SYNTHESIS OF 1-*O*-(INDOL-3-YLACETYL)-α-D-GLUCOPYRANOSE AND ITS REARRANGEMENT INTO 2-*O*-(INDOL-3-YLACETYL)-D-GLUCOPYRANOSE

D. Keglević
Tracer Laboratory, Institute "Rudjer Bošković", Zagreb (Yugoslavia)

(Received November 16th, 1970; accepted for publication in revised form, April 19th, 1971)

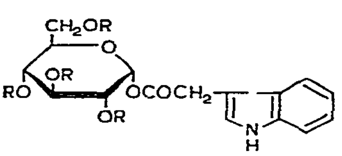
ABSTRACT

Catalytic hydrogenation of 2,3,4,6-tetra-*O*-benzyl-1-*O*-(indol-3-ylacetyl)-α-D-glucopyranose (**1**), prepared from indol-3-ylacetyl chloride and tetra-*O*-benzyl-α-D-glucopyranose, afforded 1-*O*-(indol-3-ylacetyl)-α-D-glucopyranose (**2**) which underwent 1→2 acyl migration. In order to characterize **2** and its rearrangement product, the anomeric pairs of 2,3,4,6-tetra-*O*-acetyl-1-*O*-(indol-3-ylacetyl)-D-glucopyranose (**4**) and 1,3,4,6-tetra-*O*-acetyl-2-*O*-(indol-3-ylacetyl)-D-glucopyranose (**5**) were synthesized by definitive methods. The chemical shifts of the acetyl signals in the n.m.r. spectra of **4** and **5** were assigned.

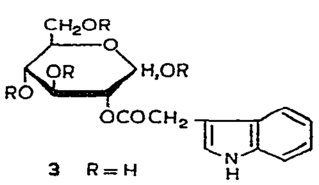
INTRODUCTION

In an earlier paper[1], the synthesis of 1-*O*-(indol-3-ylacetyl)-β-D-glucopyranose (**2β**) *via* 2,3,4,6-tetra-*O*-benzyl-1-*O*-(indol-3-ylacetyl)-D-glucopyranose (**1**) was described. In section tests with *Avena* coleoptiles and pea stems, the glycosyl ester **2β** exhibited a growth-promoting effect which exceeded that of equimolar amounts of indol-3-ylacetic acid (IAA) or equimolar mixtures of IAA and D-glucose[1]. The fact that **2β** was found[1] in intact *Avena* coleoptiles indicates that this compound might take an active part in the growth-induction mechanism in normal plant metabolism.

For purposes of comparison, the chemical and biological properties of the α anomer of **2** were examined, and we now report on the synthesis and characterization of 1-*O*-(indol-3-ylacetyl)-α-D-glucopyranose (**2**).



1 R = PhCH$_2$
2 R = H
4 R = Ac



3 R = H
5 R = Ac

RESULTS AND DISCUSSION

In order to prepare the fully benzylated, 1-*O*-(indol-3-ylacetyl) derivative **1**, the key compound for the synthesis of **2**, a method which would yield preponderantly the α-D anomer was required; the silver salt method, successfully used in the preparation of **1β**, afforded the pure α-D anomer only after extensive column chromatography and in very low yield[1]. The finding[2] that the fully benzylated 1-*O*-aroyl-D-glucopyranosiduronates synthesized by the acid chloride method were preponderantly α-D anomers prompted an examination of the reaction of indol-3-ylacetyl chloride with 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranose.

Attempts to prepare crystalline[3] indol-3-ylacetyl chloride failed. However, modifications of the procedure gave the oily acid chloride which reacted with 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranose in pyridine to give an anomeric mixture of the benzylated indolic ester **1**; from the mixture, the oily α-D anomer was isolated in high yield.

Catalytic hydrogenation of **1** proceeded faster than for the β-D anomer[1]. Although the crude product contained (t.l.c.) one major indolic product, 1-*O*-(indol-3-ylacetyl)-α-D-glucopyranose (**2**), attempted purification by chromatography on cellulose resulted in partial rearrangement into 2-*O*-(indol-3-ylacetyl)-D-glucopyranose (**3**). The partial rearrangement occurred rapidly in aqueous solution.

The 1→2 migration in 1-*O*-acylaldoses having a vicinal *cis* arrangement of these groups was established[4] for 2,3,4,6-tetra-*O*-acetyl-1-*O*-mesitoyl-α-D-glucopyranose which, with methanolic ammonia, yielded 2-*O*-mesitoyl-β-D-glucopyranose. Comparable reactions have been observed with 1,3,5-tri-*O*-benzoyl-D-ribofuranose[5] and 2,3,4,6-tetra-*O*-acetyl-1-*O*-galloyl-α-D-glucopyranose[6]. The ease with which such rearrangements occur is dependent on the relative ease of formation of the cyclic, ortho-acid intermediate[7].

The structure and configuration of the indolic esters **2** and **3** were deduced by comparing their acetylated derivatives with the α and β anomers of 2,3,4,6-tetra-*O*-acetyl-1-*O*-(indol-3-ylacetyl)-D-glucopyranose (**4**) and 1,3,4,6-tetra-*O*-acetyl-2-*O*-(indol-3-ylacetyl)-D-glucopyranose (**5**); the β anomer of **4** is known[1]. The α anomer of **4** was obtained by fusion of penta-*O*-acetyl-α-D-glucopyranose with IAA in the presence of zinc chloride; reaction of indol-3-ylacetyl chloride with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranose gave an anomeric mixture of **4**, which, although highly enriched in the α form, could not be completely resolved. The β anomer of **5** was obtained in crystalline form by application of the acid chloride and dicyclohexylcarbodi-imide (DCC) methods with 1,3,4,6-tetra-*O*-acetyl-β-D-glucopyranose. The α-anomer of **5** was synthesized by the same two methods, using 1,3,4,6-tetra-*O*-acetyl-α-D-glucopyranose as the sugar component. The anomeric configuration assigned to the α and β anomers of **4** and **5** on the basis of $J_{1,2}$ values was consistent with the optical rotation data (see Experimental).

Aryl substituents may have[8] a pronounced effect on the chemical shift of the signals of neighbouring acetyl groups in the n.m.r. spectra of appropriate sugar derivatives. In acetylated 1-*O*-arylacetyl- and 1-*O*-indolylacetyl-D-glucopyranoses and D-glucopyranosiduronates, the signal assigned to the 2-acetoxyl group appears at unusually high field[9] due to shielding by the aromatic ring. In the 1-*O*-(indol-3-ylacetyl) derivative **4**, the signal at τ 8.23 previously[1] assigned to the 2-acetoxyl group was confirmed in the present work with the anomerically pure compound. In the spectra of the α and β anomers of the tetra-*O*-acetyl-2-*O*-(indol-3-ylacetyl) derivative **5**, signals for two of the acetoxyl groups appear at higher field, indicating that the indole ring shields both of the adjacent acetoxyl groups. In **5β**, the 6-proton singlet at 8.29 is assigned to the equatorial 1- and 3-acetoxy groups. In **5α**, 3-proton singlets were observed at 8.29 and 8.08; the low-field signal (8.08) was assigned[10] to the *ax* 1-acetoxyl group.

Acetylation of the crude hydrogenolysis product of **1** gave 2,3,4,6-tetra-*O*-acetyl-1-*O*-(indol-3-ylacetyl)-α-D-glucopyranose (**4**). Thus, 1-*O*-(indol-3-ylacetyl)-α-D-glucopyranose (**2**) is the initial product of debenzylation of **1**. Acetylation of the rearrangement product of **2** gave an anomeric mixture of 1,3,4,6-tetra-*O*-acetyl-2-*O*-(indol-3-ylacetyl)-D-glucopyranose (**5**); the anomers were resolved and characterized. The structure of the rearrangement product 2-*O*-(indol-3-ylacetyl-D-glucopyranose (**3**) is thereby established.

The conversion of 2→3 should proceed[11,12] intramolecularly *via* a cyclic, ortho-ester intermediate. The finding that **2** undergoes acyl migration under neutral and acidic conditions, but that the conversion into **3** is not quantitative, suggests that, in the solvent systems investigated, an equilibrium is established. In alkaline solutions, the rearrangement of **2** is strongly suppressed by the cleavage of the C-1 ester bond, and indol-3-ylacetic acid or indol-3-ylacetamide and D-glucose are formed.

The marked tendency of 1-*O*-(indol-3-ylacetyl)-α-D-glucopyranose (**2**) to undergo acyl migration indicates that steric and electronic factors favour the formation of the cyclic, ortho-ester intermediate.

EXPERIMENTAL

Melting points are uncorrected. Specific rotations were measured at 20–23° on ~2% solutions in chloroform, unless stated otherwise. Evaporations were performed *in vacuo* in a rotatory evaporator at 35–40° (bath), if not stated otherwise. I.r. spectra were determined on a Perkin–Elmer Model 137 Infracord spectrophotometer. N.m.r. spectra were obtained for solutions in deuteriochloroform with a Varian A-60A spectrometer, using tetramethylsilane as an internal reference. Column chromatography was conducted on silica gel (Merck, 0.05–0.2 mm) or cellulose powder (Whatman, standard grade). T.l.c. was performed on Kieselgel G (Merck); spots were located with 10% sulphuric acid and heating, with Ehrlich's reagent (2% *p*-dimethylaminobenzaldehyde in 2M hydrochloric acid), or with iodine vapour. Solvent systems were *A* 3:2 ether–light petroleum; *B* 10:1 ether–light petroleum; *C* 1:1 benzene–ethyl acetate; *D* 7:2 ethyl acetate–propan-2-ol.

*2,3,4,6-Tetra-*O*-benzyl-1-*O*-(indol-3-ylacetyl)-α-D-glucopyranose* (**1**). — To a solution of freshly recrystallized IAA (525 mg, 3 mmoles) in 25 ml of dry ether, phosphorus pentachloride (1 g) was added during 1 h at −5° with vigorous stirring and exclusion of moisture; the stirring was continued at 2–6° for an additional 1.5 h. The mixture was concentrated to ~5 ml, cold light petroleum (20 ml) was added, and the mixture was filtered and concentrated to give oily indol-3-ylacetyl chloride which was dissolved in dichloromethane (10 ml) and used immediately in the next step of the reaction.

To a stirred solution of 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranose[13] (540 mg, 1 mmole) in 15 ml of dry pyridine, the above chloride solution was added dropwise at −8° with exclusion of moisture. The mixture was further stirred at −8° for 45 min and at room temperature for 2 h, whereupon it was poured on to ice and extracted with chloroform. The combined extracts were washed with cold water, 3% sulphuric acid, water, aqueous sodium hydrogen carbonate, and water, and dried (Na_2SO_4). After removal of the solvent, the remaining oil was eluted from silica gel with solvent *A* (1-ml fractions). The fractionation was monitored by t.l.c. The fractions containing the faster-moving compound yielded **1** (272 mg), subsequent fractions contained a mixture of anomers (152 mg), and the final fractions contained the β anomer of **1** (72 mg); total yield 71%. Rechromatography (solvent *A*) of the first two products gave **1** (361 mg, 52%) as a colourless syrup, $[\alpha]_D$ +58.5°. The i.r. and n.m.r. spectra were superimposable on those of **1** obtained by the silver salt method[1].

*Catalytic hydrogenation of 2,3,4,6-tetra-*O*-benzyl-1-*O*-(indol-3-ylacetyl-α-D-glucopyranose* (**1**). — To a solution of **1** (729 mg) in 2-methoxyethanol (25 ml), 10% palladium-on-charcoal (500 mg) and glacial acetic acid (0.3 ml) were added, and the mixture was shaken in the presence of hydrogen at room temperature and pressure. The reaction, which was monitored by t.l.c. (ether–light petroleum–methanol, 3:1:0.5), was complete after 2.5 h. The catalyst was removed by centrifugation and washed with 2-methoxyethanol, and the combined supernatants and washings were made up with the same solvent to 50 ml. Following t.l.c. in solvent *D*, detection with 10% sulphuric acid revealed an intense, red spot (R_F ~0.3) and several slower-moving spots of low intensity.

An aliquot (9 ml) of the solution containing the crude hydrogenolysis product was evaporated to dryness, and the residue (90 mg) was acetylated with pyridine–acetic anhydride in the usual manner. The crude, oily product (96 mg, $[\alpha]_D$ +62.4°) contained (t.l.c.) one major component with a mobility identical to that of the indolic esters **4**, **5α**, and **5β**. It was eluted from silica gel with ether–light petroleum (1.5:1), followed by ether, to give **4** as a chromatographically homogeneous, amorphous solid (56 mg, 40%), m.p. 35–38°, $[\alpha]_D$ +73.5°, which was identical with the authentic compound described below.

A second aliquot (40 ml) of the above solution was evaporated at 30° (bath)/ 0.1 mmHg, and the oily residue was eluted from a column (71 × 1.1 cm) of cellulose (30 g) with propan-2-ol–light petroleum–water (55:30:11). Fractions (1 ml/0.5 h) were examined by t.l.c. in solvent *D* and those (20–26) revealing the red spot contaminated with a greyish-blue spot (R_F ~0.4) were combined and evaporated. The residue, on drying *in vacuo*, gave a pink glass (197 mg, 70.5% calc. for **2** or **3**).

A sample of the above glass (30 mg) was dissolved in water (3 ml), silica gel (300 mg, Merck) was added, and the suspension was kept at room temperature with occasional shaking for 24 h. Monitoring by t.l.c. (solvent *D*) revealed the disappearance of the red spot associated with **2** and an increase in the slightly faster-moving, greyish-blue spot. The silica gel was filtered off and washed with water, and the combined filtrate and washings were evaporated. The residue (22 mg) was eluted from silica gel with solvent *D*. Fractions (0.5 ml) were examined by t.l.c. and those (10–17) yielding the greyish-blue spot were combined and evaporated to give 2-*O*-(indol-3-ylacetyl)-D-glucopyranose (**3**) as a chromatographically homogeneous, amorphous solid (15 mg) which did not have a definite melting-point, $[\alpha]_D$ +24° (water).

Anal. Calc. for $C_{16}H_{19}NO_7$; C, 56.97: H, 5.69; N, 4.15. Found: C, 56.93; H, 5.81; N, 4.30.

Acetylation of a sample (25 mg) of **3** with pyridine–acetic anhydride, in the usual manner, and crystallization of the crude, oily product (30 mg) from ethanol gave **5β** (9 mg), m.p. 180–183° alone and in admixture with the authentic compound described below. The mother liquor was evaporated to dryness, and the oily residue was eluted from silica gel with ether–light petroleum (5:1) to give **5α** (16 mg) as a chromatographically homogeneous foam, $[\alpha]_D$ +95.5°, identical with the authentic compound described below.

*2,3,4,6-Tetra-*O*-acetyl-1-*O*-(indol-3-ylacetyl)-α-D-glucopyranose* (**4**). — A mixture of penta-*O*-acetyl-α-D-glucopyranose (4.7 g) and IAA (1.5 g) was quickly fused at 135°. Anhydrous zinc chloride (2 g) was added, and the mixture was kept at 120°/25 mmHg for 15 min. The cooled melt was dissolved in chloroform–water (1:1, 50 ml), the organic layer was washed with water, aqueous sodium hydrogen carbonate, and water, dried (Na_2SO_4), and evaporated. The oily residue was eluted from silica gel with solvent *B*, and the fractions containing mainly **4** were combined and evaporated. The residue (900 mg) was rechromatographed with solvent *C* which removed some slower-moving impurities. The product (620 mg), still contaminated with penta-*O*-acetyl-α-D-glucopyranose, was rechromatographed four times using solvent *B*. The anomeric purity of the fractions was monitored by optical rotation and n.m.r. spectroscopy. The pure anomer **4** was obtained as a white, amorphous solid (150 mg), m.p. 42–50°, $[\alpha]_D$ +72°. N.m.r. data: τ 3.64 (d, $J_{1,2}$ 3.2 Hz, H-1), 7.93, 7.99, 8.03, and 8.23 (s, 4 OAc).

Anal. Calc. for $C_{24}H_{27}NO_{11}$: C, 57.03; H, 5.38: N, 2.77. Found: C, 56.83; H, 5.58; N, 2.98.

*1,3,4,6-Tetra-*O*-acetyl-2-*O*-(indol-3-ylacetyl)-α-*(**5α**) *and β-D-glucopyranose* (**5β**). — (*a*) A solution of crude indol-3-ylacetyl chloride in dichloromethane, prepared from IAA (525 mg), was added to a stirred solution of 1,3,4,6-tetra-*O*-acetyl-α-D-glucopyranose[14] (348 mg) in dry pyridine at −7°; the stirring was continued at −5° for 1 h and then at room temperature for 4 h. The mixture was left overnight at 0° and then worked up as described above in the preparation of **1**. The crude, oily product was eluted from silica gel with solvent *C* to give **5α** which was rechromatographed using solvent *A*. The title compound was obtained as a chromatographically homogeneous, amorphous solid (197 mg, 39%), m.p. 43–50°, $[\alpha]_D$ +104°, υ_{max}^{KBr} 3330 s (NH), 1750 vs (C=O), 1225 vs (C–O–), 750 cm^{-1} s (3-substituted indole). N.m.r. data: τ 3.65 (d, $J_{1,2}$ 3.2 Hz, H-1), 7.95, 8.01, 8.08, and 8.29 (s, 4 OAc).

Anal. Calc. for $C_{24}H_{27}NO_{11}$: C, 57.03; H, 5.38; N, 2.77. Found: C, 57.32; H, 5.37; N, 2.64.

By essentially the same method, but with chromatography using solvent *C* only, 1,3,4,6-tetra-*O*-acetyl-β-D-glucopyranose[15] (348 mg) was converted into **5β** (117 mg), m.p. 186–187° (from ethanol), $[\alpha]_D$ +7°. I.r. data: υ_{max}^{KBr} 3330 s (NH), 1750 vs (C=O), 1240 vs (C–O–), 770 cm^{-1} (3-substituted indole). N.m.r. data τ 4.30 (d, $J_{1,2}$ 8.0 Hz, H-1), 7.95, 8.01, and 8.29 (s, 4 OAc).

Anal. Calc. for $C_{24}H_{27}NO_{11}$: C, 57.03; H, 5.38; N, 2.77. Found: C, 56.82; H, 5.40; N, 2.99.

(*b*) To a solution of IAA (214 mg) in dichloromethane–tetrahydrofuran, equivalent amounts of 1,3,4,6-tetra-*O*-acetyl-α-D-glucopyranose (426 mg) in dichloromethane (6 ml) and DCC (252 mg) in dichloromethane (3 ml) were added at 0°, followed by two drops of pyridine. After 24 h, the precipitated *N,N'*-dicyclohexylurea was removed, the filtrate was evaporated, and the residual oil was purified by elution from silica gel with solvent *C* followed by rechromatography (twice) using ether–light petroleum (2:1). Chromatographically homogeneous **5α** (162 mg, 26.2%) was obtained having $[\alpha]_D$ +101° and identical with **5α** described above.

The anomer **5β** was also prepared in poor yield by essentially the same procedure.

ACKNOWLEDGMENTS

The author thanks Dr. H. G. Fletcher, Jr., for valuable discussions and a generous gift of 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranose. Thanks are due to Dr. O. Hadžija for microanalyses and to Mrs. L. Tomić for the n.m.r. spectra. The excellent technical assistance of Miss Š. Valenteković is appreciated.

REFERENCES

1 D. Keglević and M. Pokorny, *Biochem. J.*, 112 (1969) 827.
2 D. Keglević, N. Pravdić, and J. Tomašić, *J. Chem. Soc.*, *C*, (1968) 511.
3 K. N. F. Shaw, A. McMillan, A. G. Gudmunson, and M. D. Armstrong, *J. Org. Chem.*, 23 (1958) 1171.
4 H. B. Wood, Jr., and H. G. Fletcher, Jr., *J. Amer. Chem. Soc.*, 78 (1956) 2849.
5 R. K. Ness and H. G. Fletcher, Jr., *J. Amer. Chem. Soc.*, 78 (1956) 4710.
6 O. T. Schmidt and H. Reuss, *Ann.*, 649 (1961) 137.
7 S. Tejima and H. G. Fletcher, Jr., *J. Org. Chem.*, 28 (1963) 2999.
8 D. Horton, J. B. Hughes, J. S. Jewell, K. D. Philips, and W. N. Turner, *J. Org. Chem.*, 32 (1967) 1073.
9 N. Pravdić and D. Keglević, *Carbohyd. Res.*, 12 (1970) 193.
10 R. U. Lemieux, R. K. Kullnig, H. J. Bernstein, and W. G. Schneider, *J. Amer. Chem. Soc.*, 80 (1958) 6098.
11 A. P. Doerschutz, *J. Amer. Chem. Soc.*, 74 (1952) 4202.
12 P. Bladon and G. C. Forrest, *Chem. Commun.*, (1966) 481.
13 T. D. Perrine, C. P. J. Glaudemans, R. K. Ness, J. Kyle, and H. G. Fletcher, Jr., *J. Org. Chem.*, 32 (1967) 664.
14 B. Helferich and J. Zinner, *Ber.*, 95 (1962) 2604.
15 R. U. Lemieux and G. Huber, *Can. J. Chem.*, 31 (1953) 1040.