Carbohydrate Research, 75 (1979) C11–C12

Preliminary communication

Reaction of lactose with 2,2-dimethoxypropane: a tetra-acetal of novel structure*

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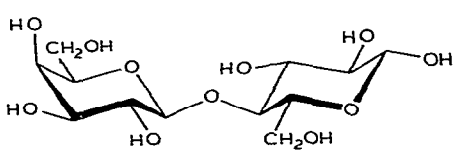
(Received June 18th, 1979; accepted for publication, June 25th, 1979)

The use of cyclic acetals as blocking groups has played a vital role in synthetic work in the carbohydrate field[1]. Until quite recently, cyclic acetal groups were introduced into carbohydrates by treatment with the appropriate aldehyde or ketone in the presence of a suitable acid catalyst, a reaction which is under thermodynamic control[1]. More recently, acetal exchange has been employed as an alternative method; these reactions are considered to be under kinetic control and have led to acetals which are not available from the direct acetalation reaction[1,2].

The most commonly used reagent for acetal exchange is 2,2-dimethoxypropane in *N,N*-dimethylformamide with a catalytic amount of toluene-*p*-sulphonic acid[2]. When we applied this reagent to lactose (**1**), several products were formed which have not yet been fully characterised. However, when the reaction was carried out at reflux temperature in the absence of *N,N*-dimethylformamide, one major product was formed which was not detected in the previous reaction. The highly crystalline product {**2**, m.p. 133–134°, $[\alpha]_D$ + 39.1° (chloroform)} was readily isolated in 45% yield.



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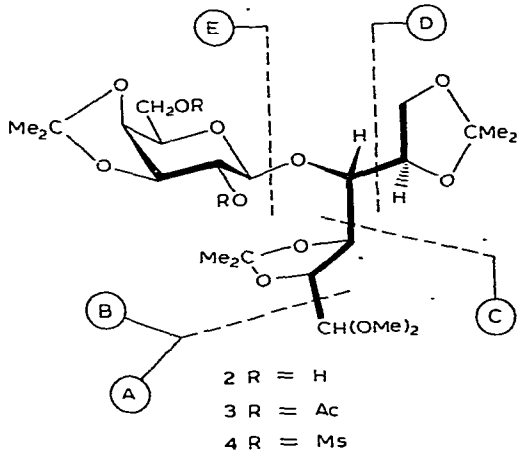

2 R = H
3 R = Ac
4 R = Ms

*The Chemistry of Cellobiose and Lactose: Part 8. For Part 7, see R. S. Bhatt, L. Hough, and A. C. Richardson, *J. Chem. Soc., Perkin Trans. 1*, (1977) 2001.

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TABLE I

MASS-SPECTRAL FRAGMENTATION OF 2 AND 3 (SEE FORMULAE FOR THE SIGNIFICANCE OF *A*–*E*)

Fragment	2	3
A	*m/e* 75 (100%)	75 (100%)
B	*m/e* 433 (0.3%)	517 (1.7%)
C	*m/e* 175 (0.2%)	–
D	*m/e* 101 (19.1%)	101 (9.6%)
E	*m/e* 203 (3.7%)	287 (16%)

It was evident from its 220-MHz ^{1}H-n.m.r. spectrum that **2** was a tri-*O*-isopropylidene derivative and that two magnetically non-equivalent *O*-methyl groups (δ 3.49, 3.50) had been introduced. The acetal was converted into the diacetate {**3**, m.p. 113–115°, $[\alpha]_D$ +25.2° (chloroform)} and a dimesylate {**4**, m.p. 142–144°, $[\alpha]_D$ +10.9° (chloroform) which indicated that the original product was a diol. With six hydroxyl groups engaged in cyclic acetal formation, two hydroxyl groups methylated, and two hydroxyl groups free, it was apparent that **1** had reacted in a form in which the reducing unit was acyclic, as in **2**. This inference was confirmed by the electron-impact mass spectra of **2** and its diacetate **3**. In both cases, the base peak was *m/e* 75, corresponding to the ion $\overset{+}{C}H(OMe)_2$ indicative of an aldehyde dimethyl acetal. A further prominent fragment had *m/e* 101 (ion *D* from cleavage of the C-4–C-5 bond), indicating the presence of a 5,6-*O*-isopropylidene group. The fragments at *m/e* 203 (for **2**) and 287 (for the diacetate **3**) were due to cleavage of the glycosidic bond (cleavage *E*) and indicated unequivocally that the two acetyl groups were located on the galactopyranosyl ring.

The 220-MHz ^{1}H-n.m.r. spectrum of the diacetate **3** was largely first-order, and assignments were made as a result of decoupling experiments. The H-2 resonance was at lowest field (δ 5.40), indicating that an *O*-acetyl group was located at this position. The resonances due to H-3′ and H-4′ were located at δ 3.91 and 3.69, respectively, in agreement with the presence of an acetal, rather than acetyl groups, at these positions. These data are in complete accord with the assignment of **2** as 2,3:5,6:3′,4′-tri-*O*-isopropylidenelactose dimethyl acetal. (This structure has since been confirmed, using X-ray crystallography, by Dr. B.E. Davison.)

The tetra-acetal **2** is an ideal, unique precursor for the modification of lactose at the 2′- and/or 6′-positions, and the use of neat 2,2-dimethoxypropane for acetal formation is being applied to other carbohydrates in order to ascertain whether its mode of action differs substantially from that when *N*,*N*-dimethylformamide is used as solvent. Preliminary results with maltose indicate that it behaves similarly, to give a mixture of the 2,3:5,6-di-*O*-isopropylidene dimethyl acetal and the 2,3:5,6:4′,6′-tri-*O*-isopropylidene dimethyl acetal.

REFERENCES

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2 M. E. Evans, F. W. Parrish, and L. Long, Jr., *Carbohydr. Res.*, 3 (1967) 453–462; A. Hasegawa and M. Kiso, *ibid.*, 63 (1978) 91–98, and earlier papers.