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2,5-DIOXABICYCLO[2.2.2]OCTANE RING SYSTEMS IN THE TAUTOMERIC FORMS OF D-*LYXO*-HEXOPYRANOSID-2-ULOSE, 1,5-ANHYDRO-D-TAGATOSE AND D-*LYXO*-HEXODIALDO-1,5-PYRANOSID-2-ULOSE DERIVATIVES

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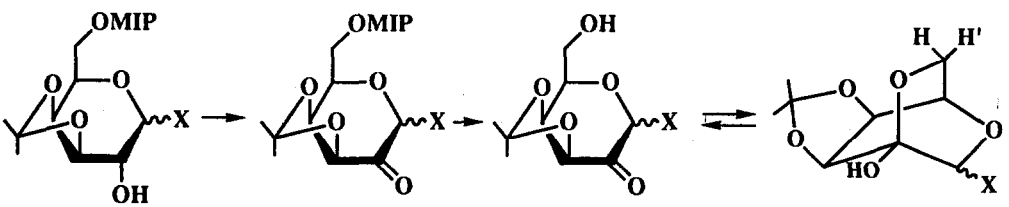
Key Words: oxidation; bicyclic hemiacetal formation; 2-ketopyranosides; 1,5-anhydro ketoses; hexodialdo-2-uloses.

Summary: *3,4-O-Isopropylidene derivatives of the title compounds have been prepared by new methods and found to exhibit a high preference for tautomeric forms deriving from hemiacetalization between 6-CH_2OH, or 6-$CH(OH)_2$, and 2-C=O functions.*

In connection with a research program involving the conversion of D-galactose derived mono- and disaccharides into the corresponding D-talosamine derivatives, we made some novel observations on the tautomeric equilibria of intermediate 2-keto derivatives, which are the subject of this preliminary communication.

The selectively protected β-D-galactopyranoside **1**[1], when oxidized with DMSO/Ac_2O, or with the Pfitzner-Moffatt reagent[2], gave the D-*lyxo*-hexopyranosid-2-ulose derivative **4**, which lost its highly acid sensitive methoxyisopropyl (MIP) acetal function, in part during work-up and completely in MeOH containing a trace of AcOH. A crystalline product[3] was obtained for which the ^1H and ^{13}C NMR spectra showed that it was not simply the deprotected form **7**, but that a more profound change in structure and ring conformation had occurred: the disappearance of the carbonyl carbon signal at 200 ppm and the concurrent appearance of a new signal at δ 93 (hemiacetal carbon), as well as significant modifications in the coupling constants between pyranose ring protons (Table I) clearly pointed to the tautomeric structure **10**, exhibiting a 2,5-dioxabicyclo[2.2.2]octane ring system. The unexpectedly high stability of this form was confirmed by the fact



1: X=β-OMe
2: X=α-OMe
3: X=H
MIP: -CMe_2OMe

4: X=β-OMe
5: X=α-OMe
6: X=H

7: X=β-OMe
8: X=α-OMe
9: X=H

10: X=β-OMe
11: X=α-OMe
12: X=H

that it was the only structure seen by NMR in several tested solvents (Table II), which, if one takes into account the sensitivity of the technique, means that at least 98% of the compound is in this hemiacetalic form at equilibrium. Also the IR spectrum of a saturated solution of **10** in CD_3CN did not show any trace of a C=O stretching band, even after 24-hr storage. Only in $(CD_3)_2SO$ small signals in the methyl region of the ^1H NMR spectrum point to the presence of about 3% of the open form **7**.

When the oxidation was repeated on the α-anomer **2**[1], similar results were obtained. The ulose **5**, when deprotected in 6, produced the compound **11**, obtained pure after crystallization from hexane[3]. In this case the preference for the bicyclic structure was less pronounced, since the open form **8** was detectable by NMR at equilibrium in all solvents except $CDCl_3$, with a maximum of 10% in $(CD_3)_2SO$. Furthermore, in CD_3OD two other products were detected, most probably the anomeric adducts **13** (Table II). The presence of some ketonic tautomer at equilibrium was also confirmed by a C=O band at 1753 cm^{-1} in the IR spectrum of **11** in CD_3CN.

Table I. Diagnostic NMR parameters

	KETONES				BICYCLIC HEMIACETALS			
	4[a]	**5**[b]	**9**[b]	**16**[c]	**10**[b]	**11**[b]	**12**[b]	**17**[b]
$J_{3,4}$	5.69	5.64	6.16	5.51	8.18	8.10	8.18	7.90
$J_{4,5}$	1.76	1.84	1.60	2.32	4.43	4.45	4.18	3.92
$J_{5,6}$	6.85	5.35	6.30	-	1.47	0.54	1.29	-
$J_{5,6'}$	5.44	7.10	5.93	-	1.82	3.00	2.13	0.92
$J_{4,6'}$	-	-	-	-	1.31	1.80	1.42	0.42
$J_{1,3}$	0.97	~0.3	0.58, 0.53	-	-	-	-	0.25
$J_{1,6}$	-	-	-	-	0.72	-	-	-
δ C(2)	200.00	200.77	205.46	197.49	93.03	93.39	93.12	94.88
δ C(6)	-	-	-	197.10	-	-	-	91.43

a) in C_6D_6; b) in CD_3CN; c) in $CDCl_3$

Table II. Equilibria in different solvents[a]

Compound	C_6D6	CD_3CN	$(CD_3)_2SO$	C_5D_5N	CD_3OD	$CDCl_3$
7/10	-/ 100/-/-	-/100/-/-	3/97/-/-	-/100/-/-	-/100/-/-	-/100/-/-
8/11	2/98/-/-	5/95/-/-	10/90/-/-	6/94/-/-	2/58/34/6	-/100/-/-
9/12	20/80/-/-	40/60/-/-	44/56/-/-	22/78/-/-	13/35/32/20	15/85/-/-

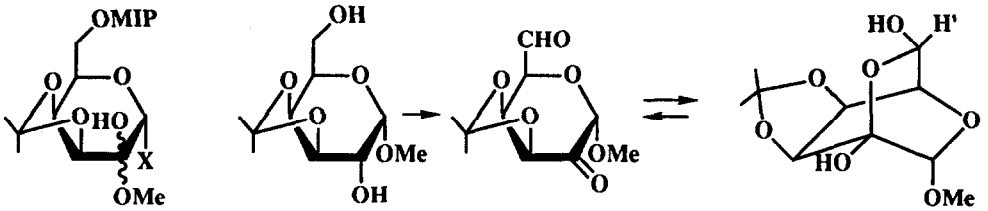
[a] Percentages of species present at equilibrium are given in the order: keto form (**7-9**), bicyclic hemiacetal (**10-12**), major and minor MeOH adduct (**13-14**).

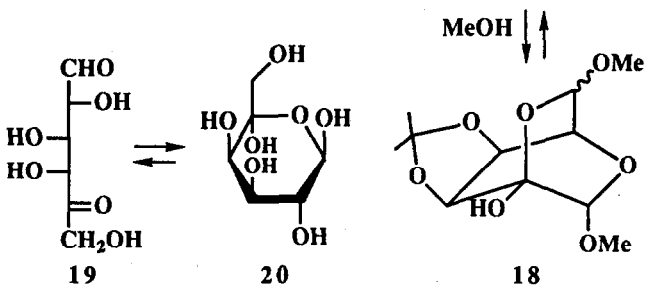
For a better evaluation of the influence of the anomeric substituent on the equilibrium ratio between ketonic and hemiacetalic forms, the study was extended to the 1-deoxy analogue of **7** and **8**, the 1,5-anhydro-D-tagatose derivative **9**[4], obtained by oxidation of the protected 1,5-anhydro-D-galactitol **3**[5], followed by deprotection in position 6 of the ulose **6**. The crude product gave, after crystallization from hexane, the cyclic tautomer **12**.[3] In this case, under equilibrium conditions in solution the ketonic form was present in definitely

higher percentage, reaching 44% in $(CD_3)_2SO$. Again, in CD_3OD, about 50% of the equilibrium mixture consisted of the two methanolic adducts **14** (Table II).

As for as we could ascertain, the tautomerism of 2-uloses having a free 6-OH group with 2,5-dioxabicyclo[2.2.2]octane type structures has not been previously reported. We cannot at this point offer entirely satisfactory explanations for this high preference for the tautomer having rings in the boat conformation[6], nor for the observed dependence of the order of relative stabilities of the two forms from the anomeric configuration. We can assume that the 3,4-fused dioxolane ring favours forms in which the C(2)-C(3)-C(4)-C(5) sequence of bonds is as close as possible to coplanarity, as is the case for the boat conformation, and that the higher energy level of the β-anomer **7** with respect to the α one **8** can, at least in part, explain the higher preference of the former for the bicyclic form, but it is not clear why **9**, having no anomeric substituent, should be the one with the least preference for this form.

One further point of interest was provided by the isolation in the oxidation of **2** under Swern conditions [DMSO/$(COCl)_2$] of a side-products, with NMR spectra very similar to those of **11**, except for signals due to a secondary hydroxyl bearing carbon in position 6. It was identified as compound **17**[3], the hydrated bicyclic form of the α,D-*lyxo*-hexodialdo-1,5-pyranosido-2-ulose derivative **16**[7]. It obviously derived by double oxidation at positions 2 and 6, the latter being deprotected in the reaction medium. The same compound was obtained in higher yield (55%) when compound **15** was oxidized with an excess of DMSO/DCC. Only one of the two possible anomeric forms at C(6) was observed, probably the one with the (6*S*) configuration, since the long-range coupling (0.42 Hz) between H'(6) and H(4), observed for **17**, can only be justified if the H(4)-C(4)-C(5)-C(6)-H(6) system in planar (W type coupling).





Compound **17** is stable in benzene solution, whereas in CD_3CN it equilibrates to an 80:20 mixture of **17** and **16**. The presence of **16** is demonstrated by carbonyl carbon signals at δ 197.10 (CHO) and 197.49 (C=O), by a CHO proton signal at δ 9.58 and, in the IR, by a band at 1744 cm^{-1} with a shoulder for the two

overlapping carbonyl stretchings. On azeotropic distillation with benzene **17** can be converted entirely into **16**. In methanol solution the methanol adduct **18** is the main species present, accompanied by other products involving methanol hemiacetal formation on both carbonyl groups of **16**.

The formation of hydrated or alcoholated pyranose forms has been reported for 5-ketoaldoses. For instance, at equilibrium in CD_3CN/D_2O, about 30% of L-*arabino*-hexos-5-ulose (**19**), exists in the form **20**[8], and similar adducts with water or alcohols were reported for derivatives of D-*xylo*-hexos-5-ulose.[9]

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REFERENCES AND NOTES

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2. Pfitzner, K.E.; Moffatt, J.G.; *J. Am. Chem. Soc.*, **1965**, *87*, 5661.
3. All products were crystallized from hexane. Specific rotations were taken on freshly prepared 1% $CHCl_3$ solutions of the pure bicyclic tautomers at 20°C, and are initial values. Mutarotation will be discussed in the full paper. **10**, m.p. 86-89°C; $[\alpha]_D$=-46°; Rf= 0.29 1:1 hexane/AcOEt; **11**, m.p. 121-124°C; $[\alpha]_D$=+87°; Rf= 0.39 1:1 hexane/AcOEt; **12**, m.p. 119-122°C; $[\alpha]_D$=+17.5°; Rf= 0.28 1:1 hexane/AcOEt ; **17**, m.p. 100-104°C; $[\alpha]_D$=+71°; Rf= 0.59 AcOEt.
4. 1,5-Anhydro derivatives of keto hexoses are a very little investigated class, the only known component of which seems to be 1,5-anhydro-D-fructose, synthesized by F.W. Lichtenthaler, E.S.H. El Ashy and V.H. Göckel (*Tetrahedron Lett.*, **1980**, *21*, 1429), who stated that it exists as an "apparent equilibrium between monomeric and dimeric forms". Baute, who obtained the same compound from a fungus, assumed that it exists in water in a bicyclic tautomeric structure analogous to that present in **12** on the basis of limited ^{13}C NMR evidence, but the absence of ^{1}H NMR data does not allow to rule out a gem-diol structure (Deffieux, G.; Baute, R.; Baute, M.A.; Atfani, M.; Carpy, A.; *Phytochemistry*, **1987**, *26*, 1391).
5. Barili, P.L.; Berti, G.; D'Andrea, F.; Gaudiosi, A. *Carbohydr. Res.*, **1991**, *212*, c5-c7.
6. X-ray diffraction data are available on some of the 2-dehydroxy analogues of **10** and **11**, the 2,6-anhydro-D-hexopyranosides. They show that the rings forming the bicyclic system deviate from the perfect $^{2,5}B(D)$ towards twist-boat forms, by a pseudo-rotation occurring in apposite direction in α and β anomers, thus decreasing eclipsing interactions (Köll, P.; Tayman, F.S.; *Chem. Ber.*, **1977**, *110*, 3297. Köll, P.; Komander, H.; Kopf, J.; *ibid*, **1980**, *113*, 3919). The similarity of the reported J values with those of our compounds point to a similar situation in the latter. We intend to confirm this by X-ray diffraction.
7. Literature references to derivatives of hexodialdo-2-ulose are extremely scarce, being limited to a few open-chain or furanose type compounds of this series. We did not found any mention of pyranosido derivatives similar to **16** or **17**.
8. Barili, P.L.; Berti, G.; Catelani, G.; D'Andrea, F.; *Gazz. Chim. Ital.*, **1992**, *122*, 135.
9. Ferrier, R.J.; Tyler, P.C.; *J. Chem. Soc., Perkin Trans.I*, **1980**, 1528; Kiely, D.E.; Talhonk, J.W.; Riordan, J.M.; Gray, K.; *J. Carbohydr. Chem.*, **1983**, *2*, 427.

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