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Note

Carbon-13 nuclear magnetic resonance-spectral study of branched-chain and 3-*gem*-di-*C*-substituted aldohexofuranoid derivatives

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^{13}C-N.m.r. spectroscopy is a powerful tool for structural studies of carbohydrates[1,2], in particular for the determination of configuration at quaternary centers in branched-chain sugars, a problem difficult to solve by other methods. In six-membered ring systems, configurational assignments based on steric-shift effects are usually straightforward because of the conformational stability of the skeleton[3–7]. In contrast, the conformational flexibility characterizing furanoid rings makes the correlations between structure and ^{13}C-n.m.r. parameters less reliable[8]; however, if partial rigidity is imposed upon the five-membered ring by, for example, a fused 1,2-*O*-isopropylidene group, such correlations can be applied to tetrahydrofuran derivatives, as shown previously in this laboratory for several acetal derivatives of branched-chain pentulofuranoses[9,10].

We have reported[11] recently the synthesis of a series of 1,2:5,6-di-*O*-isopropylidenehexofuranoses branched or *gem*-di-*C*-substituted at C-3. The ^{13}C-n.m.r. analysis of these new, branched-chain sugars and of appropriate model compounds is described herein, together with the determination of specific substituent effects which can be useful for structural assignment at quaternary centers.

The chemical shifts of the 3-monosubstituted derivatives **2**–**7**, of the pairs of epimeric, tertiary alcohols **8**–**13**, and of the *gem*-di-*C*-alkylated hexofuranoses **14**–**20** are documented in Table I, together with data previously obtained[12] for the reference 3-deoxy compound **1**. The 3-deoxy-3-*C*-methyl-D-*gluco* derivative **4** was obtained as the minor isomer (~10%) by hydrogenation of 3-deoxy-1,2-:5,6-di-*O*-isopropylidene-3-*C*-methylene-α-D-*ribo*-hexofuranose in the presence of Raney

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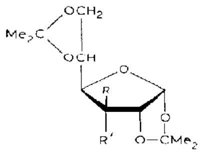


1 R = H, R' = H
2 R = OH, R' = H
3 R = H, R' = OH
4 R = Me, R' = H
5 R = H, R' = Me
6 R = H, R' = CN
7 R = H, R' = CH_2NO_2
8 R = OH, R' = Me
9 R = Me, R' = OH
10 R = OH, R' = CN
11 R = CN, R' = OH
12 R = OH, R' = CH_2NO_2
13 R = CH_2NO_2, R' = OH
14 R = Me, R' = CN
15 R = Me, R' = CH_2NO_2
16 R = Me, R' = CH_2OH
17 R = R' = CN
18 R = CN, R' = CH_2NO_2
19 R = CN, R' = CH_2CN
20 R = CH_2NO_2, R' = CH_2NO_2

nickel, the main product[13] being **5**. The different types of carbon atoms, namely methyl, methylene, methine, and quaternary, were readily identified from off-resonance, decoupled spectra. Most of the signals were then assigned on the basis of the expected chemical shift[1,9,12], and the signals for the three methine carbon atoms appearing in the region $\delta \sim 70$–85 were attributed by comparison with data reported for related pento- and hexo-furanosides[9,12]; in most cases, the signal of C-2 was observed downfield from that of C-4, the latter being downfield from that of C-5.

Compounds **1**–**20** provide a wide range of different substituents at C-3 in both of the possible configurations and allow a detailed analysis of the substituent-shift effects on the carbon nuclei of the 1,2:5,6-di-*O*-isopropylidenehexofuranose skeleton. The available $^3J_{H,H}$ coupling values (see original reference for each compound and ref. 14) indicate that, in each case, the furanoid ring adopts a $^3T_2$(D) conformation, the usual type of conformation of 1,2-*O*-isopropylidene-α-D-xylofuranoses and of the corresponding hexofuranoses[15]. It is noteworthy that inversion of the configuration at C-3 does not affect the conformation of the five-membered ring to a large degree [see, for example, $^3J_{H,H}$ values of **2** and **3** (ref. 14)]. Thus, conformational homogeneity throughout the series should make secure a consistent additivity of substituent effects.

The most interesting substituent effects were observed on C-2 and C-4. The chemical-shift changes of these nuclei caused by the introduction of a substituent at C-3 in an *exo* or in an *endo* position (with respect to the bicyclic system) were determined from the difference between the δ values for the 3-monosubstituted derivatives **2**–**7** and the corresponding δ values for **1**. The *exo*-CN and *exo*-CH_2NO_2 effects have been obtained from the difference between the shift effects of both of the substituents of the 3,3-disubstituted derivatives and the effects of the *endo* substituent (see Table II). The effects on C-2 and C-4 exhibit some interesting trends:

TABLE I

^{13}C CHEMICAL-SHIFT DATA[a]

Compound	*C-1*	*C-2*	*C-3*	*3-CH$_3$*	*3-CN*	*3-CH$_2$X*[b]	*C-4*	*C-5*	*C-6*	*OCMe$_2$O*	*OCMe$_2$O*
1[c]	105.0	79.8	34.7				77.9	76.2	66.1	108.5, 110.2	25.1, 26.0, 26.3, 26.6
2[d]	104.6	85.1	73.3				81.1	72.4	66.2	107.9, 110.7	25.3, 26.1, 26.7
3[e]	103.1	79.4	71.3				77.9	74.9	63.7	108.3, 111.3	25.4, 26.1, 26.4, 26.6
4	104.2	85.6	40.0	10.6			80.0	73.5	67.4	108.3, 110.1	25.2, 25.9, 26.3
5	104.9	82.8	41.6	10.0			82.1	77.0	66.2	108.6, 110.6	25.2, 26.5, 26.7
6	104.8	79.4[f]	36.3		116.2		79.0[f]	75.4	65.8	109.2, 119.9	25.0, 26.4
7	104.8	80.2	44.5			71.3	78.5	76.2	66.2	108.9, 111.4	25.0, 26.2
8	104.1	87.0	77.7	19.0			83.1	72.6	65.9	107.8, 111.0	25.3, 26.3, 26.5, 27.0
9	102.9	84.3	76.1	19.8			80.4	73.4	65.0	107.6, 111.2	25.0, 26.3, 26.7
10	104.5	85.0	73.5		117.5		82.2	71.3	65.8	108.8, 112.4	25.1, 26.2, 26.5, 26.7
11	103.4	82.2	75.8		118.9		79.8	74.0	65.4	108.9, 113.0	25.2, 26.3, 26.5
12	104.0	84.3	79.1			76.2	80.6	71.6	66.4	108.6, 111.6	25.1, 26.4, 26.7
13	102.9	80.8	78.3			77.5	79.4	72.4	65.8	108.6, 111.8	24.9, 26.4
14	104.1	85.0	43.1	14.9	119.1		80.8	72.4	66.8	109.2, 119.9	25.0, 26.1, 26.3, 26.6
15	103.9	85.3	47.2	14.2		77.0	80.8	72.3	67.4	108.9, 111.3	24.9, 26.3
16	103.7	86.1	49.6	14.6		61.9	81.4	73.3	67.1	108.2, 110.8	25.1, 26.2, 26.5, 26.8
17	104.9	83.4	43.9		110.7 111.3 [f]		81.2	73.9	66.5	110.2, 113.8[f]	24.8, 25.8, 26.3, 26.5
18	104.5	83.3	49.5		116.9	77.2	79.5	74.0	66.8	109.8, 112.8	24.7, 25.6, 26.0
19	104.2	83.3	49.5		116.4 117.1	40.3	79.5	74.0	66.8	109.8, 112.8	24.7, 25.6, 26.0
20	103.9	83.0	47.2			73.3 74.6	81.2	71.9	67.8	109.4, 111.6	24.7, 25.9

[a] In δ values downfield from internal tetramethylsilane signal, for solutions in di(^{2}H$_6$)methyl sulfoxide [b] X = NO$_2$, CN, or OH [c] Data taken from ref 12 [d] Values slightly different from those reported in ref 12 [e] ^{13}C chemical shifts of **3** in (^{2}H)chloroform have been reported in ref 9 [f] Assignments may be reversed.

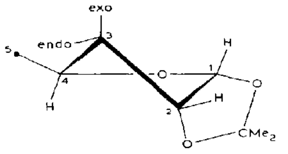
TABLE II

C-3 SUBSTITUENT EFFECTS ON ^{13}C-2 AND ^{13}C-4 CHEMICAL SHIFTS IN 1,2:5,6-DI-*O*-ISOPROPYLIDENEHEXOFURANOSES

Substituent	*Position*	$\Delta\delta^{13}C\text{-}2^{a,b}$	$\Delta\delta^{13}C\text{-}4^{a,b}$
OH	*exo*	+5.3	+3.2
	endo	−0.4	0
CH_3	*exo*	+5.8	+2.1
	endo	+3.0	+4.2
CN	*exo*[c]	+3.4(±0.6)	+2.0(±0.2)
	endo	−0.4	+1.1
CH_2NO_2	*exo*[c]	+2.1(±0.7)	+2.1(±0.6)
	endo	+0.4	+0.6

[a] In p.p.m. [b] The signs (+) and (−) denote a deshielding and shielding effect, respectively. [c] These *exo* effects have been obtained by the difference between the shift effects of both of the substituents of the 3,3-disubstituted derivatives and the effects of the *endo* substituent.

(a) The (deshielding) effect on C-2 and C-4 of a 3-*exo* substituent is always larger than that of the same substituent in the *endo* position and, as a corollary, the inversion of configuration at C-3 (in monosubstituted derivatives) always produces an upfield shift of C-2 and C-4, the only exception being the effect on C-4 of a methyl group. (b) The effect of an *exo* substituent is always larger on C-2 than on C-4. (c) The change in chemical shift accompanying the inversion of configuration at C-3 (difference between *exo* and *endo* substituent effects) is always larger for C-2 than for C-4.



Scheme 1

These observations may be rationalized by considering the most favorable conformation of the system (see Scheme 1). The 3-*exo* substituent, on adopting a quasi-*anti* disposition with respect to the substituent at C-2, is indeed expected to have a deshielding β-effect on C-2 (see ref. 8); however, because of its *cis*-relationship with O-2, a 3-*endo* substituent introduces a steric effect that leads to an upfield shift of C-2, a well-documented effect in furanosides[8]. As a result of the combined effects, the chemical shift of C-2 in 3-*endo* monosubstituted derivatives differs little from that of reference compound **1**. The chemical-shift changes of C-4 are less clear-cut in view of the fact that, in any case, the substituent at C-3 is in a pseudo-*gauche* relationship with the C-4 substituent; thus, the effects are more sensitive to the structure of the substituent and, furthermore, a slight modification of the conformational equilibrium around the C-4–C-5 bond might have an influence on the δ value for C-4. Nevertheless, the shift effects on both C-2 and C-4 are useful for structural determination at the quaternary center. As a test of their reliability, the chemical shifts of C-2 and C-4 of the 3,3-disubstituted compounds **8**, **9**, **10**, **12**, **14**, and **15** were calculated from the parameters of **1** and the appropriate shift-effects (see Table II). The deviations between the calculated and the observed values ($\Delta\delta\ C_i = \delta\ C_i^{calc} - \delta\ C_i^{obs}$) were found to be very small ($\Delta\delta$ C-2 $\leq$ 1.2, $\Delta\delta$ C-4 $\leq$ 2.2), the largest deviations occurring when the largest effects are cumulated (if **8** is omitted, $\Delta\delta$ C-4 $\leq$ 1.1). These results show clearly that the empirical substituent effects reported in Table II and the related rules can be used with a good degree of confidence in determining the configuration at C-3 of the common 1,2:5,6-di-*O*-isopropylidenefuranoid system and its structural analogs, on the basis of the chemical shifts of C-2 and C-4.

As regards the other ^{13}C nuclei of compounds **2–20**, it appears that C-5 undergoes a shielding effect from any substituent at C-3 (except for an *endo*-methyl group), the shift effect being much larger for the *exo* than for the *endo* substituents (shift effects on C-5: 3-*exo*-CH_2NO_2 or -OH, −4; 3-*exo*-CH_3, −3; and 3-*exo*-CN, −2.2 p.p.m.). These γ-effects indicate that, as expected, the steric interaction with the substituents at C-5 is greater for the quasi-axial 3-*exo* substituent than for the 3-*endo* substituent (the shielding of C-5 by a 3-*exo*-cyano group may be due to the magnetic anisotropy of this group). Moreover, as shown by the values of δ C-5 of the 3,3-disubstituted derivatives **8–20**, the introduction of the *endo* substituent as a second substituent at C-3 causes very little change in the chemical shift of C-5, a useful aid for structural determination.

Finally, comparison of the ^{13}C parameters of the C-3 epimers does not reveal any useful configurational effect on either the chemical shift of C-3 or that of the substituent itself. A weak, but interesting trend is exhibited by the chemical shifts of C-1 of the epimeric tertiary alcohols (and also of **2** and **3**): for the *allo* derivatives, the signal of C-1 is observed at $\delta \sim 103.0$ (δ C-1 $<$ 103.4 p.p.m.), whereas for the *gluco* derivatives, it is observed at a slightly lower field (δ C-1 $>$ 104.0 p.p.m.), however an effect that was observed only for a solution in di($^2H_6$)methyl sulfoxide.

EXPERIMENTAL

General. — General methods and the preparation of compounds **6**, **14**, **15**, **16**, **17**, **18**, and **20** are described in ref. 11. Compounds **5** (ref. 13), **7** (ref. 16), **8** (ref. 17), **9** (ref. 18), **10** and **11** (ref. 19), **12** and **13** (ref. 20), and **19** (ref. 21) have been prepared according to literature procedures. ^{13}C-N.m.r. spectra were recorded at 15.1 MHz with a Bruker HX-60 spectrometer equipped with a FT60M Fourier-transform accessory

3-Deoxy-1,2:5,6-di-O-isopropylidene-3-C-methyl-α-D-glucofuranose (**4**). — 3-Deoxy-1,2:5,6-di-*O*-isopropylidene-3-*C*-methylene-α-D-*ribo*-hexofuranose[13] (2

g) in ethanol (150 mL) was subjected to a hydrogen pressure of 0.33 mPa for 12 h in the presence of Raney nickel (5 mL of slurry). The reaction mixture was then filtered and the filtrate concentrated. Separation of the two components (R_F 0.63, major; R_F 0.66, minor; 5:1 v/v benzene–ethyl acetate) by column chromatography (20:1 v/v 1,1,1-trichloroethane–ethyl acetate) afforded **5** (ref. 13) as the major isomer, and the desired *gluco* epimer **4** (210 mg, 10%); $[\alpha]_D^{23}$ −8.4° (*c* 1.5, chloroform); ^{1}H-n.m.r. (chloroform-*d*): δ 5.76 (d, 1 H, $J_{1,2}$ 3.8 Hz, H-1), 4.36 (d, 1 H, H-2), 4.22-3.76 (m, 4 H, H-4, -5, -6,6′), 2.16 (m, 1 H, H-3), 1.55, 1.45, 1.39, 1.34 (4 s, 4 × 3 H, 2 CMe_2), and 0.96 (d, 3 H, $J_{3,Me}$ 7.2 Hz, C-3 Me).

Anal. Calc. for $C_{13}H_{22}O_5$: C, 60.4; H, 8.6. Found: C, 60.3; H, 8.6.

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