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Convenient Preparation of Methyl 2-Acetamido-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside

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The *O*-benzylidene group is a good protective group for preparing several sugar derivatives, but some difficulties in its preparation and the lower yield of product have sometimes been encountered in reactions of sugar with benzaldehyde and a catalyst. The use of freshly-distilled benzaldehyde and anhydrous zinc chloride seems to give a higher yield.[1] In order to eliminate some tedious treatments, the preparation of the *O*-benzylidene group by an acetal exchange reaction was attempted. Its use in the preparation of methyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside (II) led to an almost quantitative yield. When methyl 2-acetamido-2-deoxy-α-D-glucopyranoside (I) was treated with benzaldehyde dimethyl acetal and a catalytic amount of *p*-toluenesulfonic acid in dimethylformamide (DMF), the reaction was shown to be completed within 1 hr, judging from the thin-layer chromatogram of the reaction mixture. Moreover, benzaldehyde dimethylacetal was also found to be more suitable for *O*-benzylidenation because the reagent, stored for several months, gave the same yield of the *O*-benzylidenated product.

When the same reaction was performed under reduced pressure, methyl 2-acetamido-3-*O*-(α-methoxybenzyl)-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside (III) was found to be produced in the reaction mixture, but it was not produced under atmospheric conditions. The structure of (III) was confirmed by elemental analysis and NMR spectroscopy, and was also supported by the experimental evidence that (III) was formed by the reaction of (II) with benzaldehyde dimethylacetal under reduced pressure.

No 3-*O*-substitution with the α-methoxybenzyl group in 4,6-*O*-benzylidene sugar has been found so far; therefore, this seems to be the first example of a mixed acetal of benzaldehyde between the hydroxyl of sugar and simple alcohol. The 3-*O*-(α-methoxybenzyl) group was found to be more acid-labile than the 4,6-*O*-benzylidene group, as had been expected; it was removed selectively by treatment with 90% acetic acid at 0°C. The thin-layer chromatographic analysis of 90% acetic acid hydrolysis for (III) is shown in Fig. 1.

Recently, during the preparation of our manuscript, Evans[2] reported the preparation of methyl 4,6-*O*-benzylidene-α- and β-D-glucopyranosides by a similar

1) K. Freudenberg, H. Toepffer, and C. C. Andersen, *Ber.*, **61**, 1758 (1928).

2) M. E. Evans, *Carbohyd. Res.*, **21**, 473 (1972).

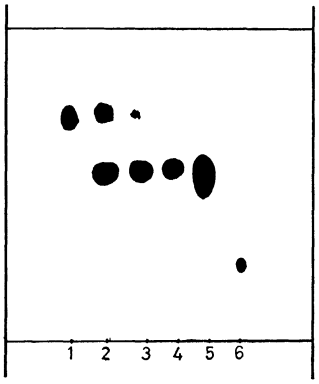

Fig. 1. Thin layer chromatogram of hydrolysates of (III).
1: Compound (III), 2: Hydrolysate of (III), sampling after 1 min, 3: Hydrolysate of (III), sampling after 1 min, 4: Hydrolysate of (III), sampling after 6 min, 5: Compound (II), 6: Compound (I).

manner and noted that the preparation of the *O*-benzylidene group with benzaldehyde dimethyl acetal and *p*-toluenesulfonic acid was a better procedure.

Experimental

The melting points were determined with a micro melting point apparatus (Yanagimoto, MFG) and uncorrected. The optical rotations were measured with a Jasco DIP-SL photoelectric automatic polarimeter at 25.0°C. The NMR spectra were recorded with a Varian T-60 NMR spectrometer. Thin-layer chromatography was performed on Silica gel H (Merck) developed with the solvent (toluene: acetone: pyridine= 2: 1: 1), and spots were detected by spraying with 5% methanol–sulfuric acid.

Benzaldehyde dimethyl acetal was prepared by the method of Claisen,[3] using methyl orthoformate instead of the ethyl derivative, and showed bp 215—218°C/760 mmHg (lit,[4] 207°C).

Reaction of I with Benzaldehyde Dimethyl Acetal under Atmospheric Pressure. To a solution of I[5] (5.0 g) in 50 ml of dimethylformamide, we added 14 ml of benzaldehyde dimethyl acetal and 0.5 g of *p*-toluenesulfonic acid; the reaction was then performed at 40°C for 1 hr. After determining the completion of the reaction by thin-layer chromatography, which indicated a spot (R_f 0.54) corresponding to authentic (II)[6] and the disappearance of (I), the reaction mixture was evaporated *in vacuo* to dryness. The white residue was suspended in a dilute sodium bicarbonate solution and collected by filtration. The crystallization of dried raw product from methanol gave a pure (II) (6.3 g, 91%); mp 255—259°C (lit,[6] 255°C), $[\alpha]_D^{25}$ +75.5° (*c*, 1.04, dimethylformamide), (lit, +19° chloroform,[6] +70° chloroform[7]). Found: C, 56.77; H, 6.68; N, 4.12%. Calcd for $C_{16}H_{21}O_6 \cdot H_2O$: C, 56.29; H, 6.79; N, 4.10%.

The $[\alpha]_D$ value observed by Kasai was referred to because his value was comparable to our value and because he used the α-glycoside purified by column chromatography. (The $[\alpha]_D$ values reported for I were +105° by Neuberger and +131° by Kasai.[7])

Reaction under Reduced Pressure. a): The same reaction mixture as above was kept at 40°C under reduced pressure (15 mmHg) for 8 hr. A similar treatment of the reaction mixture afforded 7.3 g (78%) of a crystalline (III), which showed a mp of 193—196°C and $[\alpha]_D^{25}$ +52.5° (*c*, 1.22, dimethylformamide); NMR spectrum (in deuteriochloroform, with tetramethylsilane as the internal standard). δ 7.43 m; (aromatic, 10H), 5.60 s; (CH of acetal, 2H), 4.80 d; (anomeric, 1H) 3.44 s; (OMe of acetal, 3H), 2.04 s; (OMe of glycoside, 3H) 1.15 s; (NAc, 3H). Found: C, 65.17; H, 6.85; N, 3.18%. Calcd for $C_{24}H_{29}O_7N$: C, 65.00; H, 6.59; N, 3.16%.

b): A solution of 5.0 g of (II), 14 ml of benzaldehyde dimethyl acetal, and 0.5 g of *p*-toluenesulfonic acid in 50 ml of dimethylformamide was allowed to react under reduced pressure (15 mmHg) at 40°C for 8 hr; then, the mixture was treated as has been mentioned above. The crystallization of the crude product gave 6.0 g (92%) of a crystalline III. Mp 192—196°C, $[\alpha]_D^{25}$ +51.7° (*c*, 1.02, dimethylformamide) Found: C, 64.87; H, 6.82; N, 3.16%. Calcd for $C_{24}H_{29}O_7N$: C, 65.00; H, 6.59; N, 3.16%.

The melting point was not depressed by admixture of the specimen prepared in a).

Acid Hydrolysis of III. A 10 mg portion of (III) dissolved in 1 ml of 90% acetic acid (v/v), was kept in an ice bath (0°C). Aliquots of 0.3 ml were removed at 1-, 3- and 6- min intervals and neutralized with 0.5 ml of pyridine. Each sample removed at each interval was applied to a tlc plate, and developed with toluene: acetone: pyridine (2: 1: 1). The thin-layer chromatogram of the hydrolysates is shown in Fig. 1. It can be concluded from the thin-layer chromatogram that the 3-*O*-(α-methoxybenzyl) group of III is completely hydrolysed by 90% acetic acid over 6 min at 0°C, while, on the contrary, the 4,6-*O*-benzylidene group was not affected under these conditions.

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4) E. W. Adames and H. Adkins, *J. Amer. Chem. Soc.*, **47**, 1358 (1925).
5) Z. Zilliken, C. S. Rose, G. A. Braun, and P. Gyorgy, *Arch. Biochem. Biophys.*, **54**, 392 (1955).
6) A. Neuberger, *J. Chem. Soc.*, **1941**, 550.
7) S. Kasai, The thesis for Master of Science (Osaka University), 1967.