13. The Dimeric and Polymeric Anhydride of 2,3-*O*-Isopropylidene-*β*-D-ribofuranose. An NMR Study

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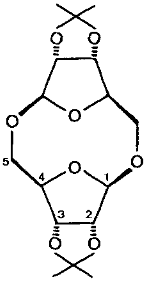
The ^{1}H- and ^{13}C-NMR data of the dimeric anhydride **1** of 2,3-*O*-isopropylidene-*β*-D-ribofuranose are reported together with the ^{1}H-NOE values. The data show that the products of the polymerization of 1,5-anhydro-2,3-*O*-isopropylidene-*β*-D-ribofuranose are *α*- and *β*-D-ribofuranans and not an *α*-D-ribofuranan and a *β*-D-ribopyranan as claimed before [2] [3].

Introduction. – The dimeric anhydride **1** of 2,3-*O*-isopropylidene-*β*-D-ribofuranose, a known compound [1], was prepared in one step from a mixture of the methyl D-ribosides (*α*- and *β*-D-ribofuranosides **3** and **4**, respectively, as well as *α*- and *β*-D-ribopyranosides **5** and **6**, respectively) and acetone/H_2SO_4/$CuSO_4$. Since in 1957 **1** was not characterized by NMR spectroscopy, the ^{1}H- and ^{13}C-NMR spectra were now recorded and the ^{1}H-NOE values determined. Searching the literature for reference compounds, it was detected that the products of the polymerization of 1,5-anhydro-2,3-*O*-isopropylidene-*β*-D-ribofuranose, described as an *α*-D-ribofuranan and a *β*-D-ribopyranan [2] [3], were in fact *α*- and *β*-D-ribofuranans. This is shown in this paper by a comparison of the reported NMR data with those of **1** and the four methyl D-ribosides **3**–**6** [4].



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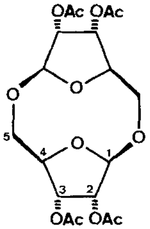

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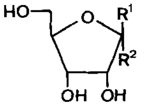

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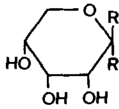
4 ($R^1 = CH_3O$, $R^2 = H$)



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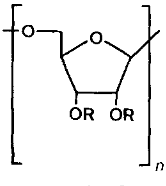

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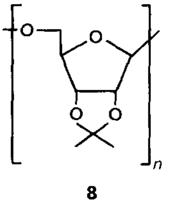

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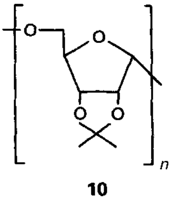

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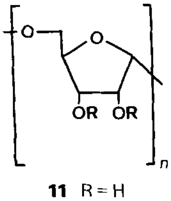


11 $R = H$
12 $R = CH_3O$

Table 1. *^{1}H-NMR Data of β-*D*-Ribofuranose Derivatives* **1**, **2**, *and* **7**

	H–C(1)	H–C(2)	H–C(3)	H–C(4)	H_{endo}–C(5)	H_{exo}–C(5)	CH_{3endo}	CH_{3exo}
1	5.05 ($J < 0.3$)	4.51 ($J(2,3) = 6$)	4.82 ($J(2,3) = 6$, $J(3,4) = 1$)	4.29	3.77 ($J(5,5) = 11.5$, $J(4,5) = 2$)	3.68 ($J(5,5) = 11.5$, $J(4,5) = 1.5$)	1.48	1.31
2 [5]	5.13 ($J = 0$)	5.48 ($J(2,3) = 5$)	5.76 ($J(2,3) = 5$, $J(3,4) = 7.3$)	3.6–4.4 ($J(5,5) = 13.5$, $J(4,5endo) = J(4,5exo) = 1.5$)				
7 [3]	5.05 ($J = 0$)	3.82 ($J(2,3) = 4.3$)	3.76 ($J(2,3) = 4.3$, $J(3,4) = 7.9$)	4.11	3.93 ($J(5,5) = 10,5$, $J(4,5) = 2.4$)	3.4 ($J(5,5) = 10.5$, $J(4,5) = 7.9$)		

Results and Discussion. – Dimer **1** is obtained in 35% yield by reacting an unseparated mixture of the four methyl D-ribosides **3**–**6** (obtained by methylation of D-ribose in MeOH/HCl) with acetone/H_2SO_4/$CuSO_4$. The ^{1}H-NMR spectra of **1**, its corresponding 2,3,2′,3′-tetraacetate **2** [5], and 2,3-di-*O*-methyl-(1→5)-β-D-ribofuranan (**7**; from [3], but as revised structure) are collected in *Table 1*. *Table 2* shows the ^{13}C-NMR data of **1** and the polymeric anhydrides **7**–**12** [2] [3], together with the data of the four methyl D-ribosides **3**–**6** [4]. The NOE values of **1** are presented in *Table 3*.

The assignment of the ^{1}H-NMR spectrum of **1** is straightforward given the rigid 2,3-*O*-isopropylidene-ribofuranose moiety, and the observed coupling constants define the β-D-ribofuranose configuration (*cf. e.g.* [6]). In addition, the NOE values *(Table 3)* corroborate the conformation of the central ten-membered ring, as determined by *Szarek* [5] for the 2,3,2′,3′-tetraacetate analogue **2** on the basis of the small vicinal coupling

Table 2. *^{13}C-NMR Chemical Shifts of* D*-Ribose Derivatives*

	C(1)	C(2)	C(3)	C(4)	C(5)	$(CH_3)_2C$	CH_3	CH_3
β-D-Series								
2,3:2′,3′-Di-*O*-isopropyliden-β-D-ribofuranose 1.5′:1′,5-dianhydride (**1**)								
in $CDCl_3$	106.6	86.5	81.8	87.6	65.2	111.7	26.4	24.9
in CD_2Cl_2	106.9	86.7	82.2	87.8	65.4	111.8	26.4	24.8
2,3-*O*-Isopropylidene (1→5)-β-D-ribofuranan (**8**) in CH_2Cl_2 [2]	109	86	82	86	70	112	27	25
(1→5)-β-D-Ribofuranan (**9**) [2]	108.2	74.7	71.9	81.7	70.4			
Methyl β-D-ribofuranoside (**4**) [4]	108.0	74.3	70.9	83.0	62.9			
Methyl β-D-ribopyranoside (**6**) [4]	103.1	71.0	68.6	68.6	63.9			
2,3-Di-*O*-methyl-(1→5)-β-D-ribofuranan (**7**) [3]	105.7	81.5[a])	82.0[a])	80.9[a])	70.8			
α-D Series								
2,3-*O*-Isopropylidene-(1→5)-α-D-ribofuranan (**10**) in CH_2Cl_2 [2]	*ca.* 103	*ca.* 82	*ca.* 82	*ca.* 82	*ca.* 70	*ca.* 116		
(1→5)-α-D-Ribofuranan (**11**) [2]	102.9	71.5	70.4	83.6	68.6			
Methyl α-D-ribofuranoside (**3**) [4]	103.1	71.1	69.8	84.6	61.9			
Methyl α-D-ribopyranoside (**5**) [4]	100.4	69.2	70.4	67.4	60.8			
2,3-Di-*O*-methyl-(1→5)-α-D-ribofuranan (**12**) [3]	102.1	81.4[a])	82.9[a])	79.1[a])	68.0			

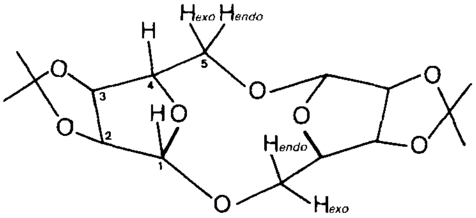
[a]) Assignment may be interchanged.

Table 3. *^{1}H-NOE Values for* **1**[a])

Proton irradiated	Proton observed					
	H–C(1)	H–C(2)	H–C(3)	H–C(4)	H_{endo}–C(5)	H_{exo}–C(5)
H–C(1)		0.05			0.05	n.d.
H–C(2)	0.07		0.17			
H–C(3)		0.15		0.04		0.03
H–C(4)			0.05		0.04	0.06
H_{endo}–C(5)	0.20			0.19		n.d.
H_{exo}–C(5)	0.06		0.09	0.17	n.d.	
CH_{3endo}	0.06			0.06		
CH_{3exo}		0.13	0.10			

[a]) n.d. = not determined.

between H–C(4), and H_{endo}–C(5) and H_{exo}–C(5) (see *Table 1*). These coupling constants are very similar in **1** indicating already an identical conformation, 'which exhibits an up-down-up-down arrangement of the four O-atoms within the ten-membered ring' [5] (*cf.* **A**). This is born out, *e.g.*, by the large NOE values between H_{endo}–C(5) and H–C(1), by the large and similar NOE values between H–C(4) and both H_{endo}–C(5) and H_{exo}–C(5), and, finally, by the NOE value of 0.09 between H_{exo}–C(5) and H–C(3). The *exo* and *endo* CH_3 groups can be differentiated nicely by their NOE values with H–C(1) and H–C(4), and H–C(2) and H–C(3), respectively, confirming thereby the β-D-configuration of the ribose moiety. A comparison of the ^{1}H coupling constants of **1** and **2** shows them to be very similar, except $J(3, 4)$ which is much smaller in **1** as a consequence of the rigidity of the 2,3-*O*-isopropylidene-ribofuranose moiety (*Table 1*). In conclusion, coupling constants and NOE values firmly establish the dimeric ribofuranose structure of **1** in agreement with the earlier work [1] [5].



A

The assignment of the ^{13}C-NMR spectrum of **1** (*Table 2*) is based on a selective ^{1}H-decoupling experiment. The data of **1** in CD_2Cl_2 allow a direct comparison with the polymeric anhydride **8** [2]. As can be seen, the chemical shift of **1** and **8** are very similar, given the precision with which the shifts can be read from *Fig. 5* in [2]. The only exception is C(5) which absorbs at higher field in **1** than in **8** due to steric compression in the dimer **1**. Polymer **8**, however, is reported to be a β-D-ribopyranan. Since **1** is undoubtedly a ribofuranose dimer, it is shown by the reported ^{13}C-NMR data of **8**, its deprotected derivative **9**, and the corresponding 2,3-di-*O*-methyl derivative **7** that these compounds are all ribofuranoses.

The chemical shift of the following three C-atoms can be used for that purpose: C(1), C(5), and C(4). The very low chemical shift of C(1) in **8** (109 ppm) and **9** (108.2 ppm) are already indicative of β-D-ribofuranoside (*cf.* the chemical shift of C(1) in methyl β-D-ribofuranoside (**4**; 108.0 ppm) with that of the α-D-anomer **3** (103.1 ppm) and of both methyl D-ribopyranosides **5** and **6** (100.4 and 103.1 ppm, resp.)). Furthermore, C(5) in **8** or **9** shows a downfield shift of *ca.* 6 ppm as compared with the same C-atom in methyl β-D-ribopyranoside (**6**). This cannot be explained by the pyranan structure as glycosidic-bond formation in 4-position should cause a small upfield shift of C(5) (*cf. e.g.* C(5) in (1→4)-oligosaccharides [7]). In a furanan structure, however, the downfield shift of C(5) is easily understood as the β-effect upon glycoside-bond formation at C(5).

Finally, C(4) absorbs at rather low field (*e.g.* 81.7 ppm in **9**). The downfield shift induced by glycosidic-bond formation at C(4) in pyranoses, though, is *ca.* 9 ppm (*cf.* C(4) in (1→4)-oligosaccharides [7]), resulting in an expected shift of 77.6 ppm for C(4) in a β-D-ribopyranan as calculated from methyl β-D-ribopyranoside (**6**). Compared with this value, the agreement of C(4) in **9** (81.7 ppm) with C(4) in methyl β-D-ribofuranoside (**4**; 83.0 ppm) is much better.

A further argument in favor of the furanan structure derives from the chemical-shift values of the α-D-isomers **10–12**, reported (correctly) to be α-D-ribofuranans. A comparison with methyl α-D-ribofuranoside (**3**) and the corresponding pyranoside **5** shows the same trends for the chemical shifts of C(1), C(5), and C(4) as discussed above for the β-D-anomers. Indeed, the shift differences ($\Delta\delta_c$) between corresponding C-atoms in **9** and **11**, and in **4** and **3**, respectively, are virtually identical (the $\Delta\delta_c$ represent the effect on δ_c induced by the change of configuration at the anomeric C-atom).

A final argument is presented by the ^{1}H-NMR spectrum of 2,3-di-*O*-methyl-(1→5)-β-D-ribofuranan (**7**; *Table 1* [3]), the δ_c of which can be correlated to β-D-ribofuranan **9** with the aid of methylation shifts (*cf. e.g.* [8]). The following coupling constants in **7** and **2** are very similar: $J(1,2)$ (0 Hz for both **7** and **2**), $J(2,3)$ (4.3 Hz for **7**, 5 Hz for **2**), $J(3,4)$ (7.9 Hz for **7**, 7.3 Hz for **2**). It is concluded again that the configuration and conformation of the ribose rings are identical in **2** and **7**. As expected, both $J(4,5)$ are completely different in the ten-membered ring compound **2** and in the extended polymer **7**. On the other hand, the coupling constants of **7** bear no resemblance to those reported for the ribopyranoses or the methyl ribopyranosides [4], a fact which was explained [3] by an unusual conformation of the six-membered ring.

On the basis of the arguments presented, the reported (1→4)-β-D-ribopyranan structures are in fact (1→5)-β-D-ribofuranans. A central claim in [2] [3] is, therefore, invalid.

Experimental. – The ^{13}C-NMR spectra were recorded on a *Varian-XL-300*, the ^{1}H-NMR spectra on a *Bruker-AM-360* spectrometer. The NOE difference spectra were obtained from a degassed $CDCl_3$ soln.

REFERENCES

[1] E. Vis, H.G. Fletcher, *J. Am. Chem. Soc.* **1957**, *79*, 1182.

[2] T. Uryu, K. Kitano, K. Ito, J. Yamanouchi, K. Matsuzaki, *Macromolecules* **1981**, *14*, 1.

[3] T. Uryu, J. Yamanouchi, T. Kato, S. Higuchi, K. Matsuzaki, *J. Am. Chem. Soc.* **1983**, *105*, 6865.

[4] K. Bock, H. Thøgersen, *Ann. Rep. NMR Spectrosc.* **1982**, *13*, 1.

[5] J.F. Stoddart, W.A. Szarek, *Can. J. Chem.* **1968**, *46*, 3061.

[6] J.D. Stevens, H.G. Fletcher, *J. Org. Chem.* **1968**, *33*, 1799.

[7] K. Bock, C. Pedersen, H. Pedersen, *Adv. Carbohydr. Chem. Biochem.* **1984**, *42*, 193.

[8] J. Reuben, *Carbohydr. Res.* **1986**, *157*, 201.