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THE INTRODUCTION OF UNSATURATED LINKAGES INTO SOME CARBOHYDRATES BY PYROLYSIS OF CYCLIC, ORTHOFORMIC ESTERS

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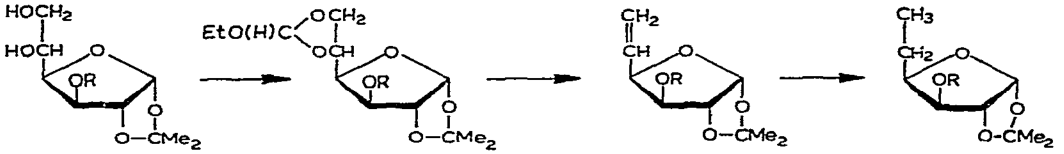
ABSTRACT

The conversion of the 5,6-diol system in two D-glucofuranose derivatives into carbon–carbon double bonds by pyrolysis of the cyclic ethyl orthoformic esters has been shown to proceed in high yield. 5,6-*O*-(Ethoxymethylene)-1,2-*O*-isopropylidene-3-*O*-methyl-α-D-glucofuranose and 3-*O*-benzyl-5,6-*O*-(ethoxymethylene)-1,2-*O*-isopropylidene-α-D-glucofuranose were prepared from the corresponding 5,6-diols by treatment with ethyl orthoformate. When these compounds were heated in the presence of a carboxylic acid, they were converted into 5,6-dideoxy-1,2-*O*-isopropylidene-3-*O*-methyl-α-D-*xylo*-hex-5-enofuranose and 3-*O*-benzyl-5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hex-5-enofuranose, respectively. On hydrogenation, the latter compounds yielded 5,6-dideoxy-1,2-*O*-isopropylidene-3-*O*-methyl-α-D-*xylo*-hexofuranose and 5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranose, respectively.

INTRODUCTION AND DISCUSSION

The number of methods available for the formation of unsaturated carbohydrates has increased in recent years, and this development has occasioned interest in such compounds for use as synthetic intermediates[1,2]. We have been concerned with devising simple procedures for converting *cis*-1,2-diols into the corresponding olefins by way of 2-alkoxy-1,3-dioxolane derivatives[3]. We are examining the carboxylic acid-catalysed, thermal breakdown of cyclic orthoformates of carbohydrate diols, to ascertain what limitations the kind of protective group, used elsewhere on the carbohydrate molecule, places on the conditions for successful elimination. This paper describes the introduction of terminal unsaturation into two D-glucofuranose derivatives.

The 2-ethoxy-1,3-dioxolanes required as intermediates are readily prepared under mild conditions by exchange between 1,2-diols and ethyl orthoformate in the presence of a carboxylic acid as the catalyst. When 1,2-*O*-isopropylidene-3-*O*-methyl-α-D-glucofuranose (**1a**) was heated with ethyl orthoformate in the presence of a trace of acetic acid, there was formed a liquid product that gave analyses corresponding to those calculated for the orthoformate expected and that showed no hydroxyl absorption in its i.r. spectrum. In the n.m.r. spectrum, the resonances of H-1 and the orthoformyl proton gave an overlapping, 2-proton triplet. One of the two peaks attributed to the resonance of the orthoformyl proton had the same chemical shift as the high-field branch of the H-1 doublet. It had been found that, where there is the possibility of stereoisomerism in 2-ethoxy-1,3-dioxolanes, both isomers are formed, except under extreme conditions of steric interaction, when a single stereoisomer may result[4]. Since there is little such interaction in the present example, the product is considered to be a mixture of diastereoisomers of 5,6-*O*-(ethoxymethylene)-1,2-*O*-isopropylidene-3-*O*-methyl-α-D-glucofuranose (**2a**). On heating this mixture in the presence of benzoic acid, ethanol and carbon dioxide were evolved, and the unsaturated compound 5,6-dideoxy-1,2-*O*-isopropylidene-3-*O*-methyl-α-D-*xylo*-hex-5-enofuranose (**3a**) was formed in 80% yield. The n.m.r. spectrum of this product showed the presence of vinylic protons in the terminal double bond[5], and the structure of the product was confirmed by catalytic hydrogenation to form 5,6-dideoxy-1,2-*O*-isopropylidene-3-*O*-methyl-α-D-*xylo*-hexofuranose (**4a**), which was identical with the compound obtained by methylation of the known[6,7] 5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranose (**4b**).



1
a R = Me
b R = PhCH$_2$

2
a R = Me
b R = PhCH$_2$

3
a R = Me
b R = PhCH$_2$

4
a R = Me
b R = H

The exchange reaction between ethyl orthoformate and 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-glucofuranose (**1b**) gave a liquid product that gave analyses corresponding to those calculated for the orthoformate, and that showed no hydroxyl absorption in its i.r. spectrum. In the n.m.r. spectrum, the H-1 doublet and the signal of the orthoformyl proton were resolved. The latter consisted of two bands, at τ 4.29 and τ 4.32, the integrated areas of which were in the approximate ratio 2:3, and the total integral of which corresponded to one proton. The product was, therefore, considered to be a mixture of the diastereoisomers of 3-*O*-benzyl-5,6-*O*-(ethoxymethylene)-1,2-*O*-isopropylidene-α-D-glucofuranose (**2b**). Pyrolysis of the mixture of diastereoisomers in the presence of triphenylacetic acid (used because it is less volatile than benzoic acid) gave an 86% yield of 3-*O*-benzyl-5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hex-5-enofuranose (**3b**). The presence of the vinyl group in this product was confirmed by its n.m.r. spectrum, and its physical properties corresponded with those described by English and Levy[8] for the compound obtained by treatment of 5,6-anhydro-3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-glucofuranose with methyllithium. The product obtained by English and Levy[8], after catalytic hydrogenation of the unsaturated compound, has been shown by Hall, Hough, and Pritchard[7] to be identical with 5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranose **(4b)** prepared by a number of other methods. Hydrogenation of our unsaturated compound **3b** gave the same product **(4b)**, the identity of which was confirmed by a separate synthesis[6,7].

EXPERIMENTAL

General methods. — Melting points were determined on a Kofler micro hot-stage and are uncorrected. Refractive indexes were determined with a Bellingham and Stanley Abbé "60" refractometer. I.r. spectra of Nujol mulls and of liquid films were recorded with either a Unicam SP-200 or a Perkin–Elmer Model 275 i.r. spectrometer, and the principal bands are reported. The n.m.r. spectra were recorded at 100 MHz with a Varian HR-100 spectrometer, in carbon tetrachloride solution with tetramethylsilane ($\tau = 10.00$) as the internal standard. Chemical shifts were determined from a side band by assuming a linear scale. Chemical-shift values are given on the τ-scale, and correspond to the mid-point of each singlet or symmetrical multiplet. For narrow, unsymmetrical multiplets, the weighted mean value is given, and, for complex multiplets, the upper and lower limits of the chemical shifts are given. Microanalyses were performed by the Australian Microanalytical Service, Melbourne.

*Preparation of the mixture of diastereoisomers of 5,6-*O*-(ethoxymethylene)-1,2-*O*-isopropylidene-3-*O*-methyl-α-D-glucofuranose* **(2a)**. — Compound **1a** (2.0 g, 8.5 mmole), ethyl orthoformate (1.3 g, 8.8 mmole), and one drop of glacial acetic acid were heated for 2 h at 115–125°, during which time ethanol distilled from the mixture. On distillation from metallic sodium, the resulting liquid, gave the mixture of diastereoisomeric orthoformic esters as a colourless oil, yield 2.23 g (90%), b.p. 120° at 0.2 torr, n_D^{25} 1.4527, $[\alpha]_D^{21}$ $-8.4°$ (*c* 9.6, ethanol); ν_{max} 1459, 1379, 1212, 1083, 1018, 853 cm^{-1}; n.m.r. data: τ 4.3 (2-proton apparent triplet, orthoformyl-proton diastereoisomers, and doublet, $J_{1,2}$ 3.5 Hz, H-1), τ 5.56 (1-proton doublet, $J_{2,3} < 0.5$ Hz, H-2), τ 5.70–6.58 (7-proton multiplet, H-3,4,5,6,6′, and ethoxy CH_2), τ 6.60 (3-proton singlet, OMe), τ 8.58, 8.74 (3-proton singlets, CMe_2), τ 8.83 (3-proton triplet, J 7 Hz, Me of ethoxyl group).

Anal. Calc. for $C_{13}H_{22}O_7$: C, 53.8; H, 7.6. Found: C, 53.9; H, 7.7.

*5,6-Dideoxy-1,2-*O*-isopropylidene-3-*O*-methyl-α-D-*xylo*-hex-5-enofuranose* **(3a)**. — The mixture of diastereoisomers **2a** (2.0 g) and benzoic acid (0.02 g) was heated from 150 to 170° over a period of 5 h, during which time ethanol and carbon dioxide (80% yield, by titration with barium hydroxide) were evolved. The residue was dissolved in ether, anhydrous potassium carbonate was added to neutralize the benzoic acid, the suspension was filtered, and the filtrate was evaporated. Distillation of the residue gave the product as a colourless liquid, yield 1.1 g (80%), b.p. 80° at 2 torr, n_D^{25} 1.4557, $[\alpha]_D^{21}$ $-43.1°$ (*c* 1.5, ethanol); ν_{max} 1360, 1200, 1145, 1065, 1015, 918, 857 cm^{-1}; n.m.r. data: τ 3.92–4.30 (2-proton multiplet, H-5 multiplet and H-1 doublet $J_{1,2}$ 4.5 Hz), τ 4.55–4.9 (2-proton multiplet, H-6,6′), τ 5.48 (2-proton multiplet, H-2,4), τ 6.38 (1-proton doublet, $J_{3,4}$ 3.5 Hz, H-3), τ 6.60 (3-proton singlets, OMe), τ 8.57, 8.74 (3-proton singlets, CMe_2).

Anal. Calc. for $C_{10}H_{16}O_4$: C, 60.0; H, 8.1. Found: C, 59.9; H, 8.0.

*5,6-Dideoxy-1,2-*O*-isopropylidene-3-*O*-methyl-α-*D-xylo*-hexofuranose* (**4a**). — On hydrogenation in ethanol solution over Adams' platinum oxide catalyst, compound **3a** (1.0 g) absorbed one molar equivalent of hydrogen. Distillation of the residue obtained on removal of the catalyst and the solvent gave the product as a colourless liquid, yield 0.96 g (95%), b.p. 60° at 0.1 torr, n_{D}^{25} 1.4314, $[\alpha]_{\mathrm{D}}^{21}$ $-53.1°$ (*c* 2.1, ethanol); $\nu_{\max}$ 1470, 1387, 1217, 1168, 1131, 1097, 1028, 896, 866 cm^{-1}; n.m.r. data: τ 4.30 (1-proton doublet, $J_{1,2}$ 3.9 Hz, H-1), τ 5.60 (1-proton doublet, $J_{2,3}$ 0.5 Hz, H-2), τ 6.11 (1-proton sextet, H-4), τ 6.57 (1-proton doublet, $J_{3,4}$ 3.2 Hz, H-3), τ 6.66 (3-proton singlet, OMe), τ 8.45 (2-proton quartet, J 7 Hz, showing evidence of a further splitting of 1.0 Hz, H-5,5′), τ 8.61, 8.77 (3-proton singlets, CMe_2), τ 9.1 (3-proton triplet, J 7 Hz, H-6,6′,6″).

Anal. Calc. for $C_{10}H_{18}O_4$: C, 59.4; H, 9.0. Found: C, 59.5; H, 9.2.

Compound[7] **4a** (0.188 g, 1.0 mmole) was added to a suspension of sodium hydride (0.06 g) in ether (5 ml), under nitrogen at one atmosphere pressure. The mixture was warmed until the evolution of hydrogen had ceased (0.5 h) and then cooled in ice, and a solution of methyl sulphate (0.1 ml) in ether (3 ml) was added dropwise. When addition had been completed, the mixture was boiled under reflux for 4 h. A further quantity of sodium hydride (0.05 g) was added, and the procedure was repeated. After the mixture had been heated under reflux and then kept overnight, it was treated with concentrated ammonia solution and kept for 2 h. The ether layer was separated, washed with water, dried ($CaSO_4$), and evaporated to dryness. Distillation of the residue gave the product as a colourless oil, yield 0.13 g (64%), b.p. 60° at 0.1 torr, n_{D}^{25} 1.4345, $[\alpha]_{\mathrm{D}}^{23}$ $-50.0°$ (*c* 1.6, ethanol), $[\alpha]_{\mathrm{D}}^{20}$ $-74°$ (*c* 5.0, chloroform). The i.r. and n.m.r. spectra were identical with those already given.

*Preparation of the mixture of diastereoisomers of 3-*O*-benzyl-5,6-*O*-(ethoxymethylene)-1,2-*O*-isopropylidene-α-*D*-glucofuranose* (**2b**). — Compound **1b** (0.52 g, 1.7 mmole), ethyl orthoformate (0.31 g, 2.1 mmole), and one drop of glacial acetic acid were heated from 110 to 120° over a period of 3 h, during which time ethanol distilled from the mixture. Distillation of the residue from metallic sodium gave the mixture of diastereoisomeric orthoformic esters as a colourless liquid, yield 0.57 g (93%), b.p. 150–155° at 0.1 torr, n_{D}^{25} 1.5321, $[\alpha]_{\mathrm{D}}^{21}$ $-15.3°$ (*c* 2.0, ethanol); $\nu_{\max}$ 1460, 1380, 1215, 1118, 1080, 1015, 950, 862, 722, 700 cm^{-1}; n.m.r. data: τ 2.74 (5-proton singlet, phenyl protons), τ 4.25 (1-proton doublet, $J_{1,2}$ 3.9 Hz, H-1), τ 4.29, 4.32 (1-proton, giving rise to two resonance maxima, the approximate ratio of the integrated peaks being 2:3; orthoformyl C-H in diastereoisomers), τ 5.43 (2-proton singlet, benzylic CH_2), τ 5.58 (1-proton doublet, $J_{2,3}$ < 0.5 Hz, H-2), τ 5.60–6.12 (5-proton multiplet, H-3,4,5,6,6′), τ 6.54 (2-proton quartet, J 7 Hz, ethoxy CH_2), τ 8.63, 8.82 (3-proton singlets, CMe_2), τ 8.84 (3-proton triplet, Me of ethoxyl group).

Anal. Calc. for $C_{19}H_{26}O_7$: C, 62.3; H, 7.2. Found: C, 62.3; H, 7.3.

*3-*O*-Benzyl-5,6-dideoxy-1,2-*O*-isopropylidene-α-*D-xylo*-hex-5-enofuranose* (**3b**).

— The mixture of diastereoisomers **2b** (0.57 g) and triphenylacetic acid (0.02 g) was heated from 150 to 170° over a period of 5 h, during which time ethanol and carbon dioxide were evolved. The residue was dissolved in ether, solid potassium carbonate was added, and, after being kept, the suspension was filtered, and the filtrate was evaporated to dryness. Distillation of the residue gave the product as a colourless liquid, yield 0.37 g (86%), b.p. 124–128° at 0.2 torr, n_D^{25} 1.5378, $[\alpha]_D^{21}$ $-55.5°$ (*c* 3.0, ethanol) [lit.[8] b.p. 124–129° at 0.2 torr, $[\alpha]_D^{28}$ $-56.4°$ (*c* 3.22, chloroform)]; ν_{max} 1458, 1379, 1207, 1182, 1079, 1018, 921, 862, 720, 700 cm^{-1}; n.m.r. data: τ 2.80 (5-proton singlet, phenyl protons), τ 3.85–4.25 (2-proton multiplet, H-5 multiplet and H-1 doublet, $J_{1,2}$ 3.8 Hz, H-1,5), τ 4.61, 4.77, 4.87 (2-proton multiplet, H-6,6′), τ 5.4–6.0 (4-proton multiplet, H-2,4, and benzylic CH$_2$), τ 6.27 (1-proton doublet, $J_{3,4}$ 3.0 Hz, H-3), τ 8.60, 8.79 (3-proton singlets, CMe$_2$).

Anal. Calc. for $C_{16}H_{20}O_4$: C, 69.5; H, 7.3. Found: C, 69.8; H, 7.4.

*5,6-Dideoxy-1,2-*O*-isopropylidene-α-*D-xylo*-hexofuranose* (**4b**). — Hydrogenation of **3b** in ethanol over palladium–carbon by the method of English and Levy[8] gave a crystalline product which, after sublimation at 70° at 0.5 torr followed by crystallisation from light petroleum (b.p. 60–80°), consisted of colourless plates that, on slow heating, partially melted from 58° and were transformed into needles that had m.p. 77–78°, $[\alpha]_D^{21}$ $-21.2°$ (*c* 3.0, ethanol), $[\alpha]_D^{22}$ $-23.6°$ (*c* 1.39, chloroform); ν_{max} 1262, 1228, 1174, 1102, 1078, 1027, 940, 897, 870, 863, 798 cm^{-1}; n.m.r. data: τ 4.29 (1-proton doublet, $J_{1,2}$ 3.5 Hz, H-1), τ 5.67 (1-proton doublet, $J_{2,3}$ < 0.5 Hz, H-2), τ 6.13 (2-proton multiplet, H-3,4), τ 7.3 (1-proton, broad singlet which disappeared on deuterium-exchange, OH), τ 8.4 (2-proton multiplet, H-5, 5′), τ 8.6, 8.78 (3-proton singlets CMe$_2$), τ 9.04 (3-proton triplet, *J* 7 Hz, H-6,6′,6″). The compound was hydrolysed with dilute acid, and the osazone was prepared at room temperature by the method of Jones and Thompson[6]. Repeated recrystallisation from ethanol–water gave dark-yellow needles, m.p. 167–169° which, after a final recrystallisation from methanol–water, had m.p. 169–171°, $[\alpha]_D^{22}$ $+31 \rightarrow +16.2°$ (24 h) [*c* 0.82, 3:2 (v/v) pyridine–ethanol]. 5,6-Dideoxy-D-*threo*-hexulose phenylosazone has been described as having m.p. 167–168°, $[\alpha]_D^{20}$ $+47 \rightarrow 20°$ (24 h) [c 0.60, 3:2 (v/v) pyridine–ethanol][9].

A sample of **4b** was prepared from 1,2-*O*-isopropylidene-5,6-di-*O*-*p*-tolylsulphonyl-α-D-glucofuranose (m.p. 154–158° from methanol) by treatment with sodium iodide in butanone followed by catalytic hydrogenation of the unsaturated intermediate[6,7]. After sublimation at 70° at 0.1 torr and recrystallisation from light petroleum (b.p. 60–80°), the compound was obtained as colourless plates which, on being heated, behaved in the way already described and had m.p. 76–78°. A mixed m.p. again showed the same behaviour, and no depression was observed. The i.r. and n.m.r. spectra of the respective compounds were also identical.

REFERENCES

1 R. J. FERRIER, *Advan. Carbohyd. Chem.*, 20 (1965) 67.
2 E. ALBANO, D. HORTON, AND T. TSUCHIYA, *Carbohyd. Res.*, 2 (1966) 349.

3 G. Crank and F. W. Eastwood, *Aust. J. Chem.*, 17 (1964) 1392.
4 J. S. Josan and F. W. Eastwood, unpublished results.
5 R. H. Bible, Jr., *Interpretation of N.M.R. Spectra*, Plenum Press, New York, 1965.
6 J. K. N. Jones and J. L. Thompson, *Can. J. Chem.*, 35 (1957) 955.
7 L. D. Hall, L. Hough, and R. A. Pritchard, *J. Chem. Soc.*, (1961) 1537; *cf.*, H. Ohle and E. Dickhäuser, *Ber.*, 58 (1925) 2593.
8 J. English and M. F. Levy, *J. Amer. Chem. Soc.*, 78 (1956) 2846.
9 P. A. J. Gorin, L. Hough, and J. K. N. Jones, *J. Chem. Soc.*, (1955) 2699.