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ASSIGNMENT OF RING SIZE IN ISOPROPYLIDENE ACETALS BY CARBON-13 N.M.R. SPECTROSCOPY

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ABSTRACT

The ^{13}C-n.m.r. spectra of a range of isopropylidene acetals of carbohydrates have been studied. Attention has been focussed on the chemical shifts of the acetal carbon and methyl groups of the acetals. These parameters are characteristic of ring-size (1,3-dioxolane, 1,3-dioxane, and 1,3-dioxepane) and can sometimes give further information on ring-fusions and conformations. An example is given of the application of the method to 1,3:2,4:5,6-tri-*O*-isopropylidene-D-glucitol.

INTRODUCTION

Isopropylidene groups, in the form of cyclic acetals, are widely used in carbohydrate chemistry for the specific protection of diol functions[1,2]. In addition to their practical value, there has been interest in the structures themselves[1–6], especially their conformational analysis[4,6–8] and the factors leading to the formation of particular ring-sizes when more than one is possible[4,6–10]. Most of the older methods of acetal formation use acetone and an acid catalyst as reagents, yielding the acetals under equilibrating conditions. More recently, the discovery[11–14] of reagents capable of forming acetals under conditions of kinetic control has extended the range of structures available.

The vast majority of isopropylidene compounds contain five- or six-membered rings, but larger rings are also known[15–17]. Structure determination of mono-isopropylidene compounds by classical methods is relatively simple, but when more than one isopropylidene group is present, the use of partial, acidic hydrolysis may cause rearrangement[10] and physical methods would have many advantages. Mass spectrometry has been used for the detection of 1,3-dioxolane rings at the end of a polyol chain[18], but the results must be interpreted with caution[13].

^{1}H-N.m.r. spectroscopy has been used[19] for the study of the methyl groups in isopropylidene compounds containing a five-membered (1,3-dioxolane) ring, and

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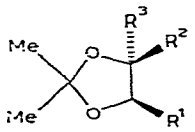
small differences in the ^{13}C-chemical shifts of the acetal carbon atom of methylene acetals having five-, six-, and seven-membered rings have been recorded[20]. The reported[21] substantial differences between the ^{13}C-chemical shifts of the acetal carbon atoms in 2,2-dimethyl-1,3-dioxolane (**1**), and the related 1,3-dioxane **5** and 1,3-dioxepane **11** prompted us to examine carbohydrate isopropylidene derivatives of known structure, paying particular attention to the chemical shifts of the quaternary acetal carbon. It was found, in addition, that the signals due to the isopropylidene methyl groups were sensitive to ring size and conformation. A preliminary paper has been published[22], and we now describe on more examples and extend the number of correlations.



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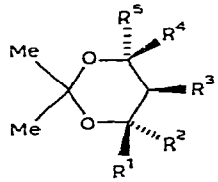

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6 $R^1 = Me, R^2 = R^3 = R^4 = R^5 = H$
7 $R^1 = R^4 = Me, R^2 = R^3 = R^5 = H$
8 $R^1 = R^5 = Me, R^2 = R^3 = R^4 = H$
9 $R^1 = R^3 = R^4 = Me, R^2 = R^5 = H$
10 $R^1 = R^3 = R^5 = Me, R^2 = R^4 = H$

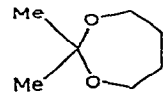

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TABLE I

CORRELATIONS OF ^{13}C-CHEMICAL SHIFT[a] FOR CARBOHYDRATE ISOPROPYLIDENE ACETALS

Ring size	*Acetal carbon*	*Methyl carbons*	*Δδ (Methyl carbons)*
5	108.1–111.4 (monocyclic or *cis*-fused to pyranoid or cyclohexane ring) 111.8–112.3 (*trans*-fused to pyranoid or cyclohexane ring) 111.3–115.7 (fused to furanoid ring)	23.3–28.2	0.0–4.6
6	97.1–99.9 (chair form of 1,3-dioxane ring)	18.2–19.3 and 28.6–29.2	9.8–10.9
	100.6–101.1 (skew form of 1,3-dioxane ring)	23.5–24.5	0.0–0.9
7	100.8–102.3	23.5–28.3	0.0–3.8

[a]In chloroform-*d*; p.p.m. downfield from Me_4Si.

TABLE II

^{13}C-CHEMICAL SHIFTS[a] FOR MODEL ISOPROPYLIDENE ACETALS

Ring size	*Compound*	*Acetal carbon*	gem-*Methyl carbons*	*Δδ* (gem-*Methyl carbons*)
5	**1**[b]	108.5	25.7 (X2)	0.0
	2[c]	108.7	25.9, 27.2	1.3
	3[d]	107.2	25.8, 28.7	2.9
	4[d]	107.4	27.4 (X2)	0.0
6	**5**[e]	97.9	24.2 (X2)	0.0
	6[f]	98.2	19.2, 30.1	10.9
	7[f]	98.4	19.9, 30.4	10.5
	8[f]	100.0	25.2	0.0
	9[g]	98.7	19.7, 30.1	10.4
	10[f]	100.3	24.2, 25.2	1.0
7	**11**[h]	100.9	25.1 (X2)	0.0

[a]In chloroform-*d*; p.p.m. downfield from Me_4Si. [b]Ref. 21, *cf.* refs. 23–25. [c]Ref. 24, *cf.* refs. 23, 25. [d]Ref. 24. [e]Ref. 26, *cf.* refs. 21, 27, 28. [f]Ref. 26, *cf.* ref. 27. [g]Ref. 26. [h]Ref. 21.

TABLE III

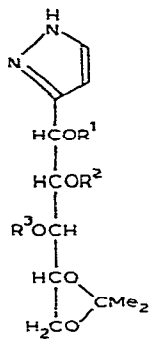
^{13}C-CHEMICAL SHIFTS[a] FOR CARBOHYDRATE 1,3-DIOXOLANES

Compound	*Acetal carbon*	*Methyl carbons*	*Δδ (Methyl carbons)*
12[b]	108.9, 109.0	25.0, 25.2, 26.2 (X2)	⩽1.2
13[b]	109.4, 109.7	25.5, 25.9, 26.9, 27.0	⩽1.5
14[c]	108.9, 109.6	24.5, 24.9, 26.0	⩽1.5
15[c]	108.5, 109.4	24.2, 24.7, 25.8	⩽1.6
16[d]	99.7[e], 108.1	20.4[e], 27.2, 27.9	0.7
17[f]	109.5	25.6, 27.3	1.7
18[f]	109.5 (X2), 112.3	23.3, 25.8, 26.0	⩽2.7
19[f]	109.9, 110.5	24.0, 25.0, 25.9, 26.1	⩽2.1
20[f]	110.3, 111.3, 112.2	23.4, 24.9, 25.8 (X2), 26.4, 27.9	⩽4.5
21[g]	110.4, 112 3	25.8, 26.7 (X2), 28.2	⩽2.4
22[h,i]	99.6[e], 111.8	(19.1, 29.0)[e], 26.3, 26.8	(9.9)[e], 0.5
23[i,j]	99.2[e], 109.6	(18.9, 29.2)[e], 26.2, 26.8	(10.3)[e], 0.6
24[k]	112.1	26.2, 26.8	0.6
25[k]	109.2, 111.4	25.1, 26.1, 26.6 (X2)	⩽1.5
26[k,l]	109.2, 112.8	24.5, 25.2, 25.9, 26.8	⩽2.3
27[l]	113.3	24.8, 26.1	1.3
28[l]	114.9	25.4, 27.3	1.9

[a]In chloroform-*d*; p.p.m. downfield from Me_4Si. [b]Refs. 22, 29. [c]Ref. 30. [d]Ref. 31. [e]1,3-Dioxane ring. [f]Ref. 32. [g]Ref. 33. [h]Ref. 11. [i]Data from Dr. N. A. Hughes. [j]Ref. 34. [k]Ref. 35. [l]Ref. 36.

RESULTS AND DISCUSSION

Table I is an extended version of the correlations given in the preliminary paper[22], and Table II is derived from published data on the parent heterocycles and certain of their methyl derivatives. In general, it is clear that the signal due to the acetal carbon atom in 1,3-dioxolanes is appreciably deshielded relative to that in 1,3-dioxanes, while the signal in 1,3-dioxepanes has an intermediate value nearer to that in the 1,3-dioxanes. We shall discuss each group in turn, giving examples of various effects.



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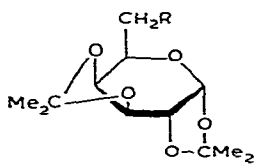
13 $R^1 = H, R^2, R^3 = CMe_2$



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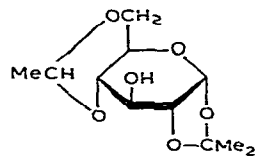

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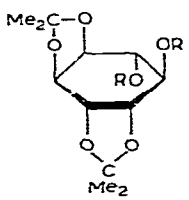

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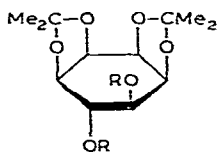
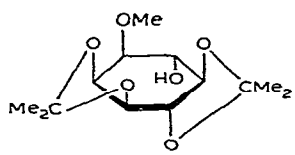


19 R = H
20 R,R = CMe_2



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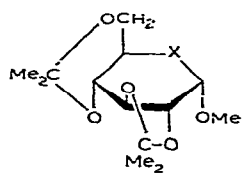
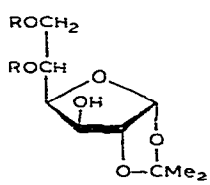
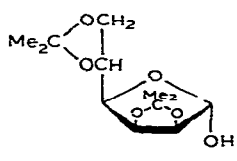


22 X = O
23 X = S



24 R = H
25 R,R = CMe_2



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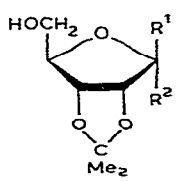


27 $R^1 = H, R^2 = CH_2CN$
28 $R^1 = CH_2CN, R^2 = H$

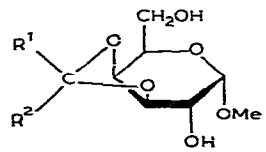
1,3-Dioxolanes. — (*a*) *The acetal carbon signal.* The chemical shift of the acetal carbon atom in 2,2-dimethyl-1,3-dioxolane (**1**) is δ 108.5 (Table II) and the carbohydrate derivatives have values in the range δ 108.1–115.7. Closer scrutiny of our results and those in the literature enables a distinction to be made between certain categories of 1,3-dioxolanes, and Table III contains examples. When the dioxolane is monocyclic or *cis*-fused to a pyranoid or cyclohexane ring, the range for the acetal carbon atom is δ 108.1–111.4 (compounds **12–21**, **25**, and **26** in Table III).

At the suggestion of Professor S. J. Angyal we have examined several inositol acetals[32,33] containing a *trans*-fused dioxolane ring (compounds **18**, **20**, and **21**). The compounds, some of them thirty-years old[32], gave excellent spectra which confirmed their structures and enabled us to assign a chemical shift to the *trans*-acetal carbon. The diacetal **17** of L-*chiro*-inositol gave only one acetal carbon signal due to the axis of symmetry. It appeared at δ 109.5, within the expected range for *cis*-fused dioxolanes. The corresponding triacetal **18** gave two signals, at δ 109.5 and 112.3, of relative intensity 2:1, indicating that the latter signal was due to the *trans*-acetal group. Similar arguments were applied to the spectra of **19** and **20**, which are derivatives of *epi*-inositol. The *trans*-acetal group can clearly be distinguished in the (—)-bornesitol derivative **21** and the glucoside **22**. The range covered is δ 111.8–112.3, distinctly deshielded in comparison with the *cis*-acetals. The difference is probably due to the extra rigidity and strain in the *trans*-acetals and it is interesting to note that in the sulphur analogue **23**, which is relatively unstrained[34], the acetal carbon signal appears at δ 109.6, well within the "normal" range.

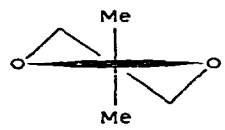
When the 1,3-dioxolane ring is fused to a furanoid ring, the acetal carbon signal is again shifted downfield, as indicated by compounds **24–28**; several other examples have also been reported[35,36]. The *C*-ribofuranosyl derivatives **27** and **28** constitute an α,β-pair and the β-D isomer **28** gives a signal for the acetal carbon at particularly low field (δ 114.9); other α,β pairs in the *ribo* and *allo* series show this effect[36] and it might have diagnostic value in the ribonucleoside field for assigning anomeric configurations[37]. Moffatt and his colleagues have already shown[36] that isopropylidene methyl-group signals may be used to assign structures to such α,β pairs as **27,28** and similar D-*ribo* and D-*allo* compounds.

(*b*) *The methyl groups.* In 2,2-dimethyl-1,3-dioxolanes, the signals due to the methyl groups appear within the range δ 23.3–28.2 (Table I). For an individual isopropylidene group, the difference ($\Delta\delta$) in chemical shift for the carbon atoms of the methyl groups is small (**2** and **3** in Table II) compared with the related dioxanes (**6**, **7**, and **9** in Table II). Senda *et al.*[24] have argued that the methyl group *cis* to the substituents on C-4 and C-5 of the dioxolane ring gives rise to the downfield signal, and similar conclusions have been reached for **29**, **30**, and related compounds, based firmly on an X-ray structure for **30**. It is likely that the small difference in chemical shift is due to the flexibility of the 1,3-dioxolane ring[39,40] and the similarity of the environment of the two methyl groups. The most probable conformation[23] of the 2,2-dimethyl-1,3-dioxolane ring is $^4T_5$ (**31**) in which the methyl groups are equivalent. It is therefore difficult to assign the methyl-group signals in the ^{13}C-n.m.r. spectrum

of a di-isopropylidene derivative of a relatively complex molecule such as a carbohydrate. It is interesting to note, however, that the compounds in Table III showing the largest spread of methyl resonance values are the inositol triacetals **18** and **20**, whose conformations are more constrained[32,33].



29 R^1 = Me, R^2 = CH_2OH
30 R^1 = CH_2OH, R^2 = Me



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1,3-Dioxanes. — The chemical shift of the acetal carbon atom in 2,2-dimethyl-1,3-dioxane (**5**) is δ 97.9 (Table II). The signals for carbohydrate derivatives lie in two ranges, δ 97.8–99.9 and 100.6–101.1, depending on the conformation of the 1,3-dioxane ring. The first class includes **22** and **23** (Table III), in which the dioxane ring is fused *trans* to a pyranoid ring, and **32**, **33**, **38**, and **39** (Table IV) where there is fusion *cis* to a pyranoid or furanoid ring. In the spectra of all of these compounds, the signals due to the dioxane methyl groups are widely separated ($\Delta\delta$ ~10 p.p.m.). This pattern[26,28] is due to an axial methyl (higher field) and equatorial methyl (lower field), and is a clear indication that the dioxane ring has a chair conformation. The spectra[26] of the model compounds **6**, **7**, and **9** (Table II), corresponding to the conformations **6C**, **7C**, and **9C**, are in complete accord with these arguments.

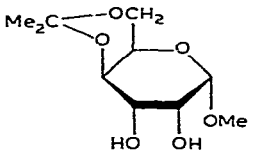
In the spectrum of the benzoate **34**[42], derived from "isodiacetone glucose", the dioxane signal appeared at lower field (δ 100.9) and the methyl group signal as a singlet whose chemical shift (δ 23.7) was midway between the two extreme values expected. Since the corresponding xylose derivative **38** behaved normally, with

TABLE IV

^{13}C-CHEMICAL SHIFTS[a] FOR CARBOHYDRATE 1,3-DIOXANES

Compound	*Acetal carbon*	*Methyl carbons*	*$\Delta\delta$ (Methyl carbons)*
32[b]	98.3	18.3, 29.1	10.8
33[c]	97.8	18.9, 28.6	9.7
34[b,d]	100.9, 112.1[e]	23.7 (X2), (26.4, 27.0)[e]	0.0, 0.6[e]
36[f]	101.0, 112.3[e]	24.2 (X2), (26.6, 27.2)[e]	0.0, 0.6[e]
37[f]	100.6, 112.0[e]	24.2 (X2), (26.7, 27.3)[e]	0.0, 0.6[e]
38[b]	97.2, 111.3[e]	18.4, 28.6, (25.9, 26.5)[e]	10.2, 0.6[e]
39[g]	98.6, 111.8[e]	19.2, 29.2, (26.1, 26.6)[e]	10.0, 0.5[e]

[a]In chloroform-*d*; p.p.m. downfield from Me_4Si. [b]Ref. 22. [c]Ref. 41. [d]Ref. 42. [e]Due to 1,2-*O*-isopropylidene group, *cf.* compounds **24** and **25** in Table III. [f]Ref. 43. [g]Ref. 44.



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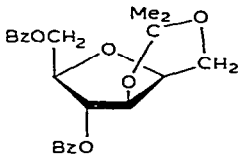

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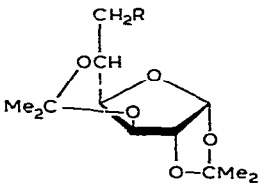

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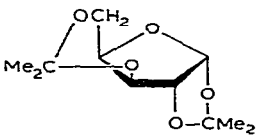

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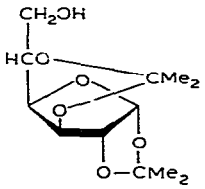

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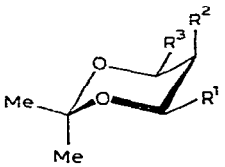
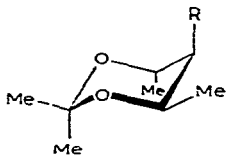


6 C R^1 = Me, R^2 = R^3 = H
7 C R^1 = R^3 = Me, R^2 = H
8 C R^1 = R^2 = R^3 = Me



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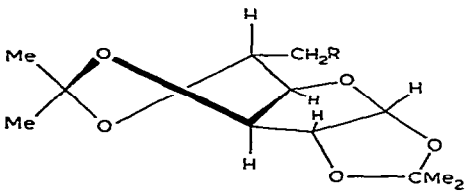
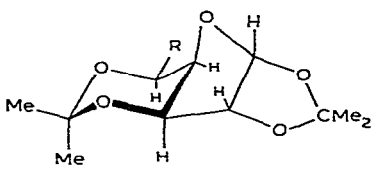
10C R = Me

8S R = H
10S R = Me





34S R = OBz
36S R = OH
37S R = H

38C R = H
39C R = CH_2OH

conformation 38C, it appeared that a non-chair form of the dioxane ring was present in **34**. Mills[4] pointed out that severe diaxial interactions are present in both of the possible chair forms of the analogous 6-deoxy-6-nitro-D-*gluco* compound **35**, and Stoddart[45] analysed the situation in terms of the model compound **8**, represented as the chair and skew forms 8C and 8S. Although a skew form of *trans*-2,2,4,6-tetramethyl-1,3-dioxane (**8**) had been proposed on thermochemical grounds[46] and by measurement of molecular rotations[47], Kellie and Riddell[27,48] were the first to obtain supporting ^{13}C-n.m.r. evidence for a skew conformation of **8** and other methyl derivatives based on the deshielding of the acetal-carbon signal. Subsequently, ^{1}H-n.m.r. spectroscopy was used[49] to establish the particular skew form 8S and more-refined ^{13}C-data were obtained[26], including the signals for the 2-methyl groups. The model compound **10**, which is the closest analogue of **34** and **35**, has[26] the skew conformation **10S** rather than the chair **10C**. The 2-methyl groups in **10S** are equivalent in conformation, so $\Delta\delta$ is small (in **8**, the methyl groups give identical signals because of the axis of symmetry). The acetal **34** therefore has the conformation **34S**.

After our preliminary publication, the ^{13}C spectra of a series of compounds related to **34** and **35** were published[43]. Two of them (**36** and **37**) are shown in Table IV. In agreement with the preceding arguments, **36** and **37** also have the dioxane ring in a skew conformation, shown in structures **36S** and **37S**. In 1,3-dioxane nomenclature[26,48], the conformation is designated as 2,5-twist; in carbohydrate nomenclature[50], it is $^{2,5}S_{a1}$. The dioxane ring of 1,2:3,5-di-*O*-isopropylidene-β-L-idofuranose (**39**) is[44] in a normal chair form **39C**, analogous to **9C** (see Table IV).

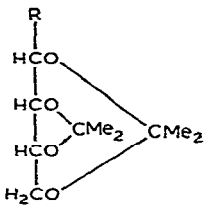
1,3-Dioxepanes. — The chemical shifts of the acetal carbon atoms are in the range δ 100.8–102.3 (Table I), and some representative examples are shown in Table V. On this basis alone, it is not possible to distinguish between a 1,3-dioxepane and a skew form of a 1,3-dioxane, but other factors can be taken into account. The ^{13}C spectrum of the erythritol derivative **40**, for example, shows two different kinds of acetal ring, one of which is a dioxolane, whereas the structure **43** is symmetrical and would show *two* six-membered rings. The methyl group signals appear to depend on whether the molecule is monocyclic (as in **42**) or bicyclic (as in **40** and **41**). The greater constraint in bicyclic systems[51] causes differences in the chemical shifts of the

TABLE V

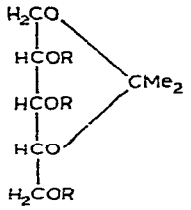
^{13}C-CHEMICAL SHIFTS[a] FOR CARBOHYDRATE 1,3-DIOXEPANES

Compound	*Acetal carbon*	*Methyl carbons*	*$\Delta\delta$ (Methyl carbons)*
40[b]	101.7, 108.4[c]	23.5, 24.7, 25.6, 28.3	$\leq$4.8
41[b]	101.6, 108.1[c]	23.5, 24.6, 25.6, 28.2	$\leq$4.7
42[d]	100.8	24.7 (2X)	0

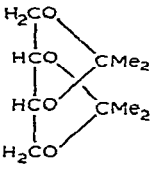
[a]In chloroform-*d*; p.p.m. downfield from Me_4Si. [b]Ref. 17. [c]1,3-Dioxolane ring. [d]Ref. 22.



40 R = H
41 R = $CH(SEt)_2$



42 R = CH_2Ph

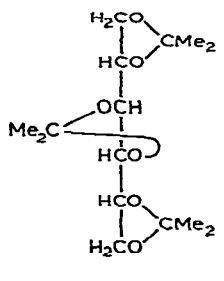


43

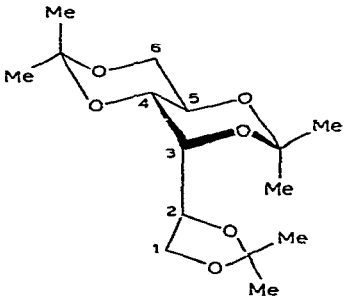
methyl groups. Further work is necessary to assign signals to individual methyl groups.

Tri-O-isopropylidene-D-glucitols. — Two tri-*O*-isopropylidene-D-glucitols are formed in the reaction of D-glucitol with acetone and zinc chloride[52]. ^{13}C-N.m.r. spectroscopy was used[52] to confirm the structure of one of the isomers, the known[53] 1,2:3,4:5,6-tri-*O*-isopropylidene-D-glucitol (**44**). Thus, the signals at δ 109.5 and 109.8 (two carbons) showed the presence of three dioxolane rings, and the six methyl-group signals were in the range δ 25.3–27.3, well within the values for dioxolane rings (Table I). The second isomer was previously unknown. Its ^{13}C spectrum showed three acetal-carbon signals at δ 98.4, 98.6, and 108.9, indicative of two dioxane and one dioxolane ring. The two structures **45** and **46** were therefore considered, and the terminal dioxolane group was confirmed by the *m/z* 101 ion as base peak in the mass spectrum[18].

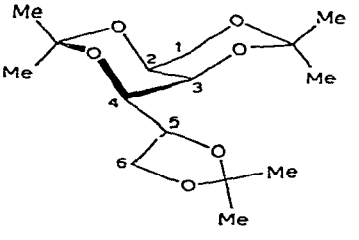
The methyl signals for the new acetal were at δ 19.0, 19.4, 25.4, 27.0, 29.1, and 29.6. It was realised[52] that the two high-field signals (δ 19.0 and 19.4) were due to steric compression of these methyl groups and therefore structure **45** was selected in which there is a very strong interaction between the axial methyl of the 3,5-*O*-isopropylidene group and the *endo* methyl of the 1,2-*O*-isopropylidene group. In the light of our work, and having access to a larger number of spectra of known compounds, we suggest that 1,3:2:4:5,6-tri-*O*-isopropylidene-D-glucitol (**46**) is the structure of the new triacetal. In our view, the methyl signals can be paired as (19.0, 29.1), (19.4, 29.6), and (25.4, 27.0), in which the first two pairs represent axial and



44



45



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equatorial methyl groups on a dioxane ring and the third pair refers to the dioxolane ring (see Table I). These assignments are all accommodated in structure **46**. It may be noted that **46** contains a favourable *O*-inside arrangement of fused dioxane-rings, and that the diaxial interaction of C-2 and the axial methyl group of the 3,5-*O*-isopropylidene group in **45** is very strong ($\geq$8.9 kcal/mol[46]) and would cause skewing of the dioxane ring with consequent effect on the ^{13}C-n.m.r. spectrum.

Related work. — While this work was in progress, we became aware of the paper by Neszmélyi *et al.*[54] who used ^{13}C-n.m.r. spectroscopy to assign configurations in dioxolane-type benzylidene acetals. Grindley and Gulasekharem[55] have described in detail the use of both ^{13}C- and ^{1}H-n.m.r. spectroscopy to study ring-size and conformations of benzylidene acetals. Sohar and his colleagues have elucidated the structures of di-*O*-benzylidene derivatives of 1,6-dibromo-1,6-dideoxy-D-mannitol[56] and of L-iditol[57] by n.m.r. methods.

The work described in this paper on isopropylidene acetals is complementary to the Hungarian and Canadian studies of benzylidene acetals, and it is now clear that ^{13}C-n.m.r. spectroscopy provides an answer to many problems of cyclic acetal structures in the carbohydrate field and in other natural products[21].

EXPERIMENTAL

^{13}C-N.m.r. spectra were recorded at 20 MHz for solutions in chloroform-*d*, with tetramethylsilane as internal standard, using a Varian CFT-20 spectrometer.

*1,3,4-Tri-*O*-benzyl-2,5-*O*-isopropylidene-*L*-ribitol* (**42**). — 2,3,5-Tri-*O*-benzyl-D-ribofuranose[58] (1.528 g, 3.64 mmol) was stirred in methanol (50 ml) while solid sodium borohydride (50 mg, 1.32 mmol) was added. After 1 h, t.l.c. showed no starting material. The solution was evaporated, ether and brine were added, and the ether layer was dried (Na_2SO_4) and evaporated, to give the diol as a pale-yellow gum (1.45 g). The gum was dissolved in acetone (10 ml) and 2,2-dimethoxypropane (10 ml), and a catalytic quantity of toluene-*p*-sulphonic acid was added. After 18 h at room temperature, the mixture was treated with solid potassium carbonate and stirred for 15 min. Filtration and evaporation of the filtrate afforded the crude acetal **42** as a gum (1.4 g). After chromatography on silica gel with hexane–ether, the acetal **42** was obtained as a rather unstable gum (0.712 g, 43%), $[\alpha]_D$ +48° (*c* 2.15, chloroform).

Anal. Calc. for $C_{29}H_{34}O_5$: C, 75.00, H, 7.33. Found: C, 75.10; H, 7.52.

*1,4:2,3-Di-*O*-isopropylidene-erythritol* (**40**). — Erythritol (2.4 g) in dry acetone (100 ml) was stirred with 2,2-dimethoxypropane (50 ml) and toluene-*p*-sulphonic acid (400 mg) for 6 min. The solution was neutralised with solid sodium carbonate, filtered, and evaporated *in vacuo*, to yield a syrup that was chromatographed on silica gel (100 g). Toluene–ethyl acetate (49:1) eluted, first, 1,2:3,4-di-*O*-isopropylidene-erythritol (2.5 g, 63%), m.p. 53–54°; lit.[59] m.p. 56°. ^{1}H-N.m.r. data (100 MHz, $CDCl_3$): δ 1.28, 1.36 (2 s, 12 H, 4 Me), and 3.80–4.04 (m, 6 H). Further elution

yielded syrupy **40** (1.2 g, 30%). ^{1}H-N.m.r. data (100 MHz, $CDCl_3$): δ 1.28, 1.43 (2 s, 12 H, 4 Me), and 3.56–4.04 (m, 6 H).

Anal. Calc. for $C_{10}H_{18}O_4$: C, 59.39; H, 8.97. Found: C, 59.02; H, 8.72.

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