Carbohydrate Research, 99 (1982) 175–179
Elsevier Scientific Publishing Company, Amsterdam – Printed in The Netherlands

Note

Synthesis of D-glucosyl esters, using unprotected β-D-glucose*

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(Received May 11th, 1981; accepted for publication, May 19th, 1981)

In the last few years, numerous naturally occurring glycosyl esters have been discovered, partly because of new and mild separation methods such as reversed-phase h.p.l.c. or droplet countercurrent chromatography. Glycosyl esters are widespread in Nature[1], and a variety of carboxylic acids, especially terpene acids (*e.g.*, stevioside or derivatives of oleanic acid), serve as aglycons. D-Glucose is the most widespread carbohydrate moiety, but xylose, arabinose, rhamnose, fucose, and apiose also occur either as monosaccharides or as components of oligosaccharides.

Mainly two routes have been employed for the synthesis of glycosyl esters, involving nucleophilic attack of the carboxylate anion at the anomeric carbon of the carbohydrate (Koenigs–Knorr-type reaction) or of HO-1 on a suitable acyl derivative (*e.g.*, AAE- and DCC-methods). These methods require the use of protecting groups in order to achieve regioselective glycosylation.

In connection with our investigation of saffron pigments[2,3], we have developed a regio- and stereo-selective synthesis of glycosyl esters by the reaction of β-D-glucose, β-D-galactose, and β-maltose with the *N*-acylimidazoles or *N*-acyltriazoles of various polyene carboxylic acids[4–6].

We now report on the synthesis of glycosyl esters with aglycons other than polyene carboxylic acids. As model compounds for aromatic, aliphatic, and sterically hindered acids, respectively, benzoic acid, stearic acid, diphenylacetic acid, and pivalic acid were chosen; the first three of these acids occur naturally as glucosyl esters[7–10].

The reaction of benzoyl chloride with 1,2,4-triazole in toluene gave the *N*-benzoyl derivative **1** (88.9%) which, with β-D-glucose in pyridine at 0° in the presence of a catalytic amount of sodium hydride, gave 1-*O*-benzoyl-β-D-glucose (**2**, 53.4%). Compound **2** and its tetra-acetate **2a** were fully characterised (see Experimental). The synthesis of **2** by Zervas[11] required four steps and afforded an overall yield of 4%. This method was modified by Fletcher[12], who obtained a 16% yield.

1-*O*-Stearoyl-β-D-glucose (**6**) was obtained in yields up to 71% by the reaction of 1-stearoylimidazole (**3**), 1-stearoyl-1,2,4-triazole (**4**), or 1-stearoyltetrazole (**5**) with

*Glycosyl Esters, Part VI. For Part V, see ref. 6.

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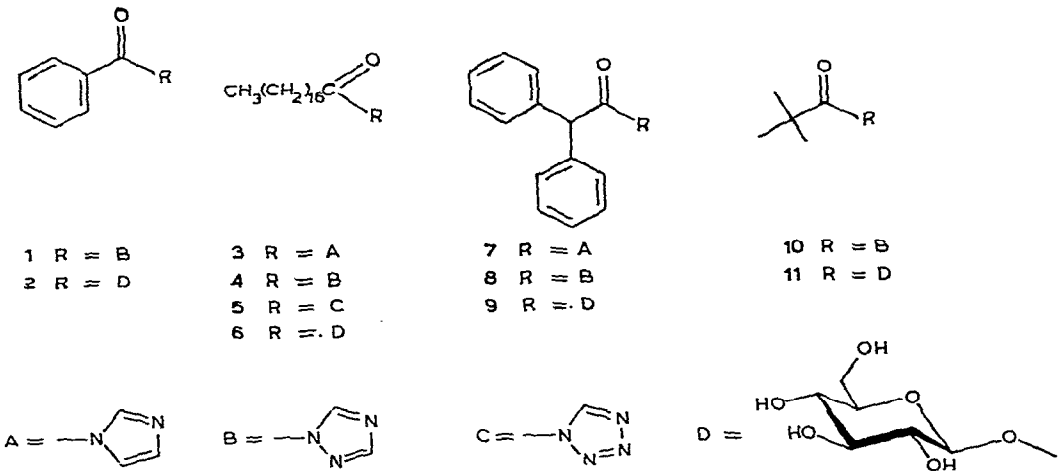

β-D-glucose. The spectroscopic data of **6** and its tetra-acetate **6a** proved the regio- and stereo-selectivity of the esterification. Compound **6** has been synthesised[13–17] by treating 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose with the acyl chloride, followed by catalytic hydrogenation. Pfeffer and co-workers[13–15] could influence the αβ-ratio of the products by variation of the solvent; tetrahydrofuran yielded mainly the α form, benzene mainly the β anomer. Nishikawa and Yoshimoto[16,17] obtained mainly the α isomer.

The hitherto unknown β-D-glucosyl ester **9** of diphenylacetic acid was obtained from the *N*-acylimidazole **7** or *N*-acyl-1,2,4-triazole **8** in considerably lower yield (27.6%) than the two previous examples. A similar yield (28%) was also obtained in the synthesis of the glucosyl ester **11** of pivalic acid, starting from 1-pivaloyl-1,2,4-triazole (**10**).

Thus, the azolide method for the synthesis of glucosyl esters is both convenient and of potential general applicability and, moreover, is regio- and stereo-selective. The regioselectivity may reflect[18] the acidity of HO-1 in the carbohydrate components of the reaction, and the stereoselectivity the low rate of mutarotation of β-D-glucose in pyridine[19].

EXPERIMENTAL

For general methods, see ref. 4. Column chromatography was performed with a prepacked Lobar column (Merck), LiChroprep RP-8 (40–63 μm) size A, and a Uvikon LCD 725 u.v. detector, with *A*, acetonitrile–water (3:2); and *B*, methanol–water (1:1).

Synthesis of azole derivatives. — To a stirred suspension of 2 equiv. of either imidazole or 1,2,4-triazole in toluene was added 1 equiv. of acyl chloride in toluene, dropwise at room temperature, with exclusion of moisture. The mixture was then

TABLE I

REACTION CONDITIONS FOR THE SYNTHESIS OF D-GLUCOSYL ESTERS

Product	*Reagent*	*Temperature*	*Equiv. of D-glucose*	*Time of reaction (h)*
2	**1**	0°	5	4
6	**3**	r.t.[a]	3	6
6	**4**	r.t.	5	5
6	**5**	r.t.	2	3
9	**7**	r.t.	5	6
9	**8**	r.t.	5	6
11	**10**	0°	3	5

[a]Room temperature.

stirred at room temperature for 24 h, filtered under nitrogen, and concentrated. The crude product was distilled, or crystallised from either benzene or acetonitrile.

The following compounds were thus obtained: 1-benzoyl-1,2,4-triazole[20] (**1**, 88.9%), m.p. 69.5° (from benzene); 1-stearoyl-1,2,4-triazole[21] (**4**, 86.6%), m.p. 71.5–72° (from acetonitrile); 1-(diphenylacetyl)imidazole[22] (**7**, 65.5%), m.p. 127° (from acetonitrile); 1-(diphenylacetyl)-1,2,4-triazole (**8**, 73%), m.p. 118.5° (from acetonitrile); 1-pivaloyl-1,2,4-triazole[23] (**10**, 51%), b.p. 187.5°/710 mmHg.

1-Stearoylimidazole[24] (**3**, m.p. 84–85°) and 2-stearoyltetrazole[25] (**5**, m.p. 62.5–64°) were prepared by literature procedures.

Synthesis of glucosyl esters. — The azole derivative (1 equiv.) was treated with 2–5 equiv. of β-D-glucose and a catalytic amount of sodium hydride in pyridine at 0° or room temperature (for details, see Table I). After 3–6 h, the mixture was diluted with an excess of phosphate buffer (pH 7) and extracted with 1-butanol, the extract was washed (4 times) with water, and the solvent was evaporated as the azeotrope with water. A solution of the residue in aqueous 90% methanol was extracted with light petroleum, and then concentrated. The residue was subjected to chromatography or crystallisation, to give the pure β-D-glucosyl esters.

1-O-Benzoyl-β-D-glucopyranose (**2**). — Column chromatography (solvent *A*) and crystallisation from methanol gave **2** (60.1%) as white needles, m.p. 183–185°, $[\alpha]_D$ +19° (1,4-dioxane); lit.[11], m.p. 193°, $[\alpha]_D$ −26.8° (water). P.m.r. data (270 MHz, Me_2SO-d_6): δ 3.12–3.24 (m, 1 H), 3.24–3.34 (m, 3 H, H-2,3,4,5), 3.47 (ddd, 1 H, $J_{6,5}$ ~5, $J_{6,OH}$ 5.8, $J_{6,6}$ −12.5 Hz, H_R-6), 3.67 (ddd, 1 H, $J_{6,5}$ ~2, $J_{6,OH}$ 5.8, $J_{6,6}$ −12.5 Hz, H_S-6), 4.62 (t, 1 H, $J_{OH,6,6}$ 5.8 Hz, HO-6), 5.04 (d, 1 H, $J_{OH,4}$ 4.5 Hz, HO-4), 5.13 (bs, 1 H, HO-3), 5.38 (d, 1 H, $J_{OH,2}$ ~5 Hz, HO-2), 5.59 (d, 1 H, $J_{1,2}$ 8 Hz, H-1), 7.56 (bt, 2 H, J_{ortho} ~8 Hz, H-3',5'), 7.70 (tt, 1 H, J_{ortho} ~8 Hz, H-4'), and 8.03 (dd, 2 H, J_{ortho} ~8 Hz, H-2',6').

The tetra-acetate of **2** had m.p. 140–141°, $[\alpha]_D$ −16° (1,4-dioxane); lit.[11], m.p. 145°, $[\alpha]_D$ −26.6° (chloroform). P.m.r. data (80 MHz, $CDCl_3$): δ 1.98 (s, 3 H, AcO), 2.05 (s with sh, 6 H, 2 AcO), 2.07 (s, 3 H, AcO), 3.75–4.02 (m, 1 H, H-5),

4.13 (dd, 1 H, $J_{6,5}$ 2, $J_{6,6}$ −12.5 Hz, H_S-6), 4.35 (dd, 1 H, $J_{6,5}$ 4.5, $J_{6,6}$ −12.5 Hz, H_R-6), 5.05–5.46 (m, 3 H, H-2,3,4), 5.95 (d, 1 H, $J_{1,2}$ 8 Hz, H-1), 7.33–7.66 (m, 3 H, H-3',4',5'), and 8.06 (dd, 2 H, J_{ortho} ~8 Hz, 2 H, H-2',6').

1-O-Stearoyl-β-D-glucopyranose (**6**). — Repeated crystallisation from methanol gave **6** (71%), m.p. 112–116°, $[\alpha]_D$ +22° (1,4-dioxane); lit.[15] for α-**6**, m.p. 112–121°, $[\alpha]_D$ +72.9° (methanol). P.m.r. data (270 MHz, Me_2SO-d_6): δ 0.85 (s, Me-18'), 1.26 (s, H-3',3'–17',17'), 2.27 (bt, H-2',2'), 2.95–3.53 (m, H-2,3,4,5 and H-6), 3.53–3.70 (m, H-6), 4.4–4.7 (m, HO-6), 4.89 (d, $J_{OH,4}$ 5 Hz, HO-4), 4.95 (d, $J_{OH,3}$ 5 Hz, HO-3), 5.05 (dd, $J_{OH,2}$ 5 Hz, HO-2), and 5.33 (d, $J_{1,2}$ 8 Hz, H-1).

Anal. Calc. for $C_{24}H_{36}O_7$: C, 64.54; H, 10.38. Found: C, 64.37; H, 10.49.

The tetra-acetate of **6** had m.p. 65–69°, $[\alpha]_D$ +7.5° (chloroform); lit.[26] m.p. 77°, $[\alpha]_D$ +4.0° (chloroform). P.m.r. data (270 MHz, $CDCl_3$): δ 0.89 (t, *J* 7 Hz), 1.26 (s, H-3',3'–17',17'), 2.01 (s, AcO), 2.02 (s, AcO), 2.03 (s with sh, 2 AcO), 2.44 (t, *J* 7 Hz, H-2',2'), 3.80–3.89 (m, H-5), 4.12 (dd, $J_{6,5}$ 2, $J_{6,6}$ −12.5 Hz, H_S-6), 4.30 (dd, $J_{6,5}$ 4.5, $J_{6,6}$ −12.5 Hz, H_R-6), 5.06–5.31 (m, H-2,3,4), and 5.72 (d, $J_{1,2}$ 8 Hz, H-1).

1-O-(Diphenylacetyl)-β-D-glucopyranose (**9**). — Column chromatography (solvent *B*) and crystallisation from acetonitrile afforded **9** (27.6%), m.p. 87°, $[\alpha]_D$ +14° (1,4-dioxane). P.m.r. data (270 MHz, Me_2SO-d_6): δ 2.95–3.28 (m, 4 H, H-2,3,4,5), 3.42 (ddd, 1 H, $J_{6,5}$ 5.5, $J_{6,OH}$ 5.8, $J_{6,6}$ −12.5 Hz, H_R-6), 3.62 (ddd, 1 H, $J_{6,5}$ 2, $J_{6,OH}$ 5.8, $J_{6,6}$ −12.5 Hz, H_S-6), 4.57 (t, 1 H, $J_{OH,6,6}$ 5.8 Hz, HO-6), 5.03 (d, 1 H, $J_{OH,4}$ 5.5 Hz, HO-4), 5.13 (d, 1 H, $J_{OH,3}$ 5 Hz, HO-3), 5.22 (s, 1 H, H-2'), 5.33 (d, 1 H, $J_{OH,2}$ 5.5 Hz, HO-2), 5.46 (d, $J_{1,2}$ 8 Hz, H-1), and 7.11–7.50 (m, 10 H, 2 Ph).

Anal. Calc. for $C_{20}H_{22}O_7$: C, 64.16; H, 5.92. Found: C, 64.10; H, 5.93.

The tetra-acetate of **9** had m.p. 141–143°, $[\alpha]_D$ −37° (chloroform); lit.[27], m.p. 144–145°, $[\alpha]_D$ −39.0° (chloroform).

1-O-Pivaloyl-β-D-glucopyranose (**11**). — P.l.c. on silica gel with ethyl acetate–2-propanol–water (5:3:1) gave **11** (28%) as a syrup, $[\alpha]_D$ +12° (1,4-dioxane). P.m.r. data (100 MHz, Me_2SO-d_6): δ 1.18 and 1.20 (s, 3 Me), 2.80–3.50 (m, H-2,3,4,5), 3.50–3.85 (m, H-6,6), 4.40–5.15 (HO-6,4,3,2), and 5.38 (d, $J_{1,2}$ 7.5 Hz, H-1).

Anal. Calc. for $C_{11}H_{20}O_7$: C, 49.99; H, 7.63. Found: C, 49.49; H, 7.77.

The tetra-acetate of **11** had m.p. 136°, $[\alpha]_D$ +8° (chloroform); lit.[27,28] m.p. 136–137°, $[\alpha]_D$ +7.2° (chloroform).

ACKNOWLEDGMENTS

We thank Drs. H. Mayer and U. Vögeli for helpful discussions, Drs. L. Chopard, C. Englert, K. Noack, and W. Vetter, and Mr. W. Meister (Hoffmann–La Roche & Co., Ltd., Basel) for the recording and interpretation of spectra, and the Swiss National Science Foundation (Project No. 2.159–0.78) for financial support.

REFERENCES

1 M. LÄDERACH, Ph.D. Thesis, University of Berne, 1979.
2 H. PFANDER AND F. WITTWER, *Helv. Chim. Acta*, 58 (1975) 1608–1620.
3 H. PFANDER AND F. WITTWER, *Helv. Chim. Acta*, 58 (1975) 2233–2336.
4 H. PFANDER AND F. WITTWER, *Helv. Chim. Acta*, 62 (1979) 1944–1951.
5 H. PFANDER, M. LÄDERACH, AND F. WITTWER, *Helv. Chim. Acta*, 63 (1980) 277–283.
6 H. PFANDER, R. DUMONT, AND M. LÄDERACH, *Chimia*, 34 (1980) 20–23.
7 A. QUILICO, F. PIOZZI, M. PAVAN, AND E. MANTICA, *Tetrahedron*, 5 (1959) 10–14.
8 B. HANSSON, I. JOHANSSON, AND B. LINDBERG, *Acta Chem. Scand.*, 20 (1966) 2358–2362.
9 M. MANDAVA AND J. W. MITCHELL, *Chem. Ind. (London)*, 23 (1972) 930–931.
10 H. R. SCHUETTE AND M. STOCK, *Excerpta Med., Int. Congr. Ser.*, 440 (1978) 225–226.
11 L. ZERVAS, *Ber.*, 64 (1931) 2289–2296.
12 H. G. FLETCHER, JR., *Methods Carbohydr. Chem.*, 2 (1963) 231–233.
13 P. E. PFEFFER, E. S. ROTHMAN, AND G. G. MOORE, *J. Org. Chem.*, 41 (1976) 2925–2927.
14 P. E. PFEFFER AND G. G. MOORE, U.S. Pat. 768,916 (1977); *Chem. Abstr.*, 87 (1977) 202017t.
15 P. E. PFEFFER, G. G. MOORE, P. D. HOAGLAND, AND E. S. ROTHMAN, *ACS Symp. Ser.*, (1976) 155–178.
16 Y. NISHIKAWA AND K. YOSHIMOTO, *Chem. Pharm. Bull.*, 25 (1977) 624–631.
17 Y. NISHIKAWA, Japan Kokai Pat., 78 34,712 (1978); *Chem. Abstr.*, 89 (1978) 110269q.
18 YU. A. ZHDANOV, V. I. MINKIN, YU. A. OSTROUMOV, AND G. N. DOROFEENKO, *Carbohydr. Res.*, 7 (1968) 156–160.
19 A. S. HILL AND R. S. SCHALLENBERGER, *Carbohydr. Res.*, 11 (1969) 541–545.
20 H. A. STAAB, M. LÜKING, AND F. H. DÜRR, *Chem. Ber.*, 95 (1962) 1275–1283.
21 H. J. GAIS AND R. B. WOODWARD, *Angew. Chem.*, 89 (1977) 251–253.
22 H. A. STAAB, *Angew. Chem.*, 74 (1962) 407–423.
23 H. A. STAAB, *Chem. Ber.*, 89 (1956) 2088–2093.
24 S. IWASAKI, *Helv. Chim. Acta*, 59 (1976) 2753–2764.
25 H. A. STAAB, *Chem. Ber.*, 89 (1956) 1927–1940.
26 Y. NISHIKAWA, K. YOSHIMOTO, G. KURONO, AND K. MICHISHITA, *Chem. Pharm. Bull.*, 23 (1975) 597–603.
27 B. HELFERICH AND L. FORSTHOFF, *Chem. Ber.*, 94 (1961) 158–163.
28 T. OGAWA, M. NOZAKI, AND M. MATSUI, *Carbohydr. Res.*, 60 (1978) c7–c10.