CHEMISTRY OF OXO-SUGARS (1). REARRANGEMENT OF 2-OXOGLYCOSIDES IN PYRIDINE: EVIDENCE OF INTRAMOLECULAR HYDRIDE SHIFT[1)]

Yoshisuke TSUDA* and Hong-Min LIU

Faculty of Pharmaceutical Sciences, Kanazawa University, 13-1 Takara-machi, Kanazawa 920, Japan

Methyl α- and β-D-*arabino*hexopyranosid-2-uloses rearranged, in pyridine, into methyl α- and β-D-*ribo*-hexopyranosid-3-uloses through intermediacy of methyl α- and β-D-*arabino*hexopyranosid-3-uloses, respectively, indicating that an intramolecular hydride shift is the initial reaction for rearrangement of 2-oxoglycosides.

KEYWORDS 2-oxoglycoside; 3-oxoglycoside; 2-oxoglycoside rearrangement; pyridine; intramolecular hydride shift; enediol intermediate; ^{13}C-NMR

Oxo derivatives of glycosides are biologically important substances in carbohydrate metabolism. However, very little is known of their chemistry, probably because of difficulty in their selective synthesis, high capability of solvation, and instability, particularly in basic media. In a pioneering work in this field, Theander[2)] reported that methyl β-D-*arabino*hexopyranosid-2-ulose (**1**, Me β-D-*arabino*-2-OG)[3)] decomposed in 1% lime-water with a half-life of *ca.* 1 min, following the scheme shown in Chart 1, to give the dioxo derivative (**6**). However, the route is rather ambiguous, since the decomposition was too rapid to definitively identify the intermediary species.

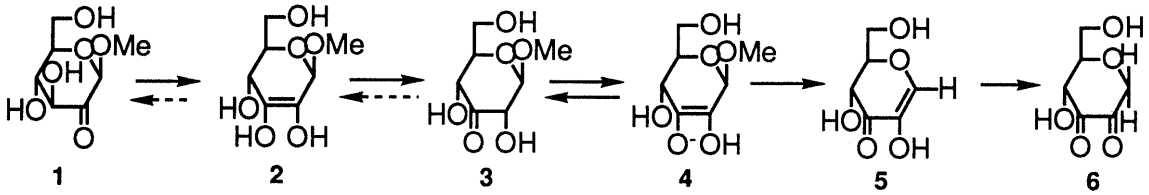


Chart 1. The Proposed Pathway for Decomposition of Methyl β-D-*arabino*Hexopyranosid-2-ulose (**1**)[2)]

We suppose that, when a weaker base such as pyridine is used, the reaction may be retarded, and thus the intermediary species is identified spectroscopically. This paper clarifies the rearrangement pathway of Me α- and β-D-*arabino*-2-OG (**7** and **1**) in pyridine-d_5.

Rearrangement of Methyl 2-Oxoglycosides

The ^{13}C-NMR spectrum of **7a** in pyridine-d_5 showed a very complex pattern due to the presence of many species such as an oxo, a hydrate, and a dimeric form, when observed immediately after dissolving. However, it converged, after 1-2 h, into the spectrum of a single compound assignable to the oxo form (Fig. 1). On remaining in the same solvent, the spectrum gradually changed, exhibiting peaks of new compound (A), which reached a maximum after 2 days at 27°C (56% of the total, Fig. 2). These peaks then disappeared with increase in those of another species (B), which reached a maximum after a week (Fig. 3) and was stable for a further several weeks at 27°C.

The spectrum of compound B was identical with that of Me α-D-*ribo*-3-OG (**10**).[4)] The intermediary species was now proved to be Me α-D-*arabino*-3-OG (**8a**) by comparison of the spectrum with that of the reference sample described below.

Obviously, **8a** is not the product of the enediol intermediate (**9**), since **9** will produce **10** as an initial product. In fact, **8** changed into **10**, when maintained in pyridine-d_5, by epimerization through the enediol intermediate. These lines of evidence suggest that the major path of the rearrangement of **7a** in pyridine-d_5 is an intramolecular hydride shift.

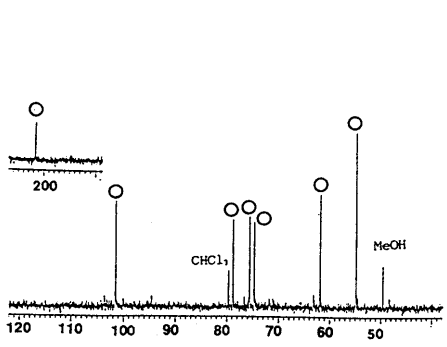


Fig. 1 **2 h**

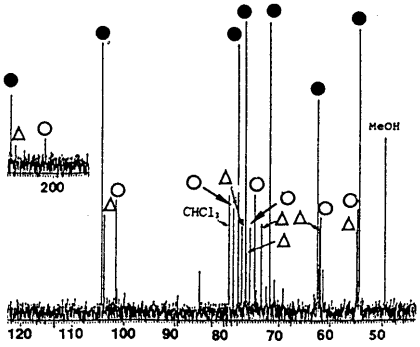


Fig. 2 **2 days**

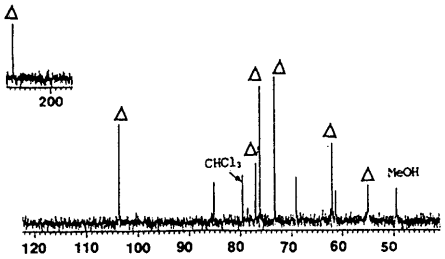


Fig. 3 **7 days**

Fig. 1-3. Changes of the ^{13}C-NMR Spectrum of Me α-D-*arabino*-2-OG (**7a**) in Pyridine-d_5

○.....**7a** ●(A).....**8a** △(B).....**10**

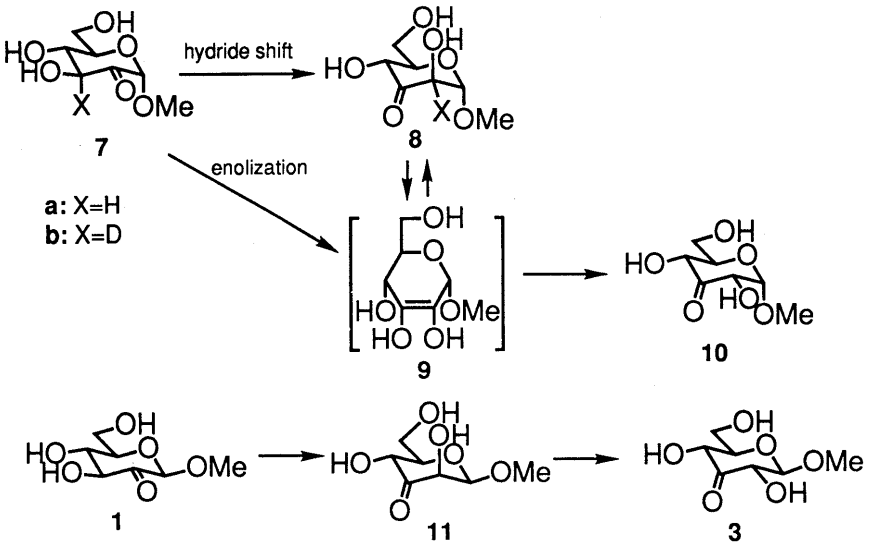


Chart 2. Rearrangement of 2-Oxoglycosides in Pyridine-d_5

In order to prove the hydride shift mechanism, the rearrangement of **7a** in pyridine-d_5 containing D_2O was examined. Although the formation of **10** from **7a** was accelerated in this condition, **8** observed in the mixture (44% at 46 h) retained 60% of hydrogen at C-2, while C-2 in **10** was completely exchanged by deuterium.

Rearrangement of the 3-deuterio derivative (**7b**) in pyridine-d_5 revealed that the deutride shift was greatly retarded compared to the hydride shift and rearrangement through the enediol intermediate predominated in this compound. However, the spectrum at the first 14 h indicated that C-2 of **8** in the mixture contained more than 30% of deuterium. A similar result was obtained for the rearrangement of **7b** in pyridine-d_5 containing H_2O. These data clearly indicate that for rearrangement of the 2-oxoglycoside (**7**) in pyridine, enolization and hydride shift mechanisms work competetively: the former predominates for the 3-D derivative and the latter predominates for the 3-H derivative.

The same hydride shift was also proved for Me β-D-*arabino*-2-OG (**1**) in pyridine-d_5. The initial product was identified as Me β-D-*arabino*-3-OG (**11**), which then epimerized into Me β-D-*ribo*-3-OG (**3**).

Synthesis of the Reference Compounds

Structures of the above compounds were proved by the following syntheses.

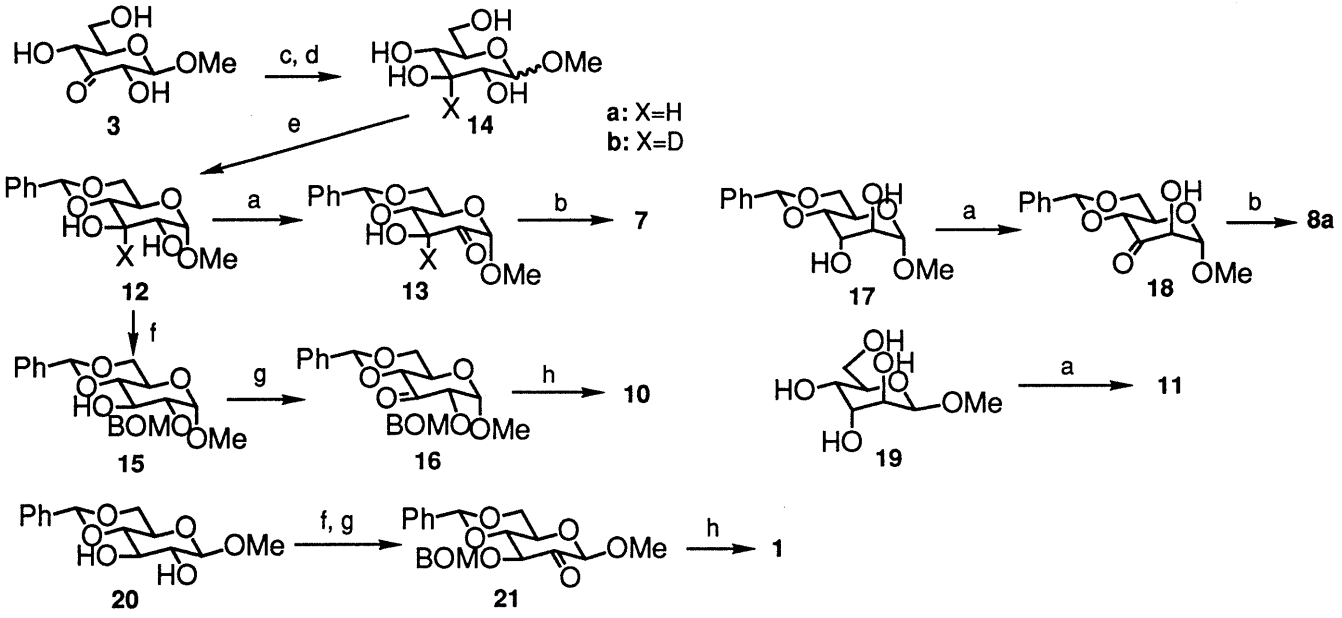
Me α-D-*arabino*-2-OG (**7a**) and its 3-deuterio derivative (**7b**) were prepared as follows. Me 4,6-*O*-benzylidene-α-D-Glc (**12a**) was

regioselectively oxidized to the 2-oxo derivative (**13a**),[4] which was deprotected to **7a** by heating with 60% AcOH. On the other hand, reduction of Me β-D-*ribo*-3-OG (**3**) with $NaBD_4$ gave a mixture of Me β-D-3-deuterio-Glc and 3-deuterio-All, which on treatment with 6% HCl-MeOH resulted in a mixture of α and β anomers. Benzylidenation and chromatographic separation of the products gave the 3-deuterio-Glc derivative (**12b**) as a pure compound. This was converted to **7b** in a similar manner as **7a**.

The 2-OH group of **12a** was regioselectively protected with benzyloxymethyl (BOM) group by the dibutyltin oxide method,[5] and the resulting **15** was oxidized with DMSO-Ac_2O to the 3-oxo derivative (**16**), which was then deprotected by hydrogenolysis over activated Pd black to **10**.

Oxidation of Me 4,6-*O*-benzylidene-α-D-Alt (**17**) by the $(Bu_3Sn)_2O$-Br_2 method[4] gave the 3-oxo derivative (**18**), which was deprotected to **8a** by heating with 60% AcOH. Compound **11** was obtained regioselectively by the $(Bu_3Sn)_2O$-Br_2 oxidation of Me β-D-Alt (**19**).

Me β-D-*arabino*-2-OG (**1**) was regioselectively prepared as in **10**. Alkylation of **20** with BOM chloride by the dibutyltin oxide method followed by oxidation of the resulting 3-*O*-BOM derivative with DMSO-Ac_2O gave the 2-oxo derivative (**21**), which was deprotected to **1**.



a: i) $(Bu_3Sn)_2O$, ii) Br_2; b: 60% AcOH; c: $NaBH_4$/MeOH; d: 6%HCl/MeOH;
e: $PhCH(OMe)_2$/p-TsOH/DMF; f: i) Bu_2SnO, ii) $PhCH_2OCH_2Cl$; g: DMSO-Ac_2O; h: H_2/Pd

All of the above synthesized oxoglycosides gave satisfactory ^1H-, ^{13}C-NMR, and high resolution mass spectral data. Details of syntheses and kinetic analyses of the rearrangement will be presented in a full publication.

REFERENCES AND NOTES

1) Part XXVI of Utilization of Sugars in Organic Synthesis. Part XXV: Y. Tsuda, Y. Sato, K. Kakimoto, and K. Kanemitsu, *Chem. Pharm. Bull.*, **40**, 1033 (1992).

2) O. Theander, *Acta Chem. Scand.*, **12**, 1887 (1958).

3) Abbreviations: Me=methyl, OG=hexopyranosidulose, Glc=glucopyranoside, All=allopyranoside, Alt=altropyranoside.

4) Y. Tsuda, M. Hanajima, N. Matsuhira, Y. Okuno, and K. Kanemitsu, *Chem. Pharm. Bull.*, **37**, 2344 (1989).

5) M. E. Haque, T. Kikuchi, K. Yoshimoto, and Y. Tsuda, *Chem. Pharm. Bull.*, **33**, 2243 (1985).

(Received May 19, 1992)