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The formation of isopropylidene acetals of erythritol and ribitol under conditions of kinetic control*

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ABSTRACT

The isopropylidenation of erythritol, under conditions of kinetic control, employing 2-methoxypropene, yielded the 1,2:3,4- (**1**, 50%), the 1,4:2,3- (**2**, 18%), and the novel 1,3:2,4-diacetal (**3**, 5%). Under similar conditions, ribitol gave the known 1,2:4,5- (**4**, 36%) and 1,4:2,3-diacetal (**7**, 3%) together with the new 1,3:4,5- (**8**, 12%) and 1,3:2,5- diacetal (**11**, 5%), a further example of a dioxepane ring. ^{13}C-N.m.r. and ^{1}H-n.m.r. spectroscopy showed that the 1,3-dioxane rings in **3**, **8**, and **11** adopt chair conformations. In **9**, the *p*-nitrobenzoate of **8**, the dioxane chair is flattened. The product composition is compared with that from the equilibrated system.

INTRODUCTION

^{13}C-N.m.r. spectroscopy[1–3] is a reliable method for the determination of the structure of cyclic isopropylidene acetals, most of which contain five- or, less commonly, six-membered rings[4–10], but larger rings may be formed[1,11–15]. The structures formed depend on the reagents used[4,16–21] and on whether equilibration occurs.

The isopropylidenation of erythritol using acetone and sulphuric acid, conditions of thermodynamic control, gave 1,2:3,4-di-*O*-isopropylidene-erythritol (**1**) as the sole product[12,22], whereas reaction with dimethoxypropane and toluene-*p*-sulphonic acid (TsOH) in *N,N*-dimethylformamide afforded **1** (63%) together with 1,4:2,3-di-*O*-isopropylidene-erythritol (**2**, 30%)[1,12]. When ribitol was treated[13] with acetone and sulphuric acid, the resulting mixture of diacetonides contained 1,2:4,5-di-*O*-isopropylideneribitol (**4**, 65%), 1,2:3,4-*O*-isopropylidene-DL-ribitol (**6**, 18%), and 1,4:2,3-di-*O*-isopropylidene-DL-ribitol (**7**, 11%).

We now describe the reaction of erythritol and ribitol with 2-methoxypropene in *N,N*-dimethylformamide, using TsOH as catalyst, at 0° and with short times of reaction[19].

RESULTS AND DISCUSSION

Treatment of erythritol with 2-methoxypropene in *N,N*-dimethylformamide, with TsOH as catalyst, for 1 min at 0°, afforded three diacetals (t.l.c.). Although the total

* Dedicated to Professor Leslie Hough in the year of his 65th birthday.
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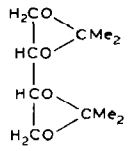
yield was not as high under these conditions as in earlier experiments[1,12] using dimethoxypropane, it was clear that the 1,2:3,4- (**1**) and the 1,4:2,3-diacetal (**2**) were the major products; the third product, shown to be the 1,3:2,4-diacetal **3**, was a minor product. Chromatography of the mixture on silica gel gave successively **3** (5%), **1** (50%), and **2** (18%). The structures of **1** and **2** were confirmed by ^{13}C-n.m.r. spectroscopy and by comparison with authentic samples[1]. The structure of **3** was shown clearly by ^{13}C-n.m.r. spectroscopy. A signal for the quaternary acetal carbon atoms appeared at δ 99.9, characteristic of a 6-membered ring, whereas those of the acetal methyl groups appeared at δ 19.2 and 29.1 ($\Delta\delta$ 9.9), corresponding to a dioxane ring in a chair conformation, as in **3C**. In the ^{1}H-n.m.r. spectrum of **3** at 200 MHz, the signals due to the erythritol protons appeared as a singlet and, therefore, gave no further information on structure or conformation. The structure **3C** is a heterocyclic analogue of *trans*-



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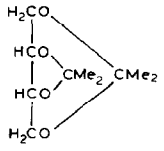

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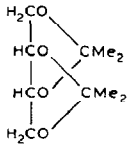

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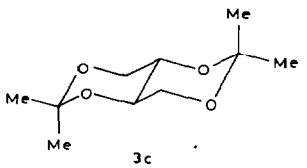

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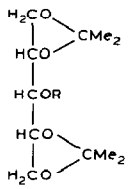

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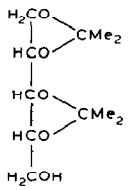

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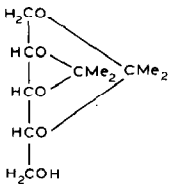

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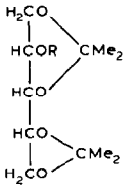

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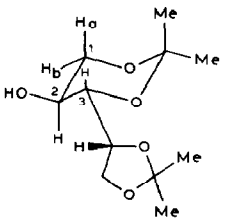

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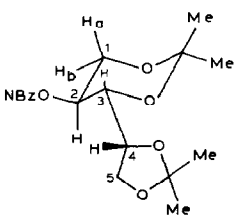

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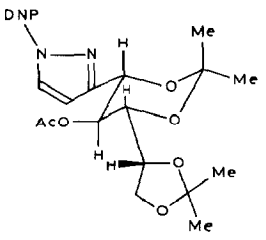

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NBz = *p*-nitrobenzoyl ; DNP = 2,4-dinitrophenyl

Only one structure is drown in the case of racemic compounds

decalin and is relatively unfavoured both kinetically and thermodynamically, presumably due to the presence of axial methyl groups.

When ribitol was treated with methoxypropene under the above conditions, four diacetals were revealed by t.l.c., and repeated chromatography on silica gel gave *A–D* in yields of 12, 36, 5, and 3%, respectively. The major component *B* was shown to be known[13,23] 1,2:4,5-di-*O*-isopropylideneribitol (**4**) by comparison of its ^{1}H- and ^{13}C-n.m.r. spectra with those of the authentic compound and by conversion into the crystalline 3-benzoate **5**. Fraction *D* (m.p. 101–102°) was identified as 1,4:2,3-di-*O*-isopropylidene-DL-ribitol (**7**) by comparison with authentic material[13]. Components *A* and *C* were new diacetals.

The ^{13}C-n.m.r. spectrum of *A* contained signals for quaternary acetal carbons at δ 98.3 and 109.7 and, for acetal methyl groups, at δ 19.2 and 28.1 ($\Delta\delta$ 8.9, dioxane ring[1]) and at δ 24.8 and 26.3 ($\Delta\delta$ 1.5, dioxolane ring[1]). Therefore, *A* must be 1,3:4,5-di-*O*-isopropylidene DL-ribitol (**8**), the only possible structure that contains both a 6- and a 5-membered acetal ring. Furthermore, the 6-membered ring must be in the chair conformation **8C** and this was confirmed by the ^{1}H-n.m.r. spectrum which showed H-1a,2 to be *trans*-diaxial ($J_{1a,2}$ 8.3 Hz). The ^{13}C-n.m.r. spectrum of **8** bore a close resemblance to that of the polyol-derived portion of the pyrazole derivative **10**[24,25] (Table I). The syrupy diacetal gave a crystalline *p*-nitrobenzoate **9** whose n.m.r. spectra showed some unusual features. The signal for the dioxane acetal carbon was at lower field (δ 99.9) compared to that (δ 98.3) of the parent **8**, and the $\Delta\delta$ value for the corresponding methyl groups was reduced to 5.2 p.p.m. Both of these tendencies may be associated with a change in conformation of the dioxane ring. In addition, in the ^{1}H-n.m.r. spectrum of **9**, $J_{1a,2}$ and $J_{1b,2}$ were 5.48 and 4.96 Hz, respectively, which suggested that a flattened conformation such as **9C** may be involved. Unfortunately, the crystals of **9** were not amenable to X-ray crystallography. Presumably, the contrast between **9C** and **10** is related to a strong preference in **10** for the substituted pyrazole ring to occupy an equatorial position on the 1,3-dioxane ring. Nevertheless, it is not clear why the nitrobenzoate **9** should adopt a conformation different from that of the parent alcohol **8**.

The structure of **C** was established as 1,3:2,5-di-*O*-isopropylidene-DL-ribitol (**11**). Its ^{13}C-n.m.r. spectrum contained signals for quaternary acetal carbon atoms at δ 98.4 and 101.8, characteristic of 6- and 7-membered acetals, respectively, and the $\Delta\delta$ value of 9.8 p.p.m. for the methyl groups associated with the 6-membered ring indicated a chair conformation as in **11C**. The ^{13}C-n.m.r. spectrum of the derived *p*-nitrobenzoate (**12**) was also consistent with a chair form for the dioxane ring (Table I). The conformation of the dioxepane ring shown in **12C** could be deduced from the coupling pattern for H-4 in the ^{1}H-n.m.r. spectrum, ($J_{3,4}$ 0.9, $J_{4,5a} = J_{4,5b} = 3$ Hz).

Primary hydroxyl groups are the favoured site for reaction with 2-methoxypropene[10,19]. For erythritol, each of the diacetals **1–3** must have a structure in which both primary hydroxyl groups are substituted. For ribitol, the diacetals **4**, **8**, and **11** are substituted on both primary hydroxyl groups and it is significant that neither the well-known 1,2:3,4-diacetal **6**[13,26] nor 1,3:2,4-di-*O*-isopropylidene-DL-ribitol (**13**) was

TABLE I

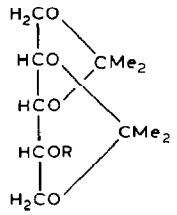
^{13}C-N.m.r. data[a]

Compound	*Acetal carbons*	*C=O*	*Aromatic carbons*	*Chain carbons*	*Gem-Me$_2$*	*Δδ gem-Me$_2$*
1	109.2[b]			67.3 76.4	25.1 26.6	1.5[b]
2	101.6[c] 108.3[b]			59.2 75.6	23.4[c], 24.7[b] 25.6[b], 28.3[c]	0.9 4.9[c]
3	99.9[d]			62.9 67.6	19.2 29.1	9.9[d]
4	109.0[b]			65.4 (×2) 71.0 75.8 (×2)	25.0 26.4	1.4[b]
5	109.5[b]	165.6	128.3 (×2) 129.7 (×3) 133.1	65.8 (×2) 73.1 74.7 (×2)	24.9 26.2	1.3[b]
7[e]	101.9[c] 108.7[b]			58.5, 63.6, 70.3, 76.4 (×2)	23.8[c], 25.1[b] 25.7[b], 28.4[c]	0.6[b] 4.6[c]
8	98.3[d] 109.7[b]			63.3, 66.7 67.2,73.6, 78.3	19.2[d], 24.8[b] 26.3[b], 28.1[d]	1.5[b] 8.9[d]
9	99.9[d] 109.7[b]	163.9	123.5 (×2) 130.8 (×2) 135.4, 150.6	62.0,66.7,70.6, 71.2,76.7	21.3[d], 25.0[b] 26.4[b], 26.5[d]	1.4[b] 5.2[d]
10[f]	99.5[d] 109.6[b]	 169.7 	108.3, 121.0, 125.6, 127.3, 130.5, 137.1 145.5, 154.8	66.1, 68.2, 68.5 71.6, 76.5	19.3[d], 25.2[b] 26.2[b], 29.0[d]	1.0[b] 9.7[d]
11	98.4[d] 101.8[c]			60.0,61.1, 62.5, 69.0,75.3	19.1[d], 24.2[c] 25.1[c], 28.9[d]	0.9[c] 9.8[d]
12	98.5[d] 101.9[c]	 164.4 	123.5 (×2), 130.9 (×2), 136.2, 150.7	59.9, 61.3, 62.5 72.5, 74.3	18.9[d], 24.4[c] 25.0[c], 28.9[d]	0.6[c] 10.0[d]

[a] In $CDCl_3$; p.p.m. downfield from Me_4Si. [b] 1,3-Dioxolane ring. [c] 1,3-Dioxepane ring. [d] 1,3-Dioxane ring. [e] In ref. 13, Table I, compound *25*; for 75.3 read 58.4. [f] Refs. 24 and 25.

detected*. The formation of the 1,4:2,3-diacetal **7**, a primary alcohol, as a minor product of the reaction of ribitol with methoxypropene at low temperature seems anomalous. However, it is conceivable that **7** is not a direct product, but may arise from rapid rearrangement of **11** *via* protonation on O-1, ring opening, and attack on the oxonium ion intermediate by O-4.

* It has been reported[27], without experimental details, that the 2,4:3,5-diacetal **14** is a product of kinetic isopropylidenation of D-ribose trimethylene dithioacetal.



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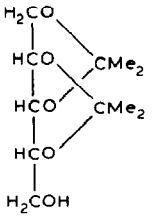
12 R = NBz



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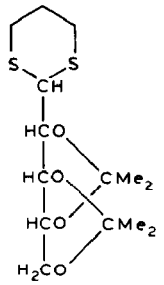

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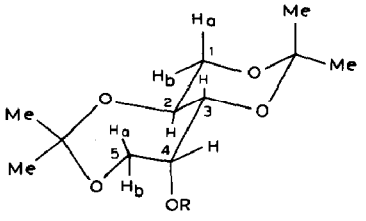

11c R = H
12c R = NBz

EXPERIMENTAL

General methods. — ^{1}H-n.m.r. spectra were recorded with Jeol MH100 and Bruker WP-200SY spectrometers. T.l.c. was carried out on Kieselgel 60 HF 254 (Merck). Adsorption chromatography was performed on silica gel (Merck, 70–230 mesh ASTM).

G.l.c. was effected with a Perkin–Elmer F-11 instrument (flame-ionisation detector) and a column of 10% diethylene glycol succinate at 180°. The N_2 carrier gas pressure was 20 lb. in.$^{-2}$.

Isopropylidenation of erythritol. — Erythritol (5 g) was stirred with 2-methoxypropene (15 mL) and *N,N*-dimethylformamide (100 mL) in the presence of toluene-*p*-sulphonic acid (0.1 g) at 0° for 1 min. The mixture was then neutralised (Na_2CO_3) and concentrated, the residue was extracted with chloroform, the extract was concentrated *in vacuo*, and xylene was evaporated from the residue to yield a syrup. Chromatography (toluene–ether, 20:1) on silica gel (150 g) followed by rechromatography of mixed fractions yielded, first, 1,3:2,4-di-*O*-isopropylidene-erythritol (**3**; 0.38 g, 5%), m.p. 108–110°. ^{1}H-N.m.r. data (200 MHz, $CDCl_3$): δ 1.39, 1.51 (2 s, each 6 H, 2 CMe_2), 3.77–3.78 (m, 6 H). Mass spectrum: *m/z* 202 (M^+), 187 ($M^+ - 15$), 159 ($M^+ - 43$), and 101 ($M^+ - 101$).

Anal. Calc. for $C_{10}H_{18}O_4$: C, 59.4; H, 8.9. Found: C, 59.6; H, 9.0.

Eluted second was 1,2:3,4-di-*O*-isopropylidene-erythritol (**1**; 4.15 g, 50%), m.p. 53°; lit.[1] m.p. 53–54°. The ^{13}C-n.m.r. spectrum was indistinguishable from that of an authentic sample[1].

Eluted third was 1,4:2,3-di-*O*-isopropylidene-erythritol (**2**; 1.5 g, 18%). Mass spectrum: *m/z* 202 (M^+), 187 ($M^+ - 15$). The ^{1}H- and ^{13}C-n.m.r. spectra were indistinguishable from those of an authentic sample[1].

Isopropylidenation of ribitol. — Ribitol (4 g) was stirred with 2-methoxypropene (12 mL) and *N,N*-dimethylformamide (50 mL) in the presence of toluene-*p*-sulphonic acid (40 mg) for 1 min at 0°. The mixture was then neutralised (Na_2CO_3) and worked-up as described above. Chromatography (toluene–ether, 40:1→20:1) of the syrupy product (3.8 g) on silica gel (100 g), followed by rechromatography of mixed fractions, yielded fractions *A–D*.

Fraction *A*, which was syrupy, was 1,3:4,5-di-*O*-isopropylidene-DL-ribitol (**8**; 0.72 g, 12%). ^{1}H-N.m.r. data (200 MHz, $CDCl_3$): δ 1.34, 1.35, 1.45, 1.46 (4 s, each 3 H, 2 CMe_2), 3.28 (d, 1 H, D_2O exchangeable, J 1 Hz, OH), 3.46 (t, 1 H, $J_{1a,1b} = J_{1a,2} = 8.5$ Hz, H-1a), 3.61 (dd, 1 H, J 10.3 and 9 Hz), 3.76 (ddt, 1 H, $J_{2,1a} = J_{2,3} = 8.5$, $J_{2,1b}$ 5.3, $J_{2,OH}$ 1 Hz, H-2), 3.84–3.96 (m, 2 H), and 4.03–4.16 (m, 2 H).

1,3:4,5-Di-O-isopropylidene-2-O-p-nitrobenzoyl-DL-ribitol (**9**). — A solution of **8** (1.1 g) in dry pyridine (10 mL) was treated with *p*-nitrobenzoyl chloride (2 g) at 0°, then kept overnight at room temperature. Isolation using chloroform yielded a crystalline product (1.79 g). Recrystallisation from 2-propanol gave **9** (1.42 g, 79%), m.p. 119–120°; ν_{max}^{KBr} 1720 (C=O), 1530, 1280 (NO_2), 1380, 1370 cm^{-1} (CMe_2). ^{1}H-N.m.r. data (360 MHz, $CDCl_3$): δ 1.23, 1.25, 1.39, 1.50 (4 s, each 3 H, 2 CMe_2), 3.787 (dd, 1 H, $J_{1a,1b}$ 12.34, $J_{1a,2}$ 5.48 Hz, H-1a), 3.894 (dd, 1 H, $J_{3,2}$ 8.42, $J_{3,4}$ 5.17 Hz, H-3), 3.910 (dd, 1 H, $J_{5a,4}$ 6.42, $J_{5a,5b}$ 8.51 Hz, H-5a), 4.061 (dd, 1 H, $J_{5b,4}$ 6.42 Hz, H-5b), 4.077 (dd, 1 H, $J_{1b,2}$ 4.96 Hz, H-1b), 4.153 (dt, 1 H, $J_{4,3}$ 5.17 Hz, H-4), 5.237 (dt, 1 H, H-2), 8.17–8.29 (m, 4 H, Ar).

Anal. Calc. for $C_{18}H_{23}NO_8$: C, 56.7; H, 6.0; N, 3.7. Found C, 56.3; H, 6.0; N, 3.5.

Fraction *B* was the syrupy 1,2:4,5-diacetal **4** (2.2 g, 36%), a portion of which (0.6 g) was converted conventionally, using benzoyl chloride in pyridine, into the benzoate **5** (0.45 g, 52%), m.p. 69–71°; lit.[13,23] m.p. 69–71°. The ^{1}H- and ^{13}C-n.m.r. spectra were indistinguishable from those[13] of authentic **5**.

Fraction *C* was syrupy 1,3:2,5-di-*O*-isopropylidene-DL-ribitol (**11**; 0.32 g, 5%). N.m.r. data (100 MHz, $CDCl_3$): δ 1.30–1.50 (m, 12 H, 2 CMe_2), 2.55–4.0 (m, 8 H).

The diacetal **11** (0.9 g) in dry pyridine (10 mL) was treated with *p*-nitrobenzoyl chloride (2.0 g) at 0° and then overnight at room temperature. Isolation using chloroform yielded the 1,3:2,5-di-*O*-isopropylidene-DL-ribitol (**12**; 0.9 g, 61%), m.p. 128–129° (from 2-propanol); ν_{max}^{KBr} 1720 (C=O), 1530, 1280 (NO_2), 1380, 1370 cm^{-1} (CMe_2). ^{1}H-N.m.r. data (200 MHz, $CDCl_3$): δ 1.27, 1.36, 1.42, 1.50 (4 s, each 3 H, 2 CMe_2), 3.67 (d, 1 H, $J_{5a,5b}$ 11.0 Hz, H-5a), 3.74–3.95 (m, 4 H), 4.10 (ddd. 1 H, $J_{2,1b}$ 6.3, $J_{2,1a}$ 11.3 or 10.1, $J_{2,3}$ 10.1 or 11.3 Hz, H-2), 5.32 (dt, 1 H, $J_{4,3}$ 3, $J_{4,5a}$ 0.9, $J_{4,5b}$ 3 Hz, H-4), 8.2–8.4 (m, 4 H, Ar). Mass spectrum: *m/z* 381 (M^+), 366 ($M^+ - 15$), 308 ($M^+ - 73$), 280 ($M^+ - 101$), 222 ($M^+ - 159$), and 150 ($M^+ - 231$).

Anal. Calc. for $C_{18}H_{23}NO_8$: C, 56.7; H, 6.0; N, 3.7. Found: C, 56.8; H, 6.0; N, 3.7.

Fraction *D* was the 1,4:2,3-diacetal **7**. Recrystallisation from light petroleum gave **7** (0.18 g, 3%), m.p. 101–102°; lit.[13] m.p. 105–107°. The ^{1}H- and ^{13}C-n.m.r. spectra were indistinguishable from those[13] of authentic **7**. Mass spectrum: *m/z* 232 (M^+), 217 ($M^+ - 15$), 187 ($M^+ - 45$), 157 ($M^+ - 75$), and 143 ($M^+ - 89$).

G.l.c. examination of the crude mixture of *A*, *B*, *C* and *D* prior to chromatography on silica gel revealed the presence of these four components in the ratios 4.5:13:2:1 with retention times of 13.2, 16.1, 26.3, and 28.8 min, respectively.

ACKNOWLEDGMENTS

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