Carbohydrate Research, 80 (1980) 37–43

PREPARATION OF NEW *C*-NUCLEOSIDES BY INTRAMOLECULAR DEHYDRATION OF 2-PENTAHYDROXYPENTYL-4,5,6,7-TETRAHYDRO-INDOL-4-ONES*

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(Received March 19th, 1979; accepted for publication, June 4th, 1979)

ABSTRACT

Acid-catalysed dehydration of the polyhydroxyalkyl chain of 6,6-dimethyl-2-(D-*gluco*-pentitol-1-yl)-4,5,6,7-tetrahydroindol-4-one and of 6,6-dimethyl-2-(D-*manno*-pentitol-1-yl)-4,5,6,7-tetrahydroindol-4-one gave 2-α-D-arabinofuranosyl-6,6-dimethyl-4,5,6,7-tetrahydroindol-4-one (**3**). In a similar way, 2-β-D-lyxopyranosyl-6,6-dimethyl-4,5,6,7-tetrahydroindol-4-one (**8**) and 2-β-D-lyxopyranosyl-4,5,6,7-tetrahydroindol-4-one (**9**) were obtained by dehydration of 6,6-dimethyl-2-(D-*galacto*-pentitol-1-yl)-4,5,6,7-tetrahydroindol-4-one and 2-(D-*galacto*-pentitol-1-yl)-4,5,6,7-tetrahydroindol-4-one, respectively. The structures of the new *C*-nucleosides described (**3**, **8**, and **9**) were elucidated by chemical and physical methods.

INTRODUCTION

Acid-catalysed dehydration of polyhydroxyl chains joined to aromatic heterocycles is a general reaction that has been widely studied[1–6]. In certain cases, it yields anhydro derivatives with inverted configuration. Thus, 2-(D-*arabino*-tetritol-1-yl)-furans give, preferentially, anhydro derivatives having the D-*ribo* configuration[7–9]. The proposed mechanism for this reaction[7] involves a resonance-stabilized C-1′ carbo-cation, which undergoes intramolecular attack by HO-4′, giving the anhydro derivatives with D-*arabino* and D-*ribo* configurations. The reversible character of these reactions explains the preferential formation of the thermodynamically more-stable compound having the D-*ribo* configuration.

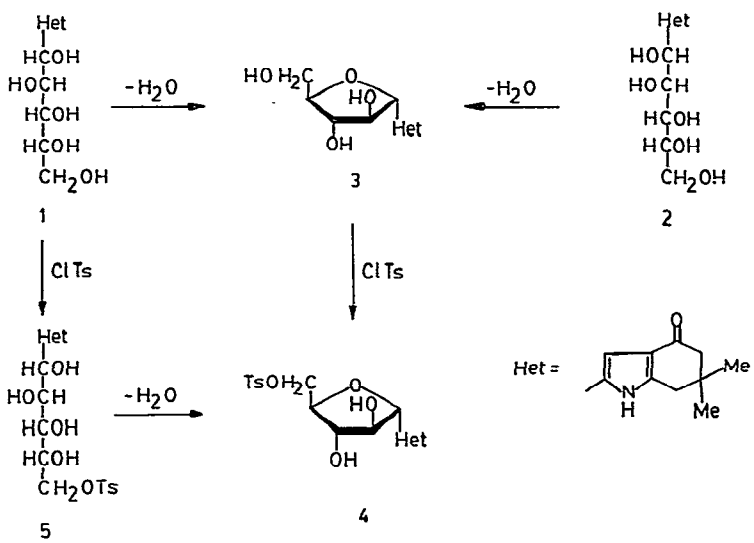
On the basis of these precedents and the easy dehydration[10] of pentahydroxypentyl-heterocycles, we have now studied the trifluoroacetic acid-catalysed dehydration of the pentahydroxypentyl-4,5,6,7-tetrahydroindol-4-ones that we described

*Presented, in part, at the 75th Anniversary Meeting of the Real Sociedad Española de Física y Química, Madrid, October 1978.

previously[11], in order to obtain new *C*-nucleosides. We consider these new compounds to be of interest, because of their structural similarity with other natural and synthetic *C*-nucleosides that are biologically active[12].

RESULTS AND DISCUSSION

Trifluoroacetic acid-catalysed dehydration of 6,6-dimethyl-2-(D-*gluco*-pentitol-1-yl)-4,5,6,7-tetrahydroindol-4-one (**1**) and 6,6-dimethyl-2-(D-*manno*-pentitol-1-yl)-4,5,6,7-tetrahydroindol-4-one (**2**) yields 2-α-D-arabinofuranosyl-6,6-dimethyl-4,5,6,7-tetrahydroindol-4-one (**3**). The reactions were carried out in aqueous solution at room temperature. Compound **3** reduced 1 mol of sodium metaperiodate, indicative of two contiguous hydroxyl groups; this result is consistent with the proposed furanoid structure. In order to demonstrate that the dehydration took place between C-1′ and C-4′, compound **3** was selectively tosylated at HO-5′, to yield the derivative **4**, which was identical with the product obtained by dehydration of 6,6-dimethyl-2-(5-*O*-tosyl-D-*gluco*-pentitol-1-yl)-4,5,6,7-tetrahydroindol-4-one (**5**).

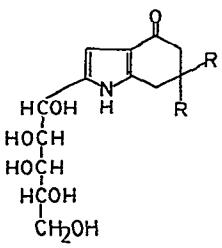


The glycosyl ring-structure of **3** was also demonstrated by its p.m.r. spectrum in $(CD_3)_2SO$ (Table I), which showed two doublets and one triplet consistent with two secondary hydroxyl groups (on C-2′ and C-3′) and one primary hydroxyl group (on C-5′). The signal for H-1′ was identified on the basis of the long-range coupling with H-3, as evidenced by double resonance. The small $J_{1',2'}$ value (~1 Hz) is consistent with a *trans* arrangement[13,14] of H-1′,2′, in agreement with the α-anomeric configuration assigned to compound **3**. The u.v. and i.r. spectra for **3** (see Experimental) also support the proposed structure, on the basis of analogy[15].

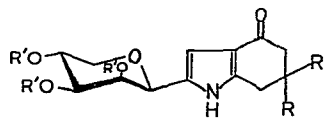
The isolation of the same product (**3**) from the pentahydroxypentyl-4,5,6,7-tetrahydroindol-4-ones having the D-*gluco* (**1**) or D-*manno* (**2**) configurations in the

polyhydroxyl chain supports the proposed mechanism for the dehydration of polyhydroxyalkyl-heterocycles[7] through an intermediate C-1′ carbocation.

In a similar way, 2-β-D-lyxopyranosyl-6,6-dimethyl-4,5,6,7-tetrahydroindol-4-one (**8**) and 2-β-D-lyxopyranosyl-4,5,6,7-tetrahydroindol-4-one (**9**) were obtained by trifluoroacetic acid-catalysed dehydration of 6,6-dimethyl-2-(D-*galacto*-pentitol-1-yl)-4,5,6,7-tetrahydroindol-4-one (**6**) and 2-(D-*galacto*-pentitol-1-yl)-4,5,6,7-tetrahydroindol-4-one (**7**), respectively.



6 R = Me
7 R = H



8 R = Me, R′ = H
9 R = R′ = H
10 R = Me, R′ = Ac
11 R = H, R′ = Ac

Compound **8** consumed two mol of metaperiodate, indicative of three adjacent hydroxyl groups, in agreement with a pyranoid structure. The p.m.r. spectrum, recorded in $(CD_3)_2SO$ (Table I), showed three doublets for secondary hydroxyl groups, and constitutes additional proof of the pyranoid structure. The p.m.r. spectrum of the tri-*O*-acetyl derivative (**10**) of **8** (Table I) showed a small $J_{1',2'}$ value (~1 Hz), consistent with a *cis* arrangement for H-1′,2′ and the β-anomeric configuration; the α anomer should have a larger coupling constant ($J_{1',2'}$ ~10 Hz), since this anomer must be almost entirely in the $^1C_4$ conformation[16].

Compound **9** consumed two mol of metaperiodate, which is consistent with the proposed pyranoid structure. The p.m.r. spectrum of the triacetate (**11**) of **9** shows (Table I) characteristics similar to those of the spectrum for compound **10**; the β-pyranoid structure is therefore proposed for compounds **9** and **11**.

The reason why the dehydration of the compounds having the D-*galacto* configuration in the polyhydroxyl side-chain yields anhydro derivatives having pyranoid structures might be because the transition state (**12**) leading to a furanoid ring would be destabilized by steric repulsions[17] between the bulky hydroxymethyl group and HO-2′ and HO-3′, all on the same side of the ring.

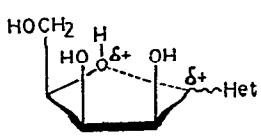


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TABLE I

CHEMICAL SHIFTS (δ) AND COUPLING CONSTANTS (J, Hz) FOR COMPOUNDS **3**, **8**, **10**, AND **11** AT 90 MHz[a,b]

Compound	*Glycosyl ring*								*Heterocycle*					
	H-1'	*H-2'*	*H-3'*	*H-4'*	*H-5'*	*H-5''*	*-OH*	*-OAc*	*H-1*	*H-3*	*2(H-5)*	*2(H-6)*	*2(H-7)*	*(Me)$_2$C-6*
3[c]	4.60m[d]			← 3.8–3.3m →			4.99d	—		6.26m	2.61s	—	2.16s	1.01s
	$J_{1',2'} \sim 1$						4.84d			$J_{1,3}$ 2.3				
	$J_{1',3} \sim 1$						4.52t							
8[c]	4.35m[d]			← 3.8–3.1m →			4.76d	—		6.19dd	2.61s	—	2.16s	1.01s
	$J_{1',2'} \sim 1$						4.71d			$J_{1,3}$ 2.3				
	$J_{1',3} \sim 1$						4.59d							
10[e]	4.72m[d]	5.55m	← 5.2m →		4.20m	3.40m	—	2.04s (3 H)	9.02[f]	6.32dd	2.63s	—	2.31s	1.07s
	$J_{1',2'} \sim 1$				$J_{5',5''}$ 11.0			2.02s (3 H)		$J_{1,3}$ 2.3				
	$J_{1',3} \sim 1$							1.98s (3 H)						
11[e]	4.72m[d]	5.56m	← 5.2m →		4.25m	3.40m	—	2.08s (6 H)	9.26[f]	6.32dd	← 2.79m (3 H) and			—
	$J_{1',2'} \sim 1$				$J_{5',5''}$ 11.0			2.00s (3 H)		$J_{1,3}$ 2.3	2.47m (3 H) →			
	$J_{1',3} \sim 1$													

[a]The spectrometer was locked on the signal of internal Me_4Si. [b]The spectra were recorded at 35.5°. Signal multiplicities: s, singlet; d, doublet; t, triplet; m, multiplet. [c]In $(CD_3)_2SO$. [d]Narrow multiplet. [e]In $CDCl_3$. [f]Broadening due to ^{14}N-quadrupole relaxation.

EXPERIMENTAL

General methods. — Solutions were evaporated *in vacuo* at temperatures below 40°. Melting points were determined with a Gallenkamp apparatus, and are uncorrected. Optical rotations were measured at 20 ±2° with a Perkin–Elmer 141 polarimeter (10-cm cell). Infrared spectra were recorded, for potassium bromide discs, with a Beckman IR-33 grating spectrophotometer. U.v. spectra were recorded with a Unicam SP-8000 instrument. P.m.r. spectra (90 MHz) were recorded at 35.5° with a Perkin–Elmer R-32 spectrometer (locked on the signal of internal tetramethylsilane) and coupling constants were measured directly from spectra recorded at 300-Hz sweep-width; the spectral assignments were confirmed by double-resonance experiments. T.l.c. was performed on silica gel (Merck GF_{254}) with ethyl acetate–ethanol (3:1), and detection with u.v. light, iodine vapour, or Ehrlich's reagent for pyrroles.

Consumption of periodate was determined by the method described by García González *et al.*[18], based on the Fleury and Lange[19] procedure.

2-α-D-Arabinofuranosyl-6,6-dimethyl-4,5,6,7-tetrahydroindol-4-one (**3**). — (*a*) 6,6-Dimethyl-2-(D-*gluco*-pentitol-1-yl)-4,5,6,7-tetrahydroindol-4-one[11] (**1**; 0.6 g, 1.92 mmol) in water (9 ml) was treated with trifluoroacetic acid (0.25 ml). There was immediate separation of crystalline **3** (0.23 g, 41%), m.p. 207–209° (from water), $[\alpha]_D$ +38.6°, $[\alpha]_{578}$ +41.2°, $[\alpha]_{546}$ +48.6°, $[\alpha]_{436}$ +94.6°, $[\alpha]_{365}$ +172.4° (*c* 0.5, chloroform); λ_{max}^{EtOH} 246 and 287 nm (ε 4,900 and 4,200); ν_{max} 3360–3250 (NH, OH), 1620 (C=O), 1570 and 1470 cm^{-1}; p.m.r. data: see Table I.

Anal. Calc. for $C_{15}H_{21}NO_5$: C, 61.01; H, 7.11; N, 4.74. Found: C, 60.91; H, 7.23; N, 4.90. Periodate consumption: 1.06 mol.

(*b*) Compound **3** (0.11 g, 41%) was also prepared from 6,6-dimethyl-2-(D-*manno*-pentitol-1-yl)-4,5,6,7-tetrahydroindol-4-one[11] (**2**; 0.33 g, 1.05 mmol) in a similar way.

6,6-Dimethyl-2-(5-O-tosyl-D-gluco-pentitol-1-yl)-4,5,6,7-tetrahydroindol-4-one (**5**). — A cooled solution of **1** (0.3 g, 0.96 mmol) in the minimum quantity of dry pyridine was treated with a cooled solution of toluene-*p*-sulphonyl chloride (0.2 g, 1.05 mmol) in the minimum quantity of the same solvent. The mixture was kept in a refrigerator for 4 days, and then evaporated under diminished pressure. Benzene and acetone were distilled repeatedly from the residue, to remove traces of pyridine. The resulting syrup was treated with ice–water, to yield **5** (230 mg, 51%), m.p. 124–126° (from acetone–water, 1:3), $[\alpha]_D$ +10.0°, $[\alpha]_{578}$ +10.6°, $[\alpha]_{546}$ +11.8°, $[\alpha]_{436}$ +22.4°, $[\alpha]_{365}$ +31.6° (*c* 0.5, chloroform); λ_{max}^{EtOH} 245 and 287 nm (ε 14,600 and 11,600); ν_{max} 3500–3230 (NH, OH), 1610 (C=O), 1590 and 1480 (C=C pyrrole) cm^{-1}.

Anal. Calc. for $C_{22}H_{29}NO_8S$: C, 56.53; H, 6.21; N, 3.00; S, 6.85. Found: C, 56.52; H, 6.44; N, 2.85; S, 6.92.

6,6-Dimethyl-2-(5-O-tosyl-α-D-arabinofuranosyl)-4,5,6,7-tetrahydroindol-4-one (**4**). — (*a*) A solution of compound **5** (120 mg, 0.25 mmol) in methanol (5 ml) and several drops of water was treated with trifluoroacetic acid (0.05 ml). After 4 h,

t.l.c. (3:1 ethyl acetate–ethanol) showed the absence of **5**. The mixture was then poured onto ice–water, to yield **4** (93 mg, 80%), m.p. 133–135° (from acetone–water, 1:3), $[\alpha]_D$ +59.0°, $[\alpha]_{578}$ +61.6°, $[\alpha]_{546}$ +70.0°, $[\alpha]_{436}$ +122.0°, $[\alpha]_{365}$ +206.2° (*c* 0.5, pyridine); λ_{max}^{EtOH} 242 and 285 nm (ε 14,700 and 12,500); ν_{max} 3380–3280 (NH, OH), 1615 (C=O), 1570 and 1475 (C=C pyrrole) cm^{-1}.

Anal. Calc. for $C_{22}H_{27}NO_7S$: C, 58.80; H, 6.01; N, 3.12; S, 7.13. Found: C, 58.52; H, 6.26; N, 2.84; S, 7.38.

(*b*) Tosylation of compound **3**, as described for **5**, gave **4** (75%).

*2-β-*D*-Lyxopyranosyl-6,6-dimethyl-4,5,6,7-tetrahydroindol-4-one* (**8**). — A solution of 6,6-dimethyl-2-(D-*galacto*-pentitol-1-yl)-4,5,6,7-tetrahydroindol-4-one[11] (**6**; 0.4 g, 1.28 mmol) in the minimum quantity of water was treated with trifluoroacetic acid (0.17 ml). There was immediate separation of crystalline **8** (0.28 g, 73%), m.p. 267–269° (from water), $[\alpha]_D$ +6.0° (*c* 0.5, water); λ_{max}^{EtOH} 246 and 287 nm (ε 4,600 and 4,100); ν_{max} 3390–3245 (NH, OH), 1620 (C=O), 1580 and 1480 (C=C pyrrole) cm^{-1}; p.m.r. data: see Table I.

Anal. Calc. for $C_{15}H_{21}NO_5$: C, 61.01; H, 7.11; N, 4.74. Found: C, 60.76; H, 7.26; N, 4.83. Periodate consumption: 2.00 mol.

*6,6-Dimethyl-2-(2,3,4-tri-*O*-acetyl-β-*D*-lyxopyranosyl)-4,5,6,7-tetrahydroindol-4-one* (**10**). — Compound **8** (0.1 g, 0.34 mmol) was treated with a mixture of acetic anhydride and pyridine (1:2, 1.5 ml). The solution was left for 24 h at low temperature (~0°) and then poured onto ice–water (15 ml), to yield **10** (0.13 g, 93%), m.p. 291–293° (from ethanol–water, 2:1), $[\alpha]_D$ −30.7° (*c* 0.5, chloroform); ν_{max} 3240 (NH), 1760 (C=O ester), 1645 (C=O ketone), 1590 and 1495 (C=C pyrrole) cm^{-1}; p.m.r. data: see Table I.

Anal. Calc. for $C_{21}H_{27}NO_8$: C, 59.86; H, 6.42; N, 3.33. Found: C, 59.97; H, 6.56; N, 3.52.

*2-β-*D*-Lyxopyranosyl-4,5,6,7-tetrahydroindol-4-one* (**9**). — A solution of 2-(D-*galacto*-pentitol-1-yl)-4,5,6,7-tetrahydroindol-4-one[11] (**7**; 0.5 g, 1.75 mmol) in the minimum quantity of water was treated with several drops of trifluoroacetic acid. After 2 h, t.l.c. (3:1 ethyl acetate–ethanol) showed the absence of **7**. The reaction mixture was neutralized with Amberlite IR-45(HO^-) resin and evaporated to a syrup that crystallized from methanol, to give **9**, m.p. 238–240°, $[\alpha]_D$ +8.4°, $[\alpha]_{578}$ +8.8°, $[\alpha]_{546}$ +11.2°, $[\alpha]_{436}$ +30.8°, $[\alpha]_{365}$ +82.0° (*c* 0.5, chloroform); λ_{max}^{EtOH} 246 and 284 nm (ε 5,100 and 4,200); ν_{max} 3430–3280 (NH, OH), 1615 (C=O), 1575 and 1475 (C=C pyrrole) cm^{-1}. Periodate consumption: 2.03 mol.

*2-(2,3,4-Tri-*O*-acetyl-β-*D*-lyxopyranosyl)-4,5,6,7-tetrahydroindol-4-one* (**11**). — Acetylation of compound **9**, as indicated for **10**, gave **11** (38%), m.p. 241–243° (from methanol–water, 3:1), $[\alpha]_D$ −57.0°, $[\alpha]_{578}$ −59.2°, $[\alpha]_{546}$ −66.4°, $[\alpha]_{436}$ −111.0°, $[\alpha]_{365}$ −189.6° (*c* 0.5, chloroform); ν_{max} 3290 (NH), 1740 and 1725 (C=O ester), 1630 (C=O ketone), 1570 and 1470 (C=C pyrrole) cm^{-1}; p.m.r. data: see Table I.

Anal. Calc. for $C_{19}H_{23}NO_8$: C, 58.01; H, 5.85; N, 3.56. Found: C, 57.77; H, 6.01; N, 3.32.

ACKNOWLEDGMENTS

We thank Professor J. Calderón, Instituto de Química Orgánica General, C.S.I.C., Madrid, for the microanalyses, and one of us (E.R.G.) thanks the Ministry of Education and Science of Spain for the award of a scholarship.

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