Carbohydrate Research, 121 (1983) 316–323
Elsevier Science Publishers B.V., Amsterdam – Printed in The Netherlands

Note

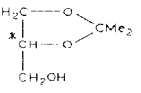
Some aspects of the reaction of glycerol with 2,2-dimethoxypropane*

GORDON J. F. CHITTENDEN
Department of Exobiology, The University, 6525 ED Nijmegen (The Netherlands)
(Received November 11th, 1982; accepted for publication, March 15th, 1983)

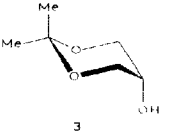
There are few substantiated examples of the formation of six-membered cyclic acetals from the reaction of ketones with acyclic polyhydric alcohols having three or more contiguous hydroxyl groups[1–4]. Certain *O*-substituted polyhydric alcohols yielded six-membered isopropylidene derivatives when alternatives were precluded[5–7]. Acetalation is usually conducted in the presence of acid catalysts and an equilibrium is established eventually, the composition of the product mixture being determined by the relative free energies of the various cyclic acetals that can be formed. The high non-bonded interactions associated with an axial alkyl group on C-2 of a 1,3-dioxane ring explains the reluctance of polyhydric alcohols to yield six-membered cyclic ketals[8]. The preferred, five-membered dioxolane ring is stabilised by a small *gem*-dimethyl effect[9] that allows greater puckering of the ring, thereby reducing the torsional strain. Thus, acid-catalysed condensation of acetone with glycerol (**1**) gives 1,2-*O*-isopropylidene-DL-glycerol (**2**) almost exclusively[10]. The corresponding 1,3-*O*-isopropylidene derivative (**3**) is formed only in trace amounts. It can be synthesised indirectly[7,11] and is also formed[12], but in low yield (2%), by the low-temperature, dilute acid-catalysed equilibration of **2**.

In continuation[13] of acetalation studies, the treatment of **1** with 2,2-dimethoxypropane under neutral conditions is now described and shown to yield a mixture of **2, 3** (in relatively high amounts compared to the normal acid-catalysed reaction), and two new acetals of acetone containing 1,2-*O*-isopropylideneglycerol residues.

1



2
*racemic



3

*Acetalation Studies, Part V. For Part IV, see ref. 13.

0008-6215/83/$ 03.00 © 1983 Elsevier Science Publishers B.V.

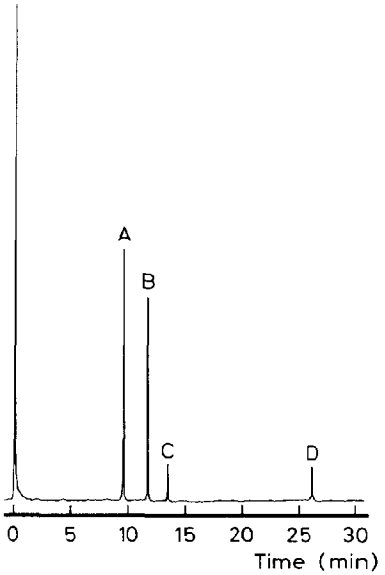
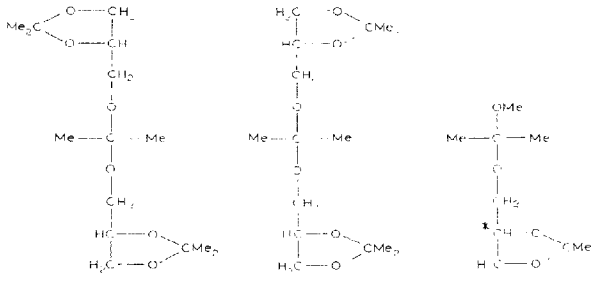


Fig. 1. Gas chromatogram of the products from the reaction of **1** with 2,2-dimethoxypropane–1,2-dimethoxyethane.

Anhydrous glycerol (**1**), when treated with a boiling mixture of 2,2-dimethoxypropane–1,2-dimethoxyethane for 72 h, gave four products, as shown by g.l.c. (Fig. 1). Peaks *B* (37%) and *C* (6%) were identified as **2** and **3**, respectively, by co-injection with authentic samples. Peaks *A* (50%) and *D* (7%) were also formed when compound **2** was treated under similar conditions and were considered to be mixed cyclic–acyclic acetals of acetone formed, presumably, by successive interchange of the methoxyl groups on 2,2-dimethoxypropane with **2**.

Treatment of **2** with one equivalent of boiling 2,2-dimethoxypropane in 1,2-dimethoxyethane gave a mixture of *A*, **2**, and *D* in the ratios 1:3:3. Fractional distillation of the crude product *in vacuo* gave 31% of *D*, the elemental analysis of which was consistent with structure **4**. The mass spectrum of *D* did not contain a peak for the molecular ion, but contained a peak at *m/z* 289 for $(M - CH_3)^+$ characteristic of *O*-isopropylidenealditols[14]. Furthermore, the presence of peaks at *m/z* 173 $(M - 101)^+$, 101, 73, 59, and 43 were consistent with structure **4**.

The ^{13}C-n.m.r. spectrum indicated *D* to be a mixture of the stereoisomers **4a** and **4b**. The signal for the acetal carbons of the 1,2-*O*-isopropylidene groups was at 109.3 p.p.m., and that for the non-acyclic acetal carbon at 100.2 p.p.m. The ring



4a (racemate, only one enantiomer shown)

4b

5 *racemic

methylene carbons gave a singlet at 75 p.p.m., and the methine carbons a singlet at 67 p.p.m., with line broadening of ~0.78 and 1.5 Hz, respectively. The exocyclic methylene carbons were not equivalent and gave singlets at 62.37 and 62.08 p.p.m. The CMe_2 groups of the cyclic isopropylidene acetals gave signals at 26.75 and 25.5 p.p.m., and the acyclic acetal a signal at 24.8 p.p.m. The ^{1}H-n.m.r. spectrum, as expected for a mixture of **4a** and **4b**, was composed of two overlapped spectra. The CMe_2 groups of the 1,2-*O*-isopropylidene groups gave characteristic[7] singlets at 1.38 and 1.42 p.p.m. The CMe_2 groups of the acyclic acetal gave a singlet at 1.36 p.p.m. The remaining protons could be assigned as follows: 3.49 (m, exocyclic methylene), 3.73 (m) and 4.05 (dd, dioxolane methylene), and 4.23 (m, dioxolane methine). The combined spectral evidence confirmed structures **4a** and **4b**.

When **2** was treated with a large excess of boiling 2,2-dimethoxypropane–1,2-dimethoxyethane, the product contained (g.l.c.) 70% of *A*, which was isolated by fractional distillation *in vacuo*. Elemental analysis was consistent with structure **5**, resulting from the exchange of only one methoxyl group on 2,2-dimethoxypropane by **2**. The mass spectrum of *A* did not contain a peak for the molecular ion, but contained a characteristic ion with *m/z* 173. Also present were peaks at *m/z* 117, 115, 101, and 73, which were in accordance[14] with the structure. This was supported further by the ^{13}C-n.m.r. spectrum, in which the signal for the quaternary carbons of the cyclic and acyclic acetals appeared at 109.3 and 100.1 p.p.m., respectively. The signal of the secondary carbon of the dioxolane ring was at 75.1 p.p.m., and those of the two methylene carbons were at 67.15 and 62.23 p.p.m. The signal for the methoxyl carbon was at 48.4 p.p.m. The CMe_2 group of the 1,2-*O*-isopropylidene residue gave signals at 26.8 and 25.6 p.p.m., whereas those of the acyclic group appeared as a singlet at 24.4 p.p.m.

The structure **5** was supported also by the ^{1}H-n.m.r. spectrum, which was a first-order, ABMXY five-spin system. A portion (3.3–4.4 p.p.m.) of the spectrum is shown in Fig. 2 ($J_{2a,1b} = J_{2a,3a} = J_{2a,3b} = 6$, $J_{1a,1b}$ 9.7, $J_{3a,3b}$ 8.1 Hz).

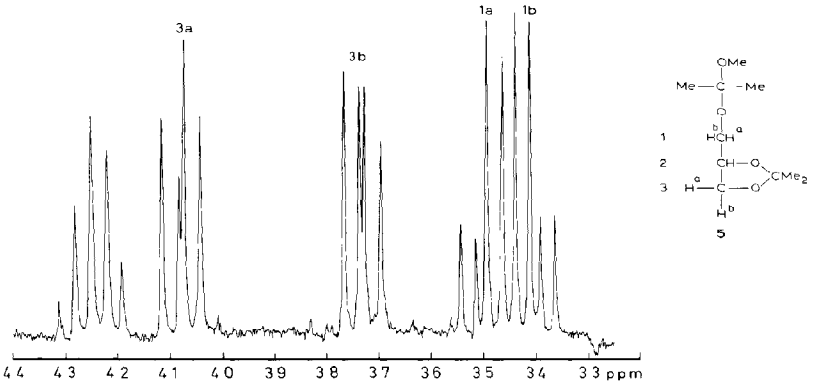


Fig. 2. P.m.r. spectrum of 2-(2,2-dimethyl-1,3-dioxolan-4-ylmethoxy)-2-methoxypropane (**5**); $CDCl_3$ solution at 200 MHz.

The MeO protons resonated as a singlet at 3.21 p.p.m., which is close to the value[15] for 2,2-dimethoxypropane. The CMe_2 group of the acyclic residue gave a singlet at 1.35 p.p.m., and those of the 1,2-*O*-isopropylidene group gave two singlets at 1.37 and 1.425 p.p.m.

G.l.c. of the products of the treatment of **4** and **5** with boiling aqueous methanol in 1,2-dimethoxyethane for 36 h revealed that only **2** was present. Treatment of the distillate from the above mixtures with *p*-nitrophenylhydrazine–acetic acid yielded acetone *p*-nitrophenylhydrazone (**6**). The distillate after similar treatment of **2** did not yield **6**.

The interchange of alkoxyl groups of acetals with primary hydroxyl groups has been noted[16,17], but secondary hydroxyl groups are unreactive[17,18] unless they are sufficiently acidic[19]. Thus, 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranose, of which HO-1 is sufficiently acidic to form salts with strong bases[20], undergoes rapid interchange with 2,2-dimethoxypropane[21]. The interchange is also temperature-dependent, as treatment of **2** with 2,2-dimethoxypropane at room temperature for 72 h did not yield **4** or **5**.

Treatment of **1** with boiling 2,2-dimethoxypropane in the absence of 1,2-dimethoxyethane gave a mixture of **2** (30%), **3** (11%), **4** (15%), and **5** (52.5%). Two other products (T 1.06, 3%; T 1.74, 2%) were presumed to be the 1,3-*O*-isopropylidene analogues of **4** and **5** because, on treatment with boiling aqueous methanol in 1,2-dimethoxyethane, these products disappeared (g.l.c.) and the proportions of **2** and **3** increased.

The reaction of hexitols with 2,2-dimethoxypropane under non-acid-catalysed conditions requires the presence of a bifunctional ether[22], but **1** appears

to be sufficiently acidic to react without assistance. The addition of a small proportion of dimethyl sulfoxide to the usual reaction mixture **1**–2,2-dimethoxypropane–1,2-dimethoxyethane increased the yield of **3** (16.5%), which was formed together with **2** (50%), **5** (33%), and a trace of **4**. The omission of 1,2-dimethoxyethane did not change the proportions of the products. The presence of **2** and **3** in this mixture was confirmed by application, in sequence, of benzyl bromide–sodium hydride, aqueous 80% acetic acid, and toluene-*p*-sulphonyl chloride–pyridine. Column chromatography then gave the known[23,24] ditosylates of 1- and 2-*O*-benzylglycerol.

When **1** was treated with boiling 2,2-dimethoxypropane–ethyl acetate, the product contained **2**–**5** in yields of 41, 10.5, 23.5, and 25%, respectively. Treatment of **1** with 2,2-dimethoxypropane–1,2-dimethoxyethane at room temperature for 72 h resulted in a reduced yield (31%) of products comprising **2** (97%) and **3** (3%). No acetal migration occurred when **2** and **3** were treated under similar reaction conditions.

Treatment of **1** with *N*,*N*-dimethylformamide–2,2-dimethoxypropane–toluene-*p*-sulphonic acid gave 91% of **2** and ~1% of **3**, proportions normally found[10,12] in the thermodynamically controlled, acid-catalysed acetonation of **1**.

The results of acetonation of glycerol under neutral conditions differ from those of the acid-catalysed reaction, in that the conditions which facilitate acetal migration and isomerisation are absent. Once a product has been formed in the absence of an acid catalyst, it will not rearrange. On elevation of the temperature (to ~80°) in such reactions, the conformer population will alter because of increased rotational–vibrational freedom and a decrease in hydrogen bonding, in turn, the rates of formation of the various products will alter and this is reflected in the increased proportion of **3** in the product mixture.

EXPERIMENTAL

T.l.c. was performed as described previously[11]. Mass spectra were recorded with a Finnigan 3100 mass spectrometer, using the direct-insertion technique. G.l.c. was performed on a Varian 3700 gas chromatograph, using a fused-silica capillary column (25 m) of CP wax 51 and a temperature programme of 4°/min from 80→170°, with helium as carrier gas at 18.5 p.s.i. (1.1 mL/min); split ratio, 1:400. Where necessary, retention times (T) and linear responses were determined with authentic samples. N.m.r. spectra were recorded with Bruker WP-60 (^{13}C) and Nicolet NT 200 (^1H at 200 MHz) spectrometers for $CDCl_3$ solutions (internal Me_4Si).

Reactions of glycerol (**1**). — *(a) With 2,2-dimethoxypropane–1,2-dimethoxyethane.* To a vigorously stirred mixture of **1** (3 g) and 1,2-dimethoxyethane (10 mL) was added 2,2-dimethoxypropane (15 mL), and the mixture was heated under reflux with continuous stirring for 72 h. The cooled solution was concentrated *in vacuo* at 35°, and a solution of the residue in ethyl acetate (60 mL) was rapidly shaken with ice–water (15 mL), dried ($NaSO_4$), and concentrated *in vacuo*. The oily residue (3.74 g) was subjected to g.l.c.

When a similar reaction mixture was stirred at room temperature for 72 h, followed by work-up in the same manner, the yield of product was 2.1 g (31%).

(b) With 2,2-dimethoxypropane–1,2-dimethoxyethane–dimethyl sulphoxide. Glycerol (**1**, 3 g) was treated as in (*a*), except that dimethyl sulphoxide (5 mL) was added to the reaction mixture (yield of product, 4.2 g).

In another experiment, 2,2-dimethoxypropane (15 mL) was added to a vigorously stirred mixture of **1** (4.6 g), 1,2-dimethoxyethane (25 mL), and dimethyl sulphoxide (10 mL), and the mixture was heated under reflux with continuous stirring for 72 h. The cooled solution was concentrated *in vacuo*, and the oily residue was stirred vigorously with 1,2-dimethoxyethane (20 mL). Methanol (20 mL) and water (10 mL) were then added and the mixture was heated under reflux with continuous stirring for 24 h.

The cooled mixture was concentrated *in vacuo* and ethanol (3 × 25 mL) was distilled *in vacuo* from the residue. To a solution of the residue in 1,2-dimethoxyethane (30 mL) was added sodium hydride (1.29 g) with rapid stirring (temperature maintained below 5°). After 40 min, the thick suspension was stirred with a solution of benzyl bromide (9.4 g) in 1,2-dimethoxyethane (20 mL) at <0°. The mixture was kept overnight at room temperature and then cooled to −10°, ice–water (10 mL) was added slowly, the resulting mixture was concentrated *in vacuo*, and a suspension of the residue in water (50 mL) was extracted with dichloromethane (3 × 50 mL). The combined extracts were washed successively with water (20 mL), 2M hydrochloric acid (20 mL), saturated aqueous sodium hydrogencarbonate (20 mL), and water (20 mL), dried (Na_2SO_4), and concentrated *in vacuo*. A solution of the crude, syrupy product in acetic acid (40 mL) was treated with water (10 mL), and the mixture was heated at 100° for 2 h. Evaporation of the solvents, followed by distillation of ethanol (3 × 25 mL) from the residue, afforded a gum (4.8 g). A solution of this product in dry pyridine (25 mL) was stirred with toluene-*p*-sulphonyl chloride (10.05 g) at room temperature for 48 h and then worked-up in the usual manner. The resulting syrup (11.3 g) was eluted from Kieselgel 60 (Merck, 240 g) with 1,2-dimethoxyethane–cyclohexane (1:1), to give, first, 2-*O*-benzylglycerol 1,3-ditoluene-*p*-sulphonate (0.76 g, 3.1%), m.p. 109–111° (from ethanol); lit.[23] m.p. 110–112°. Eluted second was 1-*O*-benzylglycerol 2,3-ditoluene-*p*-sulphonate (9.9 g, 40.5%), m.p. 60–64° (from ether); lit.[23] m.p. 65–67°; lit.[24] m.p. 60–61°.

(c) With 2,2-dimethoxypropane–ethyl acetate. Compound **1** (3 g) was treated as in (*a*) except that 1,2-dimethoxyethane (15 mL) was replaced by an equivalent volume of ethyl acetate (yield of product, 3.56 g).

(d) With 2,2-dimethoxypropane. A suspension of **1** (3 g) in 2,2-dimethoxypropane (20 mL) was heated under reflux with continuous stirring for 72 h. The cooled, homogeneous solution was worked-up as in (*a*) (yield of product, 3.82 g).

(e) With 2,2-dimethoxypropane–N,N-dimethylformamide–toluene-p-sulphonic acid. To a solution of **1** (3 g) in *N*,*N*-dimethylformamide (15 mL) were added 2,2-dimethoxypropane (15 mL) and toluene-*p*-sulphonic acid monohydrate

(25 mg). The mixture was stirred for 2 h at room temperature and then de-acidified with Amberlite IR-45 (HO^-) resin. The resin was collected and washed with methanol (3 × 20 mL), and the combined filtrate and washings were treated with triethylamine (0.05 mL) and then concentrated *in vacuo*. A solution of the oily residue in ethyl acetate (100 mL) was shaken with water (3 × 15 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The syrupy residue was distilled to give 1,2-*O*-isopropylidene-DL-glycerol (**2**; 3.91 g, 91%), b.p. 80–81°/11 mmHg, lit.[25] b.p. 80–80.5°/12 mmHg.

Reaction of (**2**) *with 2,2-dimethoxypropane–1,2-dimethoxyethane.* — A solution of **2** (10 g) in 1,2-dimethoxyethane (30 mL) was treated with 2,2-dimethoxypropane (9.3 mL, 1 equiv.), and the mixture was heated under reflux with continuous stirring for 68 h. The cooled solution was concentrated *in vacuo* at 35° and the oily residue was fractionally distilled, to give **2** (2.9 g, 29%), b.p. 52–55°/3 mmHg, and 2,2-bis(2,2-dimethyl-1,3-dioxolan-4-ylmethoxy)propane (**4**; 3.57 g, 31%), b.p. 120–122°/3 mmHg, n_D^{21} 1.4411 (Found: C, 59.2; H, 9.4. $C_{15}H_{28}O_6$ calc.: C, 59.2; H, 9.3%).

Treatment of a solution of **2** (10 g) in 1,2-dimethoxyethane (40 mL) with 2,2-dimethoxypropane (50 mL) in a similar manner gave **2** (0.94 g, 9.4%), b.p. 52–54°/3 mmHg, and 2-(2,2-dimethyl-1,3-dioxolan-4-ylmethoxy)-2-methoxypropane (**5**; 8.2 g, 53%), b.p. 69–71°/3 mmHg, n_D^{21} 1.4242 (Found: C, 58.4; H, 9.8. $C_{10}H_{20}O_4$ calc.: C, 58.8; H, 9.9%).

An intermediate fraction containing **2**, **4**, and **5** was discarded.

A solution of **5** (1.5 g) in 1,2-dimethoxyethane (10 mL) was treated with methanol (6 mL) and water (10 mL), and the mixture was heated under reflux with stirring for 36 h. The mixture was then distilled at 100° (bath), and the distillate was treated with *p*-nitrophenylhydrazine (1.0 g) and acetic acid (0.5 mL) at 50° for 30 min. Recrystallisation of the concentrated residue from ethanol gave acetone *p*-nitrophenylhydrazone (1.04 g, 74%), m.p. 146–148°; lit.[26] m.p. 149°.

Treatment of **4** in a similar manner yielded the same product (68%), m.p. 147–149°.

ACKNOWLEDGMENTS

The author thanks Dr. A. C. Richardson (Queen Elizabeth College, University of London) for determining the ^{13}C- and ^1H-n.m.r. spectra, and Coen Hofmans for technical assistance.

REFERENCES

1 A. B. Foster, M. H. Randall and J. M. Webber, *J. Chem. Soc.*, (1965) 3388–3394.
2 J. Kuszmann, P. Sohár, G. Horváth, E. Tomori, and M. Idel, *Carbohydr. Res.*, 79 (1980) 243–253.
3 J. G. Buchanan, A. R. Edgar, D. I. Rawson, P. Shahidi and R. H. Wightman, *Carbohydr. Res.*, 100 (1982) 75–86.
4 T. van Es, *Carbohydr. Res.*, 32 (1974) 370–374.

5 L. VON VARGHA, *Ber.*, 68 (1935) 18–24, 1377–1384.
6 D. G. LANCE AND J. K. N. JONES, *Can. J. Chem.*, 45 (1967) 1533–1538.
7 N. BAGGETT, K. W. BUCK, A. B. FOSTER, R. JEFFERIS, B. H. REES, AND J. M. WEBBER, *J. Chem. Soc.*, (1965) 3382–3388.
8 H. C. BROWN, J. H. BREWSTER, AND H. SCHECHTER, *J. Am. Chem. Soc.*, 76 (1954) 467–474.
9 K. I. INGOLD AND J. F. THORPE, *J. Chem. Soc.*, (1928) 1318–1321.
10 H. HIBBERT AND J. G. MORAZAIN, *Can. J. Res.*, 2 (1930) 35–41, 214–216.
11 G. J. F. CHITTENDEN, *Carbohydr. Res.*, 91 (1981) 85–88.
12 G. AKSNES, P. ALBRIKTSEN, AND P. JUVVIK, *Acta Chem. Scand.*, 19 (1965) 920–930.
13 G. J. F. CHITTENDEN, *Carbohydr. Res.*, 108 (1982) 81–87.
14 N. S. WULFSON, O. S. CHIZHOV, AND L. S. GOLOVKINA, *J. Org. Chem. USSR*, 4 (1968) 724–728.
15 V. A. STOUTE AND M. A. WINNIK, *Can. J. Chem.*, 53 (1975) 3503–3512.
16 M. E. EVANS, F. W. PARRISH, AND L. LONG, JR., *Carbohydr. Res.*, 3 (1967) 453–462.
17 A. HAMPTON, *J. Am. Chem. Soc.*, 87 (1965) 4654–4655.
18 W. L. HOWARD AND N. B. LORETTE, *J. Org. Chem.*, 25 (1960) 525–530.
19 C. H. LEE, *Carbohydr. Res.*, 22 (1972) 230–232.
20 K. FREUDENBERG AND A. WOLF, *Ber.*, 58 (1925) 300–303.
21 G. J. F. CHITTENDEN, unpublished results.
22 G. J. F. CHITTENDEN, *Carbohydr. Res.*, 87 (1980) 219–226.
23 A. J. SLOTBOOM, G. H. DE HAAS, AND L. L. M. VAN DEENEN, *Recl. Trav. Chim. Pays-Bas*, 82 (1963) 469–486.
24 A. K. M. ANISUZZAMAN AND L. N. OWEN, *J. Chem. Soc., C*, (1967) 1021–1026.
25 E. BAER AND H. O. L. FISCHER, *J. Am. Chem. Soc.*, 61 (1939) 761–765.
26 I. HEILBRON (Ed), *Dictionary of Organic Compounds*, Vol. 1, 4th edn., Eyre and Spottiswoode, London, 1965, p. 11.