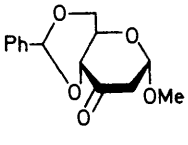
Synthesis of Derivatives of Methyl 2,6-Dideoxy-4-*O*-methyl-α-D-*ribo*-hexopyranoside: on the Structure of Variose

By **John S. Brimacombe,* Annalee S. Mengech, and Leslie C. N. Tucker,** Chemistry Department, The University, Dundee DD1 4HN

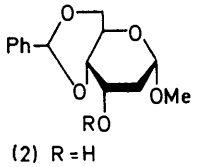
Methyl 3-*O*-benzoyl-2,6-dideoxy-4-*O*-methyl-α-D-*ribo*-hexopyranoside (10) has been synthesised by an unambiguous route from methyl 4,6-*O*-benzylidene-2-deoxy-α-D-*ribo*-hexopyranoside (2). The benzoate (10) differs from benzoylated methyl varioside (obtained by way of methanolysis of the antibiotic variamycin), which is claimed to have the same structure.

METHANOLYSIS of the antibiotic variamycin yields [1] methyl varioside, which has been identified as methyl 2,6-dideoxy-4-*O*-methyl-α-D-*ribo*-hexopyranoside (9) principally from its n.m.r. spectrum and that of the derived monobenzoate (10). However, certain features of the n.m.r. spectra of these derivatives are not readily reconciled with structures (9) and (10); in particular, the signal assigned to H-5 of the monobenzoate appears at uncharacteristically low field (τ *ca.* 4.8; see Figure) for such a proton in a pyranoid derivative. We have synthesised methyl 3-*O*-benzoyl-2,6-dideoxy-4-*O*-methyl-α-D-*ribo*-hexopyranoside (10) by an unambiguous route and have shown that its n.m.r. spectrum differs from that reported [1] for methyl varioside monobenzoate.

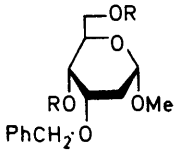
Reduction of methyl 4,6-*O*-benzylidene-2-deoxy-α-D-*erythro*-hexopyranosid-3-ulose [2] (1) with sodium borohydride in methanol–*NN*-dimethylformamide furnished methyl 4,6-*O*-benzylidene-2-deoxy-α-D-*ribo*-hexopyranoside (2), whose physical constants readily distinguished it from the epimeric D-*arabino*-compound.[3] Overend *et al.*[4] have found that reduction of the hexopyranosidulose (1) with lithium aluminium hydride also gives the D-*ribo*-hexopyranoside (2) preferentially. Benzylation [5] of compound (2) gave the 3-*O*-benzyl derivative



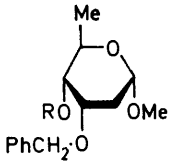
(1)



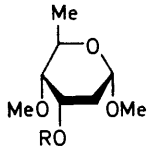
(2) R = H
(3) R = CH_2Ph



(4) R = H
(5) R = Ts



(6) R = Ts
(7) R = H
(8) R = Me

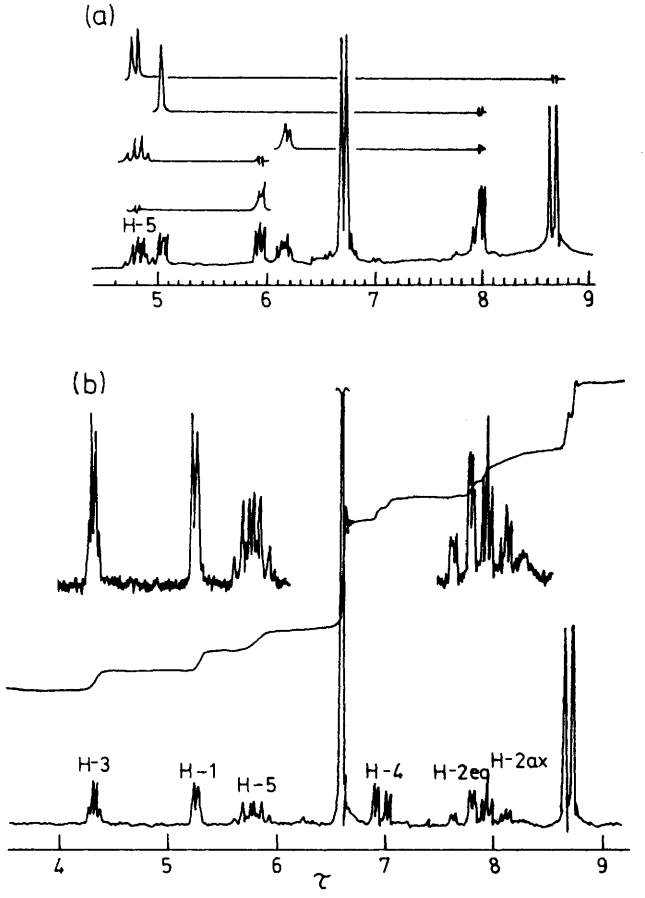


(9) R = H
(10) R = Bz

(3), which was converted into methyl 3-*O*-benzyl-2-deoxy-4,6-di-*O*-*p*-tolylsulphonyl-α-D-*ribo*-hexopyranoside (5) by consecutive treatment with dilute hydrochloric

[1] G. B. Lokshin, Yu. V. Zhdanovich, A. D. Kuzovkov, and V. I. Sheichenko, *Khim. prirod. Soedinenii*, 1973, **9**, 418.
[2] P. J. Beynon, P. M. Collins, P. T. Doganges, and W. G. Overend, *J. Chem. Soc.* (*C*), 1966, 1131.
[3] B. Flaherty, W. G. Overend, and N. R. Williams, *J. Chem. Soc.* (*C*), 1966, 398.
[4] P. J. Beynon, P. M. Collins, and W. G. Overend, *J. Chem. Soc.* (*C*), 1969, 272.
[5] J. S. Brimacombe, B. D. Jones, M. Stacey, and J. J. Willard, *Carbohydrate Res.*, 1966, **2**, 167.

acid and toluene-*p*-sulphonyl chloride in pyridine. The ditosylate (5) was transformed into methyl 3-*O*-benzyl-2,6-dideoxy-α-D-*ribo*-hexopyranoside (7) in two steps: first, reduction to the monotosylate (6) with lithium aluminium hydride in tetrahydrofuran, and then solvolysis of the monotosylate (6) with methanolic sodium methoxide. Attempts to convert the ditosylate (5) into compound (7) by prolonged treatment with lithium aluminium hydride [6] gave a product mixture of unexpected complexity. Methylation [5] of compound (7) afforded the 4-*O*-methyl derivative (8), which was



Parts of the 90 MHz n.m.r. spectra (solvent [^{2}H]chloroform) of (a) methyl *O*-benzoylvarioside (ref. 1) and (b) methyl 3-*O*-benzoyl-2,6-dideoxy-4-*O*-methyl-α-D-*ribo*-hexopyranoside (10)

converted into methyl 3-*O*-benzoyl-2,6-dideoxy-4-*O*-methyl-α-D-*ribo*-hexopyranoside (10) on catalytic debenzylation and treatment of the debenzylated compound (9) with benzoyl chloride in pyridine.

Comparison of the n.m.r. spectrum of the synthetic compound (10) with that of benzoylated methyl varioside (Figure) establishes that these compounds are not identical. The same conclusion has been reached by Takai, Yuki, and Takiura,[7] who recently described an alternative synthesis of methyl 3-*O*-benzoyl-2,6-dideoxy-4-*O*-methyl-α-D-*ribo*-hexopyranoside (10). The n.m.r. spectrum of our compound was indistinguishable from that of the compound synthesised by the Japanese workers,[7] who have suggested that methyl varioside is probably a methyl 2,6-dideoxy-3-*O*-methylhexofuranoside; this suggestion is in keeping with the shift of the H-5 n.m.r. signal to low field in the spectrum of the benzoylated derivative, although it remains for the absolute configuration of variose to be determined.

[6] R. S. Tipson, *Adv. Carbohydrate Chem.*, 1953, **8**, 107.
[7] H. Takai, H. Yuki, and K. Takiura, *Tetrahedron Letters*, 1975, 3647.

EXPERIMENTAL

T.l.c. was performed on Kieselgel G; spots were located with vanillin–sulphuric acid.[8] I.r. spectra were routinely recorded for Nujol mulls on a Perkin-Elmer Infracord spectrophotometer; in all cases, the spectra are compatible with the structures assigned. N.m.r. spectra were usually measured with a Perkin-Elmer R-10 (60 MHz) spectrometer for solutions in deuteriochloroform with tetramethylsilane as internal reference. Optical rotations were measured at ambient temperature with a Perkin-Elmer 141 automatic polarimeter. Light petroleum refers to the fraction having b.p. 60—80 °C, unless otherwise stated.

Methyl 4,6-O-*Benzylidene*-2-*deoxy*-α-D-ribo-*hexopyranoside* (2).—Sodium borohydride (25.3 g) was added in small portions over 2 h to a stirred solution of methyl 4,6-*O*-benzylidene-2-deoxy-α-D-*erythro*-hexopyranosid-3-ulose [2] (10 g) in methanol (500 ml) and *NN*-dimethylformamide (20 ml); stirring was continued for 1 h at room temperature and the solvents were then removed. The solid residue was partitioned between chloroform and water, and the separated aqueous layer was washed with chloroform (3 × 50 ml). The combined and dried ($MgSO_4$) chloroform layers were evaporated, and the crystalline residue was recrystallised (twice) from chloroform–light petroleum to give the product (2) (8.7 g), m.p. 124—126°, $[\alpha]_D$ +140° (*c* 1.2 in $CHCl_3$) {lit.,[4] m.p. 124—125°, $[\alpha]_D$ +145° (*c* 1 in $CHCl_3$)} {*cf.* methyl 4,6-*O*-benzylidene-2-deoxy-α-D-*arabino*-hexopyranoside, m.p. 151—152°, $[\alpha]_D$ +90° (*c* 1 in Me_2CO)[3]}.

Methyl 3-O-*Benzyl*-4,6-O-*benzylidene*-2-*deoxy*-α-D-ribo-*hexopyranoside* (3).—Sodium hydride (2.1 g) was added to a stirred solution of compound (2) (*ca.* 10 g) in *NN*-dimethylformamide (200 ml) at room temperature. After 45 min, freshly distilled benzyl bromide (10.1 g, 1.6 mmol) was added dropwise. Stirring was continued for 22 h, after which time t.l.c. (ethyl acetate–light petroleum, 1 : 1) revealed two products, one of which predominated. Methanol (100 ml) was carefully added to decompose the excess of reagents and, after 1 h, the solvents were removed. The residue was extracted with chloroform (150 ml), which was then washed with water (3 × 50 ml), dried ($MgSO_4$), and evaporated. Recrystallisation (twice) of the residue from chloroform–light petroleum gave the *benzyl ether* (3) (8.35 g, 63%), m.p. 96.5—98°, $[\alpha]_D$ +64° (*c* 0.7 in $CHCl_3$) (Found: C, 70.9; H, 6.5. $C_{21}H_{24}O_5$ requires C, 70.8; H, 6.8%); τ *ca.* 2.6 (10 H, aromatic), 4.38 (1 H, s, PhC*H*), 5.14 (2 H, s, CH_2Ph), and 6.57 (3 H, s, OMe).

Methyl 3-O-*Benzyl*-2-*deoxy*-4,6-*bis*-O-p-*tolylsulphonyl*-α-D-ribo-*hexopyranoside* (5).—A solution of the benzylidene acetal (3) (5 g) in aqueous methanol (900 ml; 1 : 8 v/v) containing 0.01M-hydrochloric acid (100 ml) was heated under reflux at 75—80 °C for 6.5 h; t.l.c. (ethyl acetate–light petroleum–ethanol, 2 : 4 : 1) then showed that all the

[8] E. Merck AG, 'Chromatography,' Darmstadt, 2nd edn., p. 30.

starting material had reacted to give one principal and several minor products. The acidic solution was neutralised ($PbCO_3$) and the solvents were removed to give a pale yellow syrup that was chromatographed on silica gel (elution with ethyl acetate–light petroleum–ethanol, 2 : 14 : 1) to give the diol (4) (3.1 g, 82%), $[\alpha]_D$ +101° (*c* 1 in $CHCl_3$); τ 2.64 (5 H, aromatic), 5.40 (2 H, ABq, J_{AB} 12 Hz, PhCH_2), and 6.67 (3 H, s, OMe).

To a cooled (0 °C) solution of the diol (4) (3.7 g) in dry pyridine (15 ml) was added toluene-*p*-sulphonyl chloride (10.5 g) in pyridine (30 ml), and the mixture was set aside overnight at room temperature. Water (3 ml) was added to destroy the excess of reagent and the solvents were removed. The residue was dissolved in chloroform (200 ml), which was then washed with aqueous 5% sodium hydrogen sulphite (3 × 150 ml), M-hydrochloric acid (2 × 150 ml), saturated aqueous sodium hydrogen carbonate (3 × 100 ml), and water (2 × 150 ml). Evaporation of the dried ($MgSO_4$) organic extract gave the crude ditosylate (5) (7.91 g, *ca.* 99%) as a dark yellow syrup. Chromatography of a portion on silica gel (elution with benzene–ether, 4 : 1) gave the pure *ditosylate* (5), m.p. 115—117° [from benzene–light petroleum (b.p. 80—100 °C)], $[\alpha]_D$ +67° (*c* 0.75 in $CHCl_3$) (Found: C, 58.35; H, 5.6; S, 11.1. $C_{28}H_{32}O_9S_2$ requires C, 58.3; H, 5.6; S, 11.1%); τ *ca.* 2.4 (13 H, aromatic), 6.74 (3 H, s, OMe), and 7.58 (6 H, s, 2 × Ar*Me*).

Methyl 3-O-*Benzyl*-2,6-*dideoxy*-4-O-p-*tolylsulphonyl*-α-D-ribo-*hexopyranoside* (6).—To a stirred solution of the ditosylate (5) (2.3 g) in dry tetrahydrofuran (10 ml) was gradually added a solution of lithium aluminium hydride (0.91 g) in dry tetrahydrofuran (10 ml); the mixture was then heated under gentle reflux for 75 min. The excess of reagent was destroyed by addition of moist ethyl acetate (20 ml) to the cooled solution, followed by water (20 ml). The separated organic layer was washed with water (2 × 100 ml) and combined with one obtained by washing the aqueous layer with chloroform (6 × 50 ml). Concentration of the combined and dried ($MgSO_4$) extracts left a syrup that t.l.c. (light petroleum–ethyl acetate, 2 : 1) showed to contain a number of products and some starting material. Chromatography on silica gel (elution with light petroleum–ethyl acetate, 4 : 1), gave, *inter alia*, the monotosylate (6) (0.8 g, 49%), $[\alpha]_D$ +114° (*c* 0.72 in $CHCl_3$), as a syrup that could not be induced to crystallise; τ *ca.* 2.6 (9 H, aromatic), 6.63 (3 H, s, OMe), 7.57 (3 H, s, Ar*Me*), and 8.72 (3 H, d, $J_{5.6}$ 6 Hz, HC*Me*).

Methyl 3-O-*Benzyl*-2,6-*dideoxy*-α-D-ribo-*hexopyranoside* (7).—A solution of the monotosylate (6) (0.59 g) in methanolic sodium methoxide [10 ml; from sodium (0.46 g)] was heated under reflux for 3 h; t.l.c. (light petroleum–ethyl acetate, 2 : 1) then showed that the starting material had not reacted completely, so more sodium methoxide (10 ml) was added and heating was continued for a further 18 h. Dry methanol (50 ml) was added to the cooled solution, which was then neutralised (CO_2) and concentrated. The residue was partitioned between chloroform and water; the separated organic layer was washed with water (2 × 50 ml) and dilute hydrochloric acid (50 ml) before drying ($MgSO_4$). Removal of the solvent left a mobile yellow syrup that furnished the alcohol (7) (0.24 g, 65.5%), b.p. *ca.* 145° (bath) at 0.5 mmHg, $[\alpha]_D$ +134° (*c* 2.5 in $CHCl_3$), following chromatography on silica gel (elution with light petroleum–ethyl acetate, 4 : 1). Slight decomposition of the product occurred on distillation and on storage so that satisfactory analytical data could not be obtained. However, the structure (7) is readily reconciled with the following data: τ 2.58 (5 H, aromatic), 5.40 (2 H, ABq, J_{AB} 12 Hz, PhCH_2), 6.65 (3 H, s, OMe), and 8.75 (2 H, d, $J_{5.6}$ 6 Hz, HC*Me*); $\nu_{max.}$ 3 540 and 3 450 cm^{-1} (OH).

Methyl 3-O-*Benzyl*-2,6-*dideoxy*-4-O-*methyl*-α-D-ribo-*hexopyranoside* (8).—To a stirred solution of compound (7) (0.24 g) in dry *NN*-dimethylformamide (10 ml) containing sodium hydride (0.14 g) was gradually added freshly distilled methyl iodide (0.58 g); stirring was then continued for 1 h, after which t.l.c. (light petroleum–ethyl acetate–ethanol, 50 : 10 : 1) showed that a little starting material still remained. More methyl iodide (0.09 g) was added and the mixture was stirred for 4 h. Work-up in the usual way [5] and chromatography on silica gel (elution with hexane–ethyl acetate, 5 : 1) gave the *methyl ether* (8) (0.18 g, 71%), b.p. 120° (bath) at 0.7 mmHg, $[\alpha]_D$ +162° (*c* 1 in $CHCl_3$) (Found: C, 67.9; H, 8.5. $C_{15}H_{22}O_4$ requires C, 67.7; H, 8.3%); τ 2.57 (5 H, aromatic), 5.30 (2 H, ABq, J_{AB} 12 Hz, CH_2Ph), 6.52 and 6.56 (6 H, each s, 2 × OMe), and 8.75 (3 H, d, $J_{5.6}$ 6 Hz, HC*Me*).

Methyl 3-O-*Benzoyl*-2,6-*dideoxy*-4-O-*methyl*-α-D-ribo-*hexopyranoside* (10).—A solution of the benzylated compound (8) (51 mg) in dry ethanol (10 ml) containing Adams catalyst (230 mg) was shaken under a slight overpressure of hydrogen at room temperature for 22 h, during which time complete reaction occurred. The catalyst and solvent were removed, and the resulting syrup in pyridine (5 ml) was treated overnight at room temperature with benzoyl chloride (0.11 g). Work-up in the usual way and chromatography on silica gel (elution with carbon tetrachloride–ether, 5 : 1) gave, *inter alia*, the *benzoate* (10) (27 mg, 50%), $[\alpha]_D$ +174 ± 2° (*c* 0.9 in $CHCl_3$) (Found: C, 64.6; H, 7.1. $C_{15}H_{20}O_5$ requires C, 64.3; H, 7.1%); τ 4.32 (1 H, q, $J_{3.4}$ 3 Hz, H-3), 5.27 (1 H, d, $J_{1.2ax}$ *ca.* 4 Hz, $J_{1.2eq}$ *ca.* 0 Hz, H-1), *ca.* 5.75 (1 H, m, H-5), 6.63 (6 H, s, 2 × OMe), 6.95 (1 H, q, $J_{4.5}$ *ca.* 10 Hz, H-4), 7.75 (1 H, q, $J_{2eq.3}$ *ca.* 0 Hz, H-2*eq*), 8.03 (1 H, sext, $J_{2ax.3}$ *ca.* 3 Hz, H-2*ax*), and 8.67 (3 H, d, $J_{5.6}$ 6 Hz, HC*Me*). The n.m.r. spectrum of the benzoate (10) was indistinguishable from that recorded by Takai *et al.*,[7] although it was easily distinguished from the n.m.r. spectrum reported for benzoylated methyl varioside {lit.[1] $[\alpha]_D$ +60 ± 2° (*c* 0.2 in $CHCl_3$)}.

[6/1711 *Received*, 8*th September*, 1976]