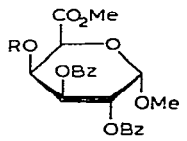
Note

Selective benzoylation of methyl (methyl α-D-galactopyranosid)uronate

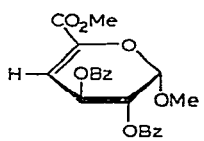
P. L. GILL, M. W. HORNER, L. HOUGH, AND A. C. RICHARDSON
Department of Chemistry, Queen Elizabeth College, London, W8 7AH (Great Britain)
(Received August 1st, 1970; accepted for publication, August 19th, 1970)

The nucleoside antibiotic Gougerotin contains 4-amino-4-deoxy-D-glucuronic acid[1] which has been synthesised[2] by a multi-stage procedure. In an attempt to synthesise this amino-uronic acid directly from a 4-sulphonate of D-galacturonic acid, the synthesis of a suitably blocked derivative was investigated.

Selective dimolar benzoylation of methyl (methyl α-D-galactopyranosid)uronate afforded, as predicted by previous work with galactopyranosides[3], the corresponding 2,3-dibenzoate **1** as a syrup in 60% yield together with a little of the crystalline 2,3,4-tribenzoate **3**. Mesylation of **1** afforded the crystalline 4-methanesulphonate **2** in good overall yield.



1 R = H
2 R = Ms
3 R = Bz



4

The position of the sulphonate group in **2** was demonstrated by comparison of its ^{1}H n.m.r. spectrum with that of the tribenzoate **3** (Table I). Both spectra were amenable to first-order analysis and showed two wide quartets (H-2 and H-3), a narrow quartet (H-4), a very narrow doublet (H-5), and a wider, lower field doublet (H-1). The most significant difference between the chemical shifts of these five pairs of resonances was between those due to H-4 (Δ = 0.52 p.p.m.); the others were small in comparison (0.07–0.17 p.p.m.). Since the deshielding effect of sulphonyloxy groups on adjacent protons is less than that of benzoyloxy substituents, the sulphonate group must be located at C-4.

When **2** was heated with sodium azide in hexamethylphosphoric triamide at 90°, it was transformed within minutes into a product, which from i.r. evidence lacked both azide and sulphonate groups, but possessed unsaturation. It was subsequently found that the same product was formed when the sulphonate was heated with sodium benzoate in hexamethylphosphoric triamide or in hexamethylphosphoric triamide alone. The structure of the product was indicated by its ^{1}H n.m.r. spectrum

which was very similar to that of the tribenzoate **3**, with the exceptions that the H-5 resonance was absent and H-4 was present as a doublet, indicative of the 4-ene **4**.

TABLE I

^{1}H N.M.R. PARAMETERS (FIRST-ORDER COUPLING CONSTANTS AND τ VALUES AT 100 MHz)[a]

Compound	**1**	**2**	**3**	**4**
H-1	4.71d	4.66d[b]	4.58d	4.63d
H-2	4.30cm	4.40q[b]	4.33q	4.44q
H-3		4.17q	4.00q	3.92q
H-4	5.30m	4.30q	3.78q	3.77d
H-5	5.37d	5.22d	5.14d	—
OMe	6.53s	6.51s	6.48s	6.44s
CO_2Me	6.18s	6.16s	6.30s	6.17s
OMs	—	6.99s	—	—
OH	7.23d	—	—	—
$J_{1,2}$	~3	3.4	3.5	2.8
$J_{2,3}$	—	10.5	10.5	8.1
$J_{3,4}$	—	2.8	3.2	2.9
$J_{4,5}$	~1.5	1.4	1.6	—

[a]s, singlet; d, doublet; q, quartet; m,. multiplet; c, complex. [b]Assignment verified by spin decoupling.

The ease of elimination of **2** is due to the acidic nature of the 5-proton which is α to the methoxycarbonyl group, and similar results have been obtained by Kiss and his co-workers[4] with 4-sulphonates of methyl (methyl 2,3-di-*O*-benzyl-α-D-galactopyranosid)uronate and the corresponding *gluco*-analogue. The fact that facile elimination occurs equally readily in both the gluco- and galacto-pyranosiduronates[4] suggests an E_1 mechanism.

EXPERIMENTAL

For general procedures, see ref. 5.

Dimolar benzoylation of methyl (methyl α-D-*galactopyranosid)uronate.* — Benzoyl chloride (5.04 ml; 2 molar equiv.) was added dropwise over 30 min to a solution of methyl (methyl α-D-galactopyranosid)uronate[6] (4.8 g) in dry pyridine (48 ml) at −40°. The reaction mixture was kept at −40° for 2 h and then at room temperature for 20 h, and finally decomposed with ice–water. The product was isolated by extraction with ether in the usual manner, and the resulting syrup was chromatographed on silica gel by using ether–light petroleum (2:1 v/v). This afforded the 2,3-dibenzoate **1** as a syrup (5.6 g; 60%), $[\alpha]_D$ +172° (*c* 1, chloroform) (Found: C, 61.2; H, 5.3. $C_{22}H_{22}O_9$ calc.: C, 61.4; H, 5.15%); and the tribenzoate **3** (0.68 g, 6%), m.p. 134–135° (from di-isopropyl ether), $[\alpha]_D$ +203° (*c*1, chloroform) (Found: C, 65.1; H, 4.75. $C_{29}H_{26}O_{10}$ calc.: C, 65.2; H, 4.85%).

*Methyl (methyl 2,3-di-*O*-benzoyl-4-*O*-mesyl-*α*-*D*-galactopyranosid)uronate* (**2**). — The 2,3-dibenzoate **1** (4.6 g) was mesylated in the usual way with mesyl chloride

(4.6 ml) and pyridine (50 ml), and the product was isolated by precipitation with water. The sulphonate **2** (3.4 g; 63%) had m.p. 122–123° (from propan-2-ol) and $[\alpha]_D$ +156° (*c* 1, chloroform) (Found: C, 54.6; H, 4.65; S, 6.35. $C_{23}H_{24}O_{11}S$ calc.: C, 54.4; H, 4.75; S, 6.3%).

*Methyl (methyl 2,3-di-*O*-benzoyl-4-deoxy-*β*-*L*-*threo*-hex-4-enopyranosid)uronate* (**4**). — The 4-sulphonate **2** (0.5 g) was heated with sodium benzoate (0.5 g) in hexamethylphosphoric triamide (3 ml) at 90° for 15 min. The mixture was then poured into water, and the product was isolated by extraction with ether. The resulting syrup was then purified on a column of silica gel, using ether–light petroleum (2:1 v/v), to give the syrupy 4-ene **4** (0.35 g; 86%), $[\alpha]_D$ +126° (*c* 1, chloroform) (Found: C, 64.6; H, 4.85. $C_{22}H_{20}O_8$ calc.: C, 64.1; H, 4.85%).

Similar results were obtained when sodium azide was used instead of sodium benzoate. When **2** was heated in hexamethylphosphoric triamide alone, it was partly transformed into **4** as indicated by t.l.c.

ACKNOWLEDGMENTS

One of us (M.W.H.) thanks the S.R.C. for a studentship, and we are grateful to the Physico-Chemical Measurements Units at Harwell for the determination of the 100 MHz n.m.r. spectra.

REFERENCES

1 T. KANZAKI, E. HIGASHIDAH, H. YAMAMOTA, M. SHIBATA, K. NAKAZAWA, H. IWASAKI, T. TAKEWAKA, AND A. MIYAKI, *J. Antibiotics* (Tokyo), *Ser. A*, 11 (1958) 1; and references quoted in Ref. 2.
2 M. P. KOTICK, R. S. KLEIN, K. A. WATANABE, AND J. J. FOX, *Carbohyd. Res.*, 11 (1969) 369.
3 J. M. WILLIAMS AND A. C. RICHARDSON, *Tetrahedron*, 23 (1967) 1369, 1641; M. W. HORNER, L. HOUGH, AND A. C. RICHARDSON, *Carbohyd. Res.*, 17 (1971) 209.
4 J. KISS AND F. BURKHARDT, *Helv. Chim. Acta*, 52 (1969) 2622; J. KISS, *Carbohyd. Res.*, 10 (1969) 328; *Tetrahedron Lett.*, (1970) 1983.
5 M. W. HORNER, L. HOUGH, AND A. C. RICHARDSON, *J. Chem. Soc.* (*C*), (1970) 1336.
6 H. W. H. SCHMIDT AND H. NEUKOM, *Helv. Chim. Acta*, 47 (1964) 865; 49 (1966) 510.