Carbohydrate Research, 113 (1983) 225–231
Elsevier Scientific Publishing Company, Amsterdam – Printed in The Netherlands

PREPARATION OF MIXED-ACETAL DERIVATIVES OF CARBOHYDRATES BY ACETAL-EXCHANGE REACTIONS

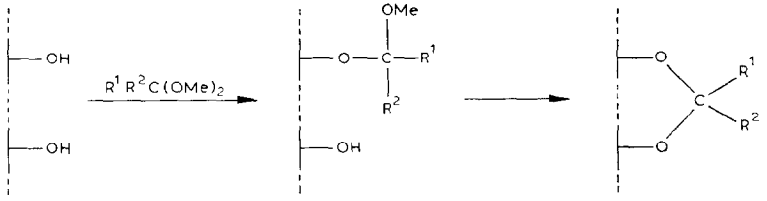
ANDRÁS LIPTÁK, PÉTER FÜGEDI, JÁNOS KERÉKGYÁRTÓ, AND PÁL NÁNÁSI
Institute of Biochemistry, L. Kossuth University, H-4010 Debrecen (Hungary)
(Received June 28th, 1982; accepted for publication, August 18th, 1982)

ABSTRACT

Acetal-exchange reactions of 2,3-disubstituted gluco- and galacto-pyranoside derivatives with acetone dimethyl acetal and acetophenone dimethyl acetal gave the 6-*O*-(methoxydimethyl)methyl and the 6-*O*-(methoxymethylphenyl)methyl derivatives as the kinetic products. Formation of 6-*O*-(methoxydimethyl)methyl derivatives in transacetalation reactions was also demonstrated where cyclisation of the mixed acetal was impossible.

INTRODUCTION

Acetal-exchange reaction of carbohydrate-derived di- and poly-ols **1** to give cyclic acetals **3** is believed[1,2] to proceed *via* mixed-acetal intermediates **2**. The transacetalation reactions of several carbohydrate derivatives have been studied in detail[3,4], but mixed acetals are generally not isolated and are considered to be unstable under the reaction conditions and isolation procedure. On the other hand, these derivatives can be synthesised, for example, by the reaction of alcohols with α-haloethers[5] or enol ethers[6], and have been used in syntheses[7,8] as alkali-stable blocking groups of hydroxyl functions.



1 2 3

Acetal-exchange reactions of simple alcohols[9] and some carbohydrate derivatives[10–12] have been reported to give mixed acetals, but these examples involve isolated hydroxyl groups where cyclisation was precluded for steric reasons. As far as we are aware, the only mixed acetal isolated where cyclisation was possible is methyl 6-*O*-(methoxydiphenyl)methyl-α-D-glucopyranoside obtained[13] by treatment

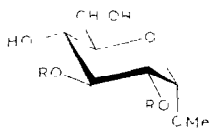
0008-6215/83/0000–0000/$ 03.00,

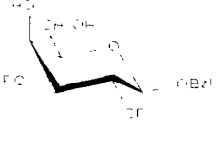
of methyl α-D-glucopyranoside with benzophenone dimethyl acetal. The formation of the mixed-acetal derivative was explained by the unfavourable axial orientation of the phenyl group in the cyclic 4,6-acetal, but recent findings[14,15] indicate an axial preference of the phenyl group in 2-alkyl-2-phenyl-1,3-dioxane derivatives.

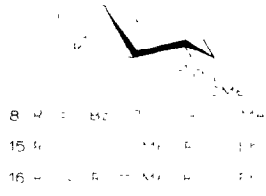
We now report on the preparation of mixed-acetal derivatives of carbohydrates by acetal-exchange reactions.

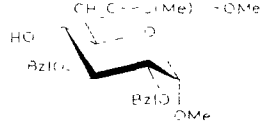
RESULTS AND DISCUSSION

We have reported[16] a modification of the trans-acetalation reaction for the preparation of isopropylidene acetals using 2,2-dimethoxypropane, and this method has been applied to methyl 2,3-di-*O*-benzyl-α-D-glucopyranoside (**4**), benzyl 2,3-di-*O*-benzyl-β-D-galactopyranoside (**5**), and benzyl β-D-galactopyranoside (**6**). In the initial phase of the reaction of **4**, a considerable amount of a compound with t.l.c. mobility between that of **4** and the expected 4,6-*O*-isopropylidene derivative (**8**) was detected, which was slowly transformed into **8**. After quenching the reaction with

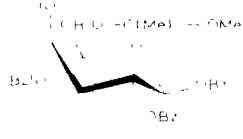




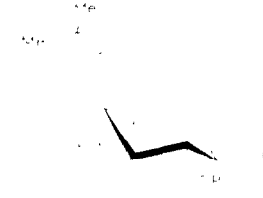


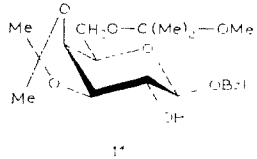


7

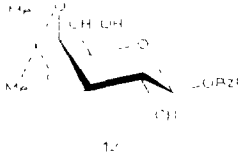


9





11



12

base at the appropriate time, this intermediate could be isolated (30%) by column chromatography, and its ^{1}H-n.m.r. spectrum showed (*inter alia*) a six-proton singlet at 1.28 p.p.m., an *O*-methyl signal at 3.14 p.p.m., and a hydroxyl resonance as a doublet at 2.80 p.p.m. consistent with the mixed-acetal structure **7**. Similarly, brief treatment of **5** with 2,2-dimethoxypropane and toluene-*p*-sulfonic acid gave the 4,6-*O*-isopropylidene (**10**, 21%) and the syrupy 6-*O*-(methoxydimethyl)methyl (**9**, 52%) derivatives.

Isopropylidenation of **6** gave three products in the ratios ~4:5:1 (related to decreasing order of t.l.c. mobility), of which the second and the third compounds were the 3,4-*O*- (**12**) and 4,6-*O*-isopropylidene (**13**) derivatives, respectively. The ^{1}H-n.m.r. spectrum of the compound having highest mobility showed one *O*-methyl signal, one secondary hydroxyl resonance, and *C*-methyl signals corresponding to 12 protons, thus indicating a structure combining a cyclic- and a mixed-acetal unit. The chemical shifts of two *C*-methyl signals (1.51 and 1.32 p.p.m.) were close to those (1.49 and 1.31 p.p.m.) of **12** and differed from that (6-proton singlet at 1.44 p.p.m.) of **13**, suggesting the structure **11**, which was confirmed by the ^{13}C-n.m.r. spectrum. One of the acetal carbons resonated at 110.0 p.p.m., and the *C*-methyl signals (28.1 and 26.2 p.p.m.) were separated by 1.9 p.p.m., values that are characteristic for a dioxolane-type isopropylidene group[17,18] and are close to that reported for 3,4-*O*-isopropylidenegalactopyranoside derivatives[19]; the corresponding resonances of the mixed-acetal unit were at 100.1, 24.36, and 24.32 p.p.m. In contrast to isopropyl ethers[20], no downfield substituent shift was found for the (methoxydimethyl)methyl substituent (the C-6 signal is at 60.4 p.p.m. in **11**), which can be explained by the general *gauche* effect[21].

Mixed acetals could also be isolated after using acetals other than 2,2-dimethoxypropane. Treatment of methyl 2,3-di-*O*-methyl-α-D-glucopyranoside (**14**) with acetophenone dimethyl acetal at room temperature afforded the mixed acetal **17** as a mixture of diastereomers, in addition to the isomeric cyclic acetals[15] (**15**, **16**). The position of the (methoxymethylphenyl)methyl group in **17** was proved by methylation followed by acid hydrolysis, which gave methyl 2,3,4-tri-*O*-methyl-α-D-glucopyranoside.

The above examples demonstrate that mixed acetals formed as intermediates in transacetalation reactions can be isolated in reasonable yields. Mixed acetals are formed regioselectively, with the 6-*O*-substituted derivatives preponderating greatly; only traces of other products (probably the 4-*O*-substituted derivatives) could be detected. This regioselectivity can be attributed to the greater reactivity of the primary hydroxyl group in acetalation reactions[6,10]*. The relatively high proportion of the mixed acetal in the early phase of the reaction is due to the fact that, in 2,2-dimethoxy-

*It might be argued that equally easy formation, at O-4 and O-6 but much faster cyclisation of a mixed acetal at O-4, would also give the mixed acetal at O-6 as the only isolable intermediate. However, we see no reason for the faster cyclisation of a mixed acetal at O-4. Preferential formation of a mixed acetal at a primary hydroxyl group is also manifested in the acetalation of **6** and **12**, where the mixed acetal **11** cannot cyclise for steric reasons.

propane, the reaction **1**→**2** proceeds at a higher rate than with a lower concentration of 2,2-dimethoxypropane in such diluents as *N*,*N*-dimethylformamide. At the same time, the rate of the reaction **2**→**3** is not greatly influenced, so that a higher steady-state concentration of **2** occurs.

The high regioselectivity by which mixed acetals are formed at primary hydroxyl groups accords with the finding that the kinetic products in the preparation of cyclic acetals involve one primary and one secondary hydroxyl group. On the other hand, the frequent statement that transacetalation results in the formation of kinetic products deserves some comment. In the isopropylidenation of **6**, the main product is the 3,4-*O*-isopropylidene derivative **12** and the yield of the 4,6-acetal **13** is low. Reaction of **12** or **13** with 2,2-dimethoxypropane gave the same equilibrium mixture as the reaction of **6**, namely, a ~4:5:1 mixture of **11**, **12**, and **13**, which means that acetal exchange, at least under our conditions, can also give the thermodynamically more-stable compounds. Acetalation of **12** also demonstrates that isopropylidenation with 2,2-dimethoxypropane is a powerful acetalation method, which results in at least partial reaction of isolated hydroxyl groups to give mixed acetals.

As expected, the isolated mixed-acetals were sensitive towards acids and moderately stable at room temperature, but **11** was stable for several months at ~0°. Quenching the acetalation mixture with base is necessary; addition of water to the reaction mixture of **6** resulted in the complete disappearance of **11** within 1 min, and the 3,4-*O*-isopropylidene derivative (**12**) could be isolated in high yield[16]. Despite the sensitivity of the mixed acetals towards acids, the high regioselectivity of their formation suggests that they may find some application in synthesis. In this respect, the preparation of hexopyranosides having only HO-4 free and the preparation in one step from **6** of the partially protected galactoside derivative **11** having only HO-2 free are noteworthy.

EXPERIMENTAL

Melting points (uncorrected) were determined with a Kofler apparatus. Optical rotations were measured with a Perkin-Elmer 241 polarimeter for solutions in chloroform. N.m.r. spectra were recorded with JEOL MH-100 (^{1}H) and Bruker WP 200 SY spectrometers (^{1}H, ^{13}C) for solutions in $CDCl_3$ (internal Me_4Si).

Solutions in organic solvents were dried with sodium sulfate, and evaporations were performed *in vacuo* at <40° (bath). T.l.c. was performed on Kieselgel 60 F_{254} (Merck), and Kieselgel G (Reanal, Budapest) was used for short-column chromatography. Detection in t.l.c. was effected under u.v. light and or by charring with sulfuric acid.

*Methyl 2,3-di-*O*-benzyl-6-*O*-(methoxydimethyl)methyl-α-*D*-glucopyranoside* (**7**). — To a stirred suspension of **4**[22] (5 g) in 2,2-dimethoxypropane (16.3 mL, 10 equiv.) at room temperature was added toluene-*p*-sulfonic acid (20 mg). Dissolution occurred in 2 min, and the reaction was stopped after 4 min by adding aqueous 5% $NaHCO_3$ (20 mL). The mixture was diluted with dichloromethane (100 mL), and the organic

layer was washed with water (3 × 20 mL), dried, and concentrated. The syrupy residue (5.24 g) was eluted from a column of Kieselgel G (150 g) with dichloromethane–acetone (9:1), to give, first, methyl 2,3-di-*O*-benzyl-4,6-*O*-isopropylidene-α-D-glucopyranoside (**8**; 1.82 g, 32.9%), m.p. 76–78° (from ethanol–water, 2:1), $[\alpha]_D$ +9° (*c* 0.9), R_F 0.90 (dichloromethane–acetone, 9:1). ^{1}H-N.m.r. data: δ 4.80 (s, 2 H, PhCH_2), 4.72 (q, 2 H, PhCH_2), 4.52 (d, 1 H, $J_{1,2}$ 3.0 Hz, H-1), 3.34 (s, 3 H, OMe), 1.44 (s, 3 H, CMe*e*), and 1.38 (s, 3 H, CMe*a*).

Anal. Calc. for $C_{24}H_{30}O_6$: C, 69.54; H, 7.29. Found: C, 70.06; H, 7.32.

Eluted second was syrupy **7** (1.80 g, 30.2%), $[\alpha]_D$ +13° (*c* 1), R_F 0.59. ^{1}H-N.m.r. data: δ 3.33 (s, 3 H, MeO-1), 3.14 (s, 3 H, Me_2CO*Me*), 2.80 (d, 1 H, HO-4), and 1.28 (s, 6 H, CMe_2).

Anal. Calc. for $C_{25}H_{34}O_7$: C, 67.24; H, 7.67. Found: C, 67.45; H, 7.83.

*Benzyl 2,3-di-*O*-benzyl-6-*O*-(methoxydimethyl)methyl-β-*D*-galactopyranoside* (**9**). — Compound **5**[23] (1.8 g) was treated with 2,2-dimethoxypropane (4.1 mL) and toluene-*p*-sulfonic acid (10 mg) as described above. After complete dissolution (1 min), the mixture was stirred for 3 min. The syrupy residue obtained after work-up was eluted from a column of Kieselgel G (100 g) with dichloromethane–acetone (92:8), to give, first, benzyl 2,3-di-*O*-benzyl-4,6-*O*-isopropylidene-β-D-galactopyranoside (**10**; 0.42 g, 21.4%), m.p. 100–102° (from ethyl acetate–light petroleum), $[\alpha]_D$ −52° (*c* 0.9), R_F 0.82 (dichloromethane–acetone, 92:8). ^{1}H-N.m.r. data: δ 7.45–7.20 (m, 15 H, 3 Ph), 5.02–4.50 (m, 6 H, 3 PhCH_2), 4.36 (d, 1 H, $J_{1,2}$ 8.0 Hz, H-1), 4.08–3.90 (m, 3 H, H-5,6,6'), 3.78 (dd, 1 H, $J_{2,3}$ 10.0 Hz, H-2), 3.40 (dd, 1 H, $J_{3,4}$ 3.9 Hz, H-3), 3.10 (bs, 1 H, H-4), 1.52 (s, 3 H, CMe*e*), and 1.38 (s, 3 H, CMe*a*).

Anal. Calc. for $C_{30}H_{34}O_6$: C, 73.44; H, 6.98. Found: C, 73.56; H, 7.02.

Eluted second was **9** (1.08 g, 51.7%), $[\alpha]_D$ −19° (*c* 0.6), R_F 0.47. ^{1}H-N.m.r. data: δ 7.40–7.20 (m, 15 H, 3 Ph), 5.00–4.64 (2 q and 1 s, 6 H, 3 PhCH_2), 4.46 (d, 1 H, H-1), 3.97 (dd, 1 H, H-4), 3.80–3.60 (m, 3 H, H-5,6,6'), 3.32–3.20 (m, 2 H, H-2,3), 3.18 (s, 3 H, OMe), 2.74 (d, 1 H, HO-4), and 1.32 (s, 6 H, CMe_2).

Anal. Calc. for $C_{31}H_{38}O_7$: C, 71.24; H, 7.33. Found: C, 71.50; H, 7.45.

*Benzyl 3,4-*O*-isopropylidene-6-*O*-(methoxydimethyl)methyl-β-*D*-galactopyranoside* (**11**). — A suspension of **6**[24] (2.7 g) in 2,2-dimethoxypropane (12.3 mL) was treated with toluene-*p*-sulfonic acid (47 mg) as described for **7**. After 1 h, aqueous $NaHCO_3$ was added, and the mixture was worked-up. The crude product was eluted from a column of Kieselgel G (200 g) with dichloromethane–acetone (4:1), to give, first, syrupy **11** (1.44 g, 37.7%), $[\alpha]_D$ −20° (*c* 0.7), R_F 0.55 (dichloromethane–acetone, 4:1). N.m.r. data: ^{1}H, δ 7.40–7.20 (m, 5 H, Ph), 4.77 (q, 2 H, PhCH_2), 4.23 (d, 1 H, $J_{1,2}$ 8.3 Hz, H-1), 4.18–3.50 (m, 6 H, H-2,3,4,5,6,6'), 3.24 (s, 3 H, OMe), 2.92 (bs, 1 H, OH), 1.51 (s, 3 H, CMe), 1.37 (s, 6 H, MeOCMe_2), and 1.32 (s, 3 H, CMe); ^{1}H [$(CD_3)_2SO$], δ 5.44 (d, 1 H, exchangeable with deuterium, OH); ^{13}C, δ 110.0 (dioxolane CMe_2), 100.9 (C-1), 100.1 (mixed acetal CMe_2), 60.4 (C-6), 48.4 (OMe), 28.1 (dioxolane C*Me*), 26.2 (dioxolane C*Me*), 24.36 (mixed-acetal C*Me*), and 24.32 (mixed-acetal C*Me*).

Anal. Calc. for $C_{20}H_{30}O_7$: C, 62.81; H, 7.91. Found: C, 63.03; H, 7.95.

Eluted second was benzyl 3,4-*O*-isopropylidene-β-D-galactopyranoside (**12**; 1.40 g, 45.0%), m.p. 127–128° (from ethyl acetate–light petroleum), $[\alpha]_D$ −2° (*c* 0.9), R_F 0.28; lit.[16] m.p. 125°, $[\alpha]_D$ −2° (*c* 1.26, chloroform). ^{1}H-N.m.r. data: δ 7.40–7.20 (m, 5 H, Ph), 4.76 (q, 2 H, PhCH_2), 4.23 (d, 1 H, $J_{1,2}$ 8.0 Hz, H-1), 4.10–3.30 (m, 7 H, H-2,3,4,5,6,6′ and HO-2), 2.87 (t, 1 H, HO-6), 1.49 (s, 3 H, CMe), and 1.31 (s, 3 H, CMe).

Eluted last was benzyl 4,6-*O*-isopropylidene-β-D-galactopyranoside (**13**; 0.22 g, 7.1%), m.p. 127–128° (from ethyl acetate–light petroleum), $[\alpha]_D$ −73.5° (*c* 0.9), R_F 0.17; lit.[25] m.p. 124.5–125.5°, $[\alpha]_D$ −66° (*c* 1.03, chloroform). ^{1}H-N.m.r. data: δ 7.40–7.20 (m, 5 H, Ph), 4.75 (q, 2 H, PhCH_2), 4.26 (d, 1 H, $J_{1,2}$ 8.0 Hz, H-1), 4.10–3.00 (m, 8 H, H-2,3,4,5,6,6′ and 2 OH), and 1.44 (s, 6 H, CMe_2).

Similar treatment of **12** or **13** afforded **11**–**13** in yields similar to those noted above.

Methyl 2,3-di-O-methyl-6-O-(methoxymethylphenyl)methyl-α-D-glucopyranoside (**17**). — A solution of **14**[26] (1.2 g) in *N*,*N*-dimethylformamide (5 mL) was treated with acetophenone dimethyl acetal (2.5 g) and toluene-*p*-sulfonic acid (20 mg) for 2.5 h at room temperature. T.l.c. (light petroleum–ethyl acetate, 3:2) of the mixture then revealed components with R_F 0.55, 0.42, and 0.22. The mixture was neutralised with aqueous $NaHCO_3$ and diluted with dichloromethane (60 mL), and the organic layer was washed with water (3 × 10 mL), dried, and concentrated. The syrupy residue was eluted from a column of Kieselgel G (100 g) with light petroleum–ethyl acetate (3:2), to give syrupy **16**[15] (0.355 g, 20%), $[\alpha]_D$ +154° (*c* 0.6), R_F 0.55.

Eluted second was the *R*-cyclic acetal **15**[15] (0.67 g, 38%), m.p. 95–96° (from light petroleum), $[\alpha]_D$ +64° (*c* 1.45), R_F 0.42.

Eluted last was syrupy **17** (0.255 g, 13.2%), $[\alpha]_D$ +79° (*c* 0.2), R_F 0.22. N.m.r. data: ^{1}H, δ 7.55–7.25 (m, 5 H, Ph), 4.88 (d, 1 H, $J_{1,2}$ 3.6 Hz, H-1), 3.65, 3.50, 3.45, and 3.20 (4 s, 12 H, 4 OMe), 1.58 (s, 3 H, CMe); ^{13}C, δ 101.7 (PhC), 97.3 (C-1), 83.0 (C-2), 81.8 (C-3), 71.3 (C-4), 69.8 (C-5), 61.2 (C-6), 61.2, 58.4, and 55.0 (3 OMe), 49.2 (PhCO*Me*), 26.43 and 26.28 (PhC*Me*).

REFERENCES

1 R. CORTES-GARCIA, L. HOUGH, AND A. C. RICHARDSON, *J. Chem. Soc., Perkin Trans. 1*, (1981) 3176–3181.
2 F. A. J. MESKENS, *Synthesis*, (1981) 501–522.
3 Y. UENO, K. HORI, R. YAMAUCHI, M. KISO, A. HASEGAWA, AND K. KATO, *Carbohydr. Res.*, 96 (1981) 65–72; and references therein.
4 M. E. EVANS AND F. W. PARRISH, *Carbohydr. Res.*, 54 (1977) 105–114; and references therein.
5 S. DAVID, A. THIEFFRY, AND A. VEYRIÈRES, *J. Chem. Soc., Perkin Trans. 1*, (1981) 1796–1801.
6 M. L. WOLFROM, A. BEATTIE, AND S. S. BHATTACHARJEE, *J. Org. Chem.*, 33 (1968) 1067–1070.
7 F. R. SEYMOUR, *Carbohydr. Res.*, 30 (1973) 327–335.
8 M. PIETRASZKIEWICZ AND P. SINAŸ, *Tetrahedron Lett.*, (1979) 4741–4744.
9 U.-A. SCHAPER, *Synthesis*, (1981) 794–796.
10 A. HAMPTON, *J. Am. Chem. Soc.*, 87 (1965) 4654–4655.
11 T. MAEDA, *Bull. Chem. Soc. Jpn.*, 40 (1967) 2122–2128.
12 C. H. LEE, *Carbohydr. Res.*, 22 (1970) 230–232.
13 M. E. EVANS, F. W. PARRISH, AND L. LONG, JR., *Carbohydr. Res.*, 3 (1967) 453–462.

14 W. F. BAILEY, H. CONNON, E. L. ELIEL, AND K. WIBERG, *J. Am. Chem. Soc.*, 100 (1978) 2202–2209.
15 A. LIPTÁK AND P. FÜGEDI, *Angew. Chem.*, in press.
16 A. LIPTÁK, J. IMRE, AND P. NÁNÁSI, *Carbohydr. Res.*, 92 (1981) 154–156.
17 A. LIPTÁK, P. NÁNÁSI, A. NESZMÉLYI, AND H. WAGNER, *Carbohydr. Res.*, 86 (1980) 133–136.
18 J. G. BUCHANAN, M. E. CHACÓN-FUERTES, A. R. EDGAR, S. J. MOORHOUSE, D. I. RAWSON, AND R. WIGHTMAN, *Tetrahedron Lett.*, (1980) 1793–1796.
19 S. A. ABBAS, J. J. BARLOW, AND K. L. MATTA, *Carbohydr. Res.*, 98 (1981) 37–49.
20 P. A. J. GORIN AND M. MAZUREK, *Carbohydr. Res.*, 48 (1976) 171–186.
21 D. G. GORENSTEIN, *J. Am. Chem. Soc.*, 99 (1977) 2254–2258.
22 D. J. BELL AND J. LORBER, *J. Chem. Soc.*, (1940) 453–455.
23 J. R. TURVEY AND T. P. WILLIAMS, *J. Chem. Soc.*, (1962) 2119–2122.
24 B. HELFERICH AND A. PORCK, *Justus Liebigs Ann. Chem.*, 586 (1954) 239–244.
25 A. LEVY, H. M. FLOWERS, AND N. SHARON, *Carbohydr. Res.*, 4 (1967) 305–311.
26 H. BREDERECK, *Ber.*, 68 (1935) 777–783.