Carbohydrate Research, 40 (1975) C6–C8

Preliminary communication

Anomalous reduction of a glycosulose derivative: deuterium incorporation alpha to the ketone group

DAVID C. BAKER, CHARLES BOEDER, JACQUES DEFAYE, ANDRÉE GADELLE, and DEREK HORTON

Centre de Recherches sur les Macromolécules Végétales, CNRS, B.P. 53, 38041 Grenoble (France) and Department of Chemistry, The Ohio State University, Columbus, Ohio 43210 (U.S.A.)

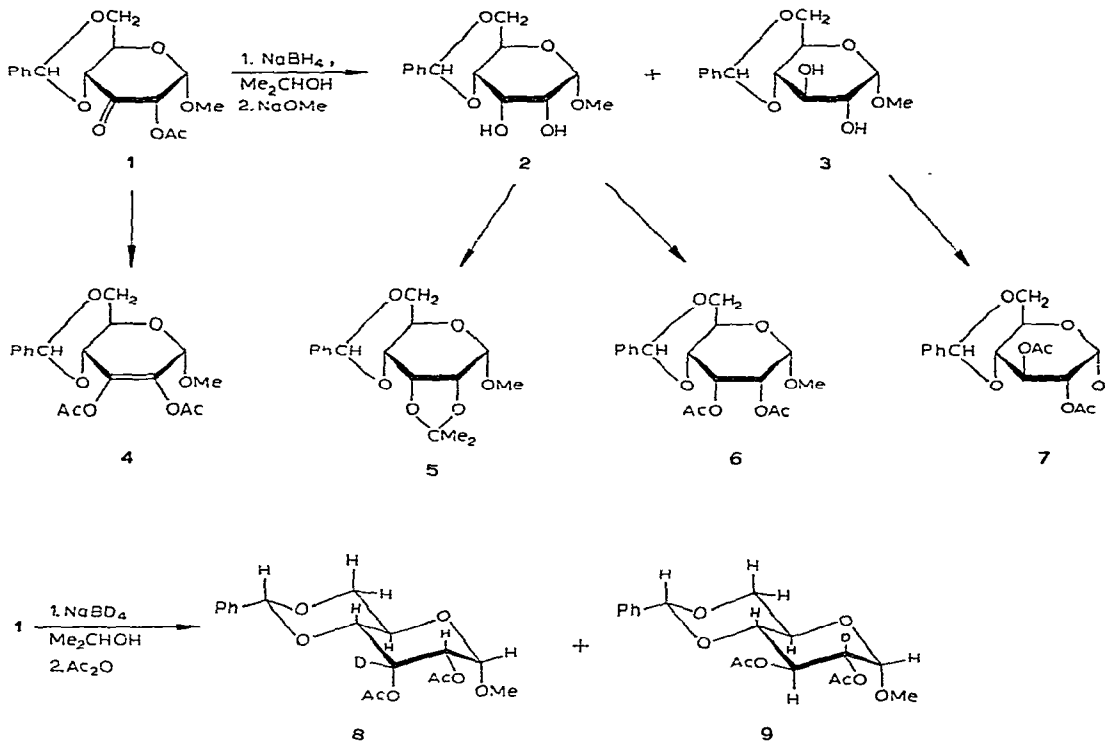
(Received February 1st, 1975; accepted for publication, February 19th, 1975)

Reduction of glycosulose derivatives gives mixtures of two secondary alcohols, isomeric at the original ketone position, in relative proportions strongly controlled by steric factors; the oxidation–reduction sequence is commonly used[1] to prepare alcohols of inverted stereochemistry from the precursor, and for "marking", by deuterium, the site of oxidation. The present study developed from investigations[2] designed to furnish specifically deuterated sugars, and from a program[3,4] concerning the mechanism whereby metal salts protect cellulose from oxidative degradation during bleaching. It is shown that the reduction of a glycosidulose may involve attack by the reductant at the position alpha to the carbonyl group, so that use of deuterated reductants may thus cause labelling at a position adjacent to the original ketone group.

Methyl 2-*O*-acetyl-4,6-*O*-benzylidene-α-D-*ribo* hexopyranosid-3-ulose[4,5] (**1**) underwent reduction by sodium borohydride in methanol to give, after saponification with sodium methoxide, a quantitative yield of chromatographically homogeneous methyl 4,6-*O*-benzylidene-α-D-allopyranoside* (**2**), m.p. 58–60° (dihydrate, from dichloromethane–hexane), 167–168° (anhydrous, from benzene), $[\alpha]_D$ +128° (*c* 1, chloroform); lit.[6] m.p. 60° for dihydrate, m.p.[6] 148–149°, m.p.[7] 175–177°, $[\alpha]_D$ +126° (in *N,N*-dimethylformamide[6]). The product was further characterized by (*a*) treatment with acetone–anhydrous copper(II) sulfate, as its 2,3-isopropylidene acetal **5**, m.p. 119–121°, $[\alpha]_D^{25}$ +131° (chloroform), (*b*) hydrolysis to D-allose, and (*c*) the n.m.r. spectrum (100 and 250 MHz, benzene-d_6) of its syrupy diacetate **6**: δ 4.61 d, $J_{1,2}$ 4 Hz, H-1; 4.94 t, $J_{2,3}$ 3.5 Hz, H-2; 5.83 t, $J_{3,4}$ 3.5 Hz, H-3 and 5.29 s, PhC*H*.

The same compound (**2**) was obtained as the sole product when **1** was reduced with lithium aluminum hydride in tetrahydrofuran or with[6] sodium borohydride in methanol–*N,N*-dimethylformamide. Reduction of **1** with sodium borodeuteride in methanol followed by saponification, gave exclusively the *allo* isomer, whose diacetate (**8**) gave an

*All products described were homogeneous by t.l.c.; known compounds had melting points and specific rotations in agreement with literature values. New compounds and specifically deuterated derivatives gave acceptable elemental analyses, and first-order n.m.r. spectra free from extraneous signals were obtained at either 100 or 250 MHz.



n.m.r. spectrum identical to that of 6 except that the H-3 signal was absent and the signal for H-2 (doublet, $J_{1,2}$ 4 Hz) showed proton–proton coupling with H-1 only; this result shows that essentially exclusive and complete deuterium incorporation at C-3 had occurred to give the *3-d* derivative 8.

In contrast, reduction of the ketone 1 with sodium borohydride in dry isopropyl alcohol gave, after saponification, a 1:1 mixture of the *allo* isomer 2 and methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (3), both of which were isolated, and characterized in crystalline form. The diacetate 7 of 3, m.p. 106.5–107° (lit.[8] m.p. 108–109°) gave a first-order n.m.r. spectrum (C_6D_6) identical with that[9] of authentic material, and acid hydrolysis gave D-glucose exclusively. It might thus be supposed that the reduction proceeds by hydride attack at C-3 from either the equatorial direction (to give 2) or the axial direction (to give 3). Use of zinc borohydride in dimethoxyethane[10] led to the crystalline 2-acetate of 2 (m.p. 67–71°, $[\alpha]_D^{25}$ +60° in chloroform) and of 3 (m.p. 133–134°, $[\alpha]_D^{25}$ + 112° in chloroform; lit.[11] m.p. 133–134°, $[\alpha]_D^{29}$ +112° in chloroform) in the ratio of 4:1.

However, examination of the product of reduction of 1 by sodium borodeuteride in dry isopropyl alcohol showed that, although the acetylated *allo* isomer (8) was exclusively labeled by deuterium at C-3, the acetylated D-*gluco* isomer (9), obtained in equal amount, was exclusively monodeuterated at C-2, not at C-3. The crystalline diacetate 9 [whose R_F value of 0.74 (silica gel G with 9:1 ether–hexane) made it readily separable

from 8 (R_F 0.58)] was identical with an authentic sample[9], except that no H-2 signal was observed in its n.m.r. spectrum (100 and 250 MHz, benzene-d_6: δ 4.91 s, H-1; 6.02 d, $J_{3,4}$ 10 Hz, H-3; and 5.30 s, PhC*H*) and the $J_{1,2}$ and $J_{2,3}$ proton–proton couplings observed in the spectrum of the nondeuterated analogue 7 were absent from the spectrum of 9.

No other reduction products were formed; in particular, it was verified that the corresponding D-*manno* isomer was absent. Mass spectra confirmed that the two products were monodeuterated, and the n.m.r. spectra of the two monodeuterated products 8 and 9 showed no evidence of deuteration at positions other than the fully labeled positions indicated.

The classical reduction-mechanism can account for the formation of 8, but the *gluco-2-d* product 9 must arise through attack of the reductant at C-2, presumably *via* a 2,3-enolic species. A somewhat related reaction is the epimerization observed[12] at the alpha position when menthone, 3-thujone, and 3-isothujone are each reduced by borohydride in dry solvents. Acetic anhydride–pyridine at 60° converted the ketone 1 into the enediol diacetate 4; m.p. 185–187°, *m/e* 364 M^{+}.

These results point out the need for caution in assigning structures to products arising when carbohydrate derivatives containing ketonic carbonyl groups are reduced with borodeuteride. As the proportion of D-*gluco* product (fully labeled at C-2) from the 3-ketone 1 becomes negligible when a small proportion of water is included in the solution of borodeuteride in isopropyl alcohol, the avoidance of dry alcoholic solvents for such reductions is indicated if exclusive labeling at the original keto position is desired. At the same time, these observation offer extended scope for synthetic reactions designed to furnish specifically labeled sugars.

ACKNOWLEDGMENTS

This work was supported by NIH grant No. GM-11976 (OSURF Project 1820) and by a research grant from the Société L'AIR LIQUIDE, Paris.

REFERENCES

1 D. C. Baker, D. Horton, and C. G. Tindall, Jr., *Carbohydr. Res.*, 24 (1972) 192–197; J. Defaye and A. Gadelle, *ibid.*, in press.
2 D. Horton and J. S. Jewell, *Carbohydr. Res.*, 3 (1966) 255–256; D. Horton, J. S. Jewell, E. K. Just, and J. D. Wander, *ibid.*, 18 (1971) 49–56; D. Horton, J. S. Jewell, E. K. Just, J. D. Wander, and R. L. Foltz, *Biomed. Mass Spectrom.*, 1 (1974) 145–153.
3 J. Defaye and A. Gadelle, *Pulp Paper Mag. Can.*, 75 (1974) 50–53; J. Defaye, H. Driguez, and A. Gadelle, *Carbohydr. Res.*, 38 (1974) C4–C6.
4 J. Defaye and A. Gadelle, *Carbohydr. Res.*, 35 (1974) 264–269.
5 Y. Kondo and F. Takao, *Can. J. Chem.*, 51 (1973) 1476–1481.
6 Y. Kondo, *Carbohydr. Res.*, 30 (1973) 386–389.
7 B. R. Baker and D. H. Buss, *J. Org. Chem.*, 30 (1965) 2304–2308.
8 D. S. Mathers and G. J. Robertson, *J. Chem. Soc.*, (1933) 696–698.
9 D. Horton and J. H. Lauterbach, *J. Org. Chem.*, 34 (1969) 86–92.
10 P. Crabbé, G. A. Garcia, and C. Rius, *J. Chem. Soc. Perkin I*, (1973) 810–816.
11 E. J. Bourne, M. Stacey, C. E. M. Tatlow, and J. C. Tatlow, *J. Chem. Soc.*, (1951) 826–832; R. W. Jeanloz and D. A. Jeanloz, *J. Amer. Chem. Soc.*, 79 (1957) 2579–2583; see also, ref. 4.
12 V. Hach, E. C. Fryberg, and E. McDonald, *Tetrahedron Lett.*, (1971) 2629–2632.