Benzylidene Acetals of the D-Ribonolactones: a Structural Reassessment

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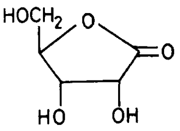
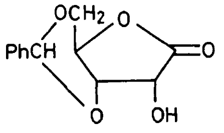
The product of the reaction of D-ribono-1,4-lactone with benzaldehyde and concentrated HCl has been shown, by *X*-ray crystallography of its acetate, to be 3,4-*O*-(*R*)-benzylidene-D-ribono-1,5-lactone and not the 3,5-acetal as previously suggested; with $ZnCl_2$ as catalyst the products are 2,3-*O*-(*R*)- and -(*S*)-benzylidene-D-ribono-1,4-lactone, the former preponderating.

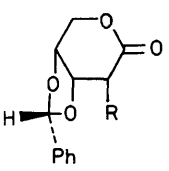
D-Ribono-1,4-lactone (**1**)[1] has been a starting material in several natural product syntheses.[2—5] In one recent study[3,4] a benzylidene acetal, first prepared by Zinner *et al.*[6] by the reaction of (**1**) with benzaldehyde and concentrated HCl, was used. The 3,5-*O*-benzylidene structure (**2**) was suggested by Zinner,[6] in preference to the 2,3-acetal structure (**3**), and was apparently confirmed in the later work[3,4] by spectral data together with some chemical transformations. Although the ultimate syntheses were successful we were not convinced that Zinner's *O*-benzylidene-D-ribonolactone was a 3,5-acetal since, to our knowledge, no other genuine 3,5-cyclic acetals of furanoid derivatives of ribose, or arabinose, formed under equilibrating conditions, have been described.† Moreover, molecular models suggest that a 3,5-acetal such as (**2**) would be more highly strained than the corresponding 2,3-acetal (**3**). We have, therefore, re-examined Zinner's acetal and some derivatives to resolve the apparent structural ambiguity.



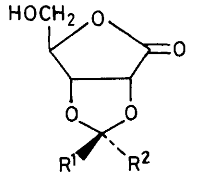
(1)



(2)



(**4**) R = OH
(**5**) R = OAc
(**6**) R = OCOPh
(**7**) R = OCS_2Me
(**8**) R = H



(3)
a; $R^1 = H$, $R^2 = Ph$
b; $R^1 = Ph$, $R^2 = H$

Treatment of lactone (**1**) with benzaldehyde and concentrated HCl afforded in high yield the crystalline benzylidene derivative described previously.[3,4,6] This was subsequently converted into the corresponding acetate and benzoate derivatives by literature procedures.[6] Pertinent spectroscopic data for these compounds are listed in Table 1. Correlation of ^1H and ^{13}C n.m.r. data with structure[10—13] leads to the conclusions that the Zinner acetal and its derivatives have structures (**4**)—(**8**), since (i) they are 1,3-dioxolanes, probably

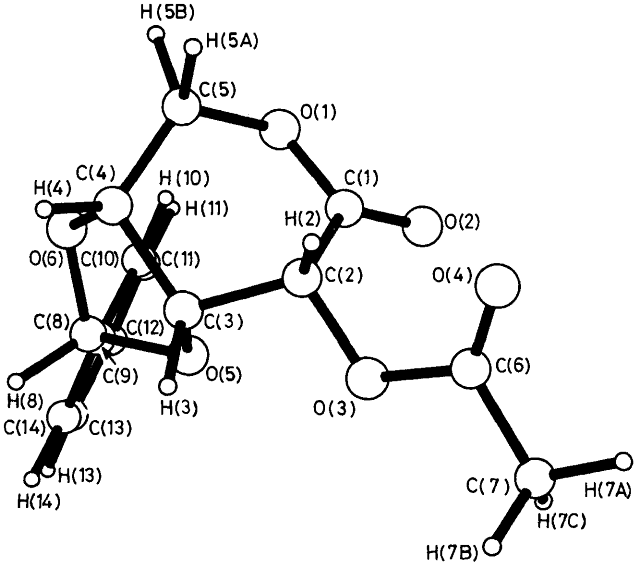


Figure 1. Crystal structure of acetate derivative (**5**) with the crystallographic numbering scheme. The absolute configuration is assumed to be directly related to that of D-ribono-1,4-lactone (**1**).

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† The alleged 3′,5′-*O*-benzylideneguanosine[7,8] was later shown to be the 2′,3′-isomer.[9]

Table 1. I.r., ^{1}H n.m.r., and ^{13}C n.m.r. data.

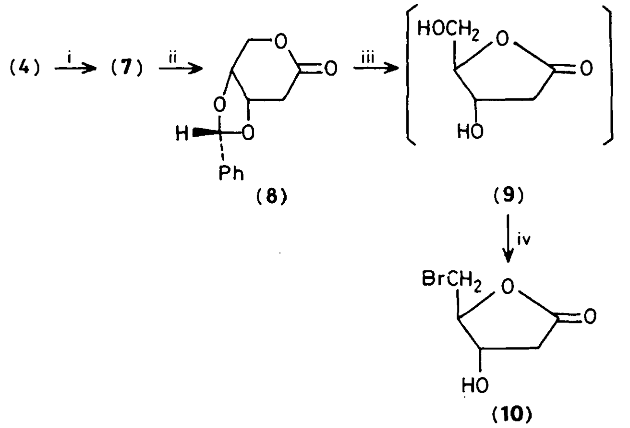
Compound	$\nu_{max.}$ (KBr) (C=O)/cm^{-1}	δ_H^{a,b} PhC*H*	δ_H^{a,b} C(2)H	δ_C^{c,b} PhCH
(**4**)	1749	5.73	4.62dd	102.6
(**4**)^d	1750	5.74	4.62dd	102.6
(**5**)	1730, 1780	5.79	5.53d	105.0
(**6**)	1740, 1767	5.83	5.77d	105.0
(**7**)^d	1785	5.81	6.45d	104.8
(**8**)^d	1745	5.76	2.63dd, 3.05dd	103.8

^{a} 200 MHz spectra. ^{b} In $(CD_3)_2SO$ for (**4**), $CDCl_3$ for (**5**)—(**8**), Me_4Si reference. ^{c} 20 MHz spectra. ^{d} Data from ref. 4.

of the *R*-configuration (i.e. *endo*-phenyl),‡ rather than 1,3-dioxanes as would be required for (**2**) and its derivatives, and (ii) the C(2) oxygen atom is available for acylation and is not part of an acetal ring as in (**3**). To corroborate these assignments, the structure of the acetate derivative (**5**) was determined by *X*-ray crystallography.§

The crystal structure of (**5**) is depicted in Figure 1 and consists of a central δ-lactone ring, in a boat conformation, *cis*-fused to a five-membered-ring benzylidene acetal. The acetal carbon centre has the *R*-configuration as anticipated. It is noteworthy that the insolubility of (**4**) together with its formation under equilibrating conditions enable it to be so readily isolable as a single diastereoisomer.

The chemical transformations described by Joullié[3,4] can now be explained by the sequence outlined in Scheme 1. The hydrolysis of (**8**) to (**9**) is clearly the critical step in which the 1,4-lactone ring is regenerated and hence the previous error in structural assignment is cancelled out.



Scheme 1. *Reagents:* i, NaH, CS_2, MeI, DMF (dimethylformamide); ii, Bu^n_3SnH, azoisobutyronitrile, PhMe, reflux; iii, CF_3CO_2H–H_2O–$CHCl_3$ (1 : 1 : 4), reflux; iv, CBr_4, PPh_3, MeCN.

D-Ribonolactone reacts with benzaldehyde and zinc chloride to give a mixture of the 2,3-*O*-(*R*)-benzylidene derivative (**3a**) together with the (*S*)-isomer (**3b**).¶ The former is probably identical to an acetal described by Zinner[6] and assigned the structure '2,4-*O*-benzylidene-D-ribono-1,5-lactone.'

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‡ In the ^{1}H n.m.r. spectra of compounds (**4**)—(**8**), the acetal proton chemical shifts lie in the range δ 5.76—5.83, well within that expected for 1,3-dioxolanes but outside the range δ 5.44—5.58 observed for analogous 1,3-dioxanes.[12] In addition, the ^{13}C resonance of the acetal carbon centres all lie within the range δ 101.9—105.8 generally found for 2-phenyl-1,3-dioxolanes.[12] These data also support the *endo*-phenyl group assignment since (i) the acetal proton signal is normally found at higher field (δ 5.8—5.9) in the *endo*-isomer than in the corresponding *exo*-isomer (δ 5.95—6.32)[10,11] and (ii) the ^{13}C shifts of the acetal carbon atoms in compounds (**5**)—(**8**) are consistent with previous data (*endo*: δ 103.8—104.7; *exo*: δ 102.9—103.4, $CDCl_3$ solutions).[11,13]

§ *Crystal data:* compound (**5**), $C_{14}H_{14}O_6$, $M = 278.2$, orthorhombic, $a = 7.5578(4)$, $b = 11.4703(14)$, $c = 15.1547(11)$ Å, $U = 1313.8$ Å^3, space group $P2_12_12_1$ (No. 19), $Z = 4$, $D_m = 1.403$ (flotation in CCl_4–hexane), $D_c = 1.406$ g cm^{-3}, $\mu(\text{Cu}K_{\bar{\alpha}}) = 8.97$ cm^{-1}, $F(000) = 584.0$, m.p. 173—174 °C (long thin colourless needles from ethanol), crystal dimensions (*ca.*) 0.2 × 0.4 × 0.1 mm. The intensity data were collected on a CAD-4 diffractometer [Cu-$K_{\bar{\alpha}}$ radiation ($\lambda = 1.5418$ Å), ω–2θ scanning] and corrected for Lorentz and polarisation effects. Of the 1450 unique data measured ($2 < \theta < 70°$), 1184 had $I > 2\,\sigma(I)$. The structure was solved by direct methods (SHELX 84) and refined (SHELX 76) by full-matrix least squares methods (all non-hydrogen atoms anisotropic). All the hydrogen atoms were located on difference-Fourier map and included in the refinement with a fixed isotropic thermal parameter ($U_{iso.} = 0.10$ Å). The phenyl and methyl groups were treated as idealised rigid groups (d_{C-H} 1.080 Å). At convergence, R and R_w $\{w = 1/[\sigma^2(F) + 0.004\,F^2]\}$ were 0.047 and 0.068 respectively. The bond distances and angles were close to expected values with e.s.d.s in the ranges 0.004—0.007 Å and 0.2—0.6° respectively.

The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.

¶ Compound (**3a**): yield 59.6%; m.p. 163—164 °C; $[\alpha]_D$ −70° (DMF); $\nu_{max.}$ (KBr) 1780 cm^{-1}; δ_H 5.92 [$(CD_3)_2SO$]. Compound (**3b**): yield 17.5%; m.p. 87—88 °C; $[\alpha]_D$ −40° ($CHCl_3$); $\nu_{max.}$ (KBr) 1775 cm^{-1}; δ_H 5.94 [$(CD_3)_2SO$]. *Cf.* m.p. 160—164 °C; $[\alpha]_D$ −70.2° (DMF) for '2,4-*O*-benzylidene-D-ribono-1,5-lactone,'[6]