Tetrahedron Letters No.28, pp. 3239-3242, 1968. Pergamon Press. Printed in Great Britain.

A NEW ROUTE TO BRANCHED-CHAIN SUGARS BY C-ALKYLATION OF METHYL GLYCOPYRANOSIDULOSES

R.F. Butterworth, W.G. Overend and N.R. Williams

Department of Chemistry, Birkbeck College (University of London), Malet Street, London, W.C.1

(Received in UK 9 April 1968; accepted for publication 22 April 1968)

The isolation and chemical study of new antibiotic substances during recent years has resulted in the discovery of several interesting branched-chain sugars and has led to an examination of methods for the chemical synthesis of sugars of this type. Several procedures have been reported (1-5) which utilise derivatives of either methyl glycosiduloses or glycosuloses as intermediates. We report now on the C-alkylation of methyl glycopyranosiduloses using either barium oxide and methyl iodide or the enamine alkylation method of Stork et al. (6) to give branched-chain sugar derivatives.

For example, methyl 4,6-O-benzylidene-3-deoxy-α-D-erythro-hexopyranosidulose (I), m.p. 113-114°, $[\alpha]_D$ + 105° (c 1, chloroform), prepared in 80% yield by oxidation of methyl 4,6-O-benzylidene-3-deoxy-α-D-arabino-hexopyranoside with ruthenium tetroxide (7), when treated in N,N-dimethylformamide with excess of methyl iodide in the presence of barium oxide afforded methyl 4,6-O-benzylidene-3-deoxy-3-C-methyl-α-D-hexopyranosidulose (III)* (65%) as a colourless syrup, $[\alpha]_D$ + 48° (c 1, chloroform), $\nu_{max.}$ 1750 $cm.^{-1}$ (C=O). When sodium hydride was used instead of barium oxide the same C-methyl product (III) was formed together with some decomposition products, as shown by thin layer chromatography.

When the glycopyranosidulose (I) was heated under reflux with a slight excess of pyrrolidine in benzene with passage of the condensate through a

molecular sieve to remove water produced in the reaction, a crystalline pyrrolidine enamine (II) was formed in 90% yield, m.p. 138-139°, $[\alpha]_D$ + 42° (c 1, chloroform). The infrared and n.m.r. spectral characteristics of this compound were in accord with the assigned structure (II). Treatment of compound (II) with methyl iodide and subsequent hydrolysis gave the C-methylated compound (III) (70%), identical (t.l.c., n.m.r., i.r.) with a sample prepared from compound I with methyl iodide and barium oxide.

From the n.m.r. spectrum[4] of compound III an unambiguous proton count of 18 was obtained and these were assigned as follows: the five protons at τ 2.55 were the phenyl protons and the singlet at τ 4.45 was assigned to the benzylic proton; the anomeric proton appeared as a singlet at τ 5.45 and the four protons at τ 5.5-6.3 were assigned to H-4, H-5, H-6(e), and H-6(a); the singlet at τ 6.55 (3 protons) was due to the protons of the methoxyl group; H-3 gave rise to a multiplet centred at τ 7.0. The doublet at τ 8.62 (3 protons) was assigned to the methyl substituent at C-3.

The stereochemistry at C-3 in compound III was indicated by the fact that methyl 4,6-O-benzylidene-3-deoxy-3-C-methyl-α-D-altropyranoside (8) could be oxidised with ruthenium tetroxide to afford compound III in 82% yield. Assuming that epimerisation had not occurred during the oxidation, this implies that the methyl group at C-3 in compound III is disposed axial. The identity of the samples of compound III prepared by the three different methods was supported by the similarity of their n.m.r. spectra. [These spectral results indicated that the samples of product from the methylations contained a small amount of an isomeric contaminant in which the C-3 methyl group was equatorial.] When compound III in wet dimethylformamide containing a trace of triethylamine was stored for one week it was epimerised quantitatively into the isomeric compound (IV) which had the methyl group at C-3 located in an equatorial position (i.r. and n.m.r. spectral evidence).

The methods described have been used to C-methylate other methyl glycopyranosidulose derivatives (e.g. methyl 4,6-O-benzylidene-2-deoxy-α-D-erythro-hexopyranosid-3-ulose which alkylates at C-2, and methyl 3,4-O-isopropylidene-α-D-erythro-pentopyranosidulose which is methylated at C-3). The results of these and related syntheses will be reported later.

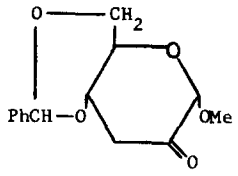
The new branched-chain sugar derivatives of types III and IV are of considerable interest because, by virtue of reactions at the carbonyl group of the kind already reported from our Laboratory, they can be induced to undergo further reactions to give modified sugars containing branching at two sites and to afford branched-chain amino-sugars. Preparations of modified sugars of these types are being examined.

REFERENCES

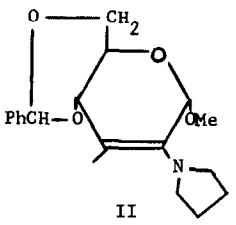
1. J.S. Burton, W.G. Overend and N.R. Williams, J. Chem. Soc., 3433 (1965).
2. W.G. Overend and N.R. Williams, J. Chem. Soc., 3446 (1965).
3. A.A.J. Feast, W.G. Overend and N.R. Williams, J. Chem. Soc. C, 303 (1966).
4. B. Flaherty, W.G. Overend and N.R. Williams, J. Chem. Soc. C, 398 (1966).
5. A. Rosenthal and L. (Benzing) Nguyen, Tetrahedron Letters, 2393 (1967).
6. G. Stork, R. Terrell and J. Szmuszkovicz, J. Am. Chem. Soc., 76, 2029 (1954).
7. P.J. Beynon, P.M. Collins, P.T. Doganges and W.G. Overend, J. Chem. Soc. C, 1131 (1966); P.J. Beynon, P.M. Collins, D. Gardiner and W.G. Overend, Carbohydrate Res., in the press.
8. A.A.J. Feast, W.G. Overend and N.R. Williams, J. Chem. Soc., 7378 (1965).

*Satisfactory elemental analyses were obtained for all new compounds.

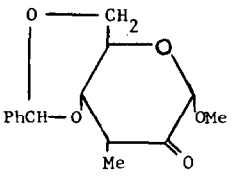
^{1}N.m.r. spectra were measured on solutions in $CDCl_3$ with Me_4Si as internal standard with a Varian A-60 (60 MHz) instrument.



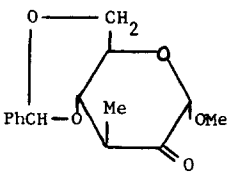
I



II



III



IV