both **6** and **10**. P.c. of mixture B gave D-glucose (**4**) and D-fructose (**8**). The ratio of mixtures A and B was ~2:3, indicative of incomplete esterification due to the short reaction time.

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