Note

Selective hydrolysis of the C–Br linkage in 1,2,3-tri-*O*-benzoyl-4-bromo-4-deoxy-L-erythritol

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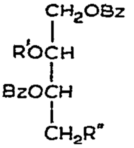
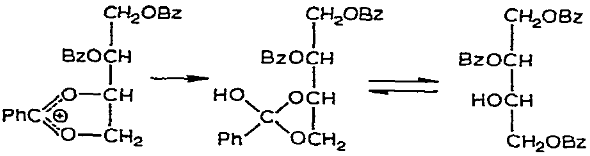
In the course of developing a new synthesis for 2-deoxy-D-*erythro*-pentose, the displacement of bromide from 1,2,3-tri-*O*-benzoyl-4-bromo-4-deoxy-L-erythritol (**1**) by cyanide has been attempted in various solvents[1]. In *N,N*-dimethylformamide, products free of nitrogen and bromine were isolated, and in this communication, the identification of these products is described.

On boiling a solution of **1** in *N,N*-dimethylformamide for 1 h, the mixture became acidic, and 1,2,3-tri-*O*-benzoyl-L-erythritol (**3**), m.p. 135–136°, $[\alpha]_D^{29}$ $+51°$, was isolated (11%) and identified on the basis of i.r. spectral and elemental analyses, and on a comparison of physical constants with those[2] (m.p. 135–136°, $[\alpha]_D^{25}$ $-56.2°$) for 1,2,3-tri-*O*-benzoyl-D-erythritol. Benzoylation of **3** gave tetra-*O*-benzoylerythritol (**2**).



1 R' = Bz, R'' = Br
2 R' = Bz, R'' = OBz
3 R' = Bz, R'' = OH
6 R' = PhCH₂, R'' = OBz



7 **8** **4**, L-form

When **1** was heated in *N,N*-dimethylformamide for several hours, monitoring by t.l.c. showed the conversion of the initial product **3** into another product **4**; **4** was a tri-*O*-benzoyltetritol, m.p. 108°, which retained the *erythro* configuration since benzoylation gave **2**.

Reaction of **4** with benzyl bromide in the presence of silver oxide yielded an optically inactive tri-*O*-benzoyl-*O*-benzylerythritol (**5**). For comparison purposes, 1,3,4-tri-*O*-benzoyl-2-*O*-benzyl-L-erythritol (**6**), $[\alpha]_D^{24}$ $+22°$, was prepared by acid hydrolysis of 2-*O*-benzyl-1,3-*O*-ethylidene-L-erythritol[3] followed by benzoylation. The benzyl ethers **5** and **6** were indistinguishable by i.r. spectroscopy, mixture m.p.,

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and t.l.c., but from the difference in their optical activities it was clear that **5** was 1,2,4-tri-*O*-benzoyl-3-*O*-benzyl-DL-erythritol, which must be a racemic, solid solution of **6** and its enantiomorph, since **5** and **6** melt at 97° separately and in admixture. It follows that **4** is 1,2,4-tri-*O*-benzoyl-DL-erythritol. Ohle and Melkonian[6] assigned structure **4** to an optically inactive tri-*O*-benzoylerythritol, m.p. 108–108.5°, obtained from erythritol by partial benzoylation; their assignment is herewith confirmed.

Compound **3** was not affected by boiling *N,N*-dimethylformamide, but when an equimolar quantity of hydrogen bromide was added (as is formed during the hydrolysis of **1**), the sole product was **4**.

The source of water for the hydrolysis **1**→**3** is, presumably, trace amounts in the *N,N*-dimethylformamide. The addition of water had no effect on the reaction. The reaction mixture becomes acidic due to the formation of hydrogen bromide, and it is unlikely that free hydroxide anion acts as a nucleophile in the formation of **3**. Since *N,N*-dimethylformamide accepts hydrogen bonds readily, it would strongly bond a hydrogen atom of the water molecule, thereby enhancing the nucleophilicity of the hydroxyl group for direct displacement of bromide (mechanism *A*) (*cf.* Refs. 5 and 6).

Alternatively (mechanism *B*), displacement of bromide by the neighbouring benzoate group would give the cation **7** which could then rearrange *via* the ortho-acid **8** to give **3** or the L form of **4**. That **3** is formed initially and racemic **4** is the major product on prolonged heating would not preclude this mechanism if **3** were assumed to be the kinetic product of the rearrangement of **8**, and **4** (L form) the thermodynamic product.

The benzoyl migration **3**→**4** is acid catalysed, and there is no change in configuration, in keeping with the $A_{AC}2$ mechanism for ester exchange. The transformation constitutes a case of a racemisation mechanism that requires no inversion of configuration and provides a further example of limitations[6,7] to the use of *N,N*-dimethylformamide as a reaction medium.

EXPERIMENTAL

After azeotropic distillation of added benzene, *N,N*-dimethylformamide was stored over alumina and vacuum distilled before use. Pyridine was dried with potassium hydroxide. Light petroleum refers to the 60–80° fraction, unless otherwise stated. Benzene solutions were dried over magnesium sulphate. Evaporations were carried out under vacuum. Melting points were determined in a Buchi oil-bath apparatus (Tottoli). Optical rotations were determined for chloroform solutions with a Bellingham polarimeter Model A and 1-dm cells. Reaction mixtures were stirred magnetically. Elemental analyses were carried out by the Microanalysis Laboratory of the Weizman Institute of Science, Rehovot, Israel. Infrared spectra were obtained with a Perkin–Elmer grating spectrophotometer, Model 337. T.l.c. was performed on 0.3-mm layers of Camag Silica Gel D-5 with ethyl acetate–cyclohexane (1:1), and iodine vapour for visualisation.

*1,2,4-Tri-O-benzoyl-*DL*-erythritol* (**4**). — (*a*) A solution of **1** (4 g, 8 mmoles) in *N,N*-dimethylformamide (60 ml) was refluxed for 6 h. The clear, acidic (litmus paper) reaction mixture, which did not contain **1** (t.l.c.), was diluted with benzene (120 ml), washed with water, dried, and concentrated. Recrystallisation of the bromine-free product from benzene (25 ml) gave **4** (1.7 g, 49%), m.p. 108°, $[\alpha]_D^{26}$ ~0° (*c* 3.5), R_F 0.5; i.r. data (Nujol): 3440 (HO), 1715, 1277, and 1118 cm^{-1} (benzoate).

Anal. Calc. for $C_{25}H_{22}O_7$ (434): C, 69.11; H, 5.10. Found: C, 69.33; H, 5.04.

A solution of **4** (174 mg, 0.4 mmole) in pyridine (1 ml) was treated with benzoyl chloride (0.1 ml, 0.9 mmole). After 18 h, the reaction mixture was poured into water. The crystals of **2** that separated were filtered off and washed with water (210 mg, 98.5%); m.p. 188–188.5°, mixture m.p. with authentic[4] **2** 189–190° (*cf.* tetra-*O*-benzoyl-L-threitol[8] m.p. 97°).

(*b*) A solution of **3** (601 mg, 1.38 mmoles) and 48% hydrobromic acid (0.157 ml, 1.39 mmoles of hydrogen bromide, 6.8 mmoles of water) in *N,N*-dimethylformamide (15 ml) was refluxed for 4 h. The cooled solution was diluted with benzene (30 ml) and washed with water (4 × 15 ml). The benzene layer was dried and concentrated to a small volume. Addition of light petroleum (b.p. 40–60°) yielded crystals (384 mg, 64%), m.p. 97°, elevated to 99–102° on recrystallisation and unchanged on admixture with **4**. No reaction occurred when the hydrobromic acid was omitted.

*1,2,4-Tri-O-benzoyl-3-O-benzyl-*DL*-erythritol* (**5**). — Benzylation was performed as described by Klemer[9]. To a solution of **4** (1.3 g, 3 mmoles) in benzene (15 ml, dried over sodium), there were added silver oxide (2.8 g, 12 mmoles) and benzyl bromide (2.24 ml, 18.9 mmoles). The reaction mixture was stirred for 9 days at ambient temperature in the dark. Inorganic salts were removed by filtration and washed with chloroform. The combined filtrates were concentrated to a syrup which crystallised on storage at −20° under light petroleum. The product was extracted with a little benzene, and the residue was crystallised from methanol to give unchanged **4** (150 mg, 12%), m.p. 106°. The benzene extract (free of **4**, t.l.c.) was passed through an alumina column (9 × 155 mm) with light petroleum to give **5** (300 mg, 19%), m.p. 87–89° (from methanol). Two further crystallisations from benzene–light petroleum gave material having m.p. 97°, $[\alpha]_D^{26}$ ~0° (*c* 0.6); R_F 0.61; i.r. data (KBr): 1720, 1267, 1110 cm^{-1} (benzoate).

Anal. Calc. for $C_{32}H_{28}O_7$ (525): C, 73.27; H, 5.38. Found: C, 73.41; H, 5.38.

*1,3,4-Tri-O-benzoyl-2-O-benzyl-*L*-erythritol* (**6**). — A solution of 2-*O*-benzyl-1,3-*O*-ethylidene-L-erythritol[3] (1.40 g, 5.9 mmoles) and 2.5M sulphuric acid (10 ml) in ethanol (25 ml) was heated in an oil bath (90°) for 2 h with suction of air through the solution. T.l.c. then showed the absence of starting material and the appearance of a product, which reacted as an alditol with the periodate–benzidine spray[10]. Sodium carbonate (10 g) was added to the cooled solution, which was then stirred until alkaline to litmus. Inorganic salts were removed by filtration and washed with ethanol. The combined filtrates were concentrated to a syrup that was dissolved in pyridine (31 ml). Benzoyl chloride (3.1 ml, 26.5 mmoles) was added, and the next day the reaction mixture was poured into water to yield crystals that were dissolved in benzene. After the usual washings with aqueous acid and alkali, the benzene solution was dried and concentrated to a solid that was crystallised from ethanol; m.p. 98° (2.6 g, 84%). A further crystallisation from ethanol and two recrystallisations from benzene–light petroleum yielded compound **6**, m.p. 97–97.5°; mixture m.p. with **5** 97°; R_F 0.61; $[\alpha]_D^{24}$ +22° (*c* 1); i.r. data (KBr) 1720, 1270, and 1107 cm^{-1} (benzoate).

Anal. Calc. for $C_{32}H_{28}O_7$ (525): C, 73.27; H, 5.38. Found: C, 73.49; H, 5.14.

*1,2,3-Tri-*O*-benzoyl-*L*-erythritol* (**3**). — A solution of **1** (1 g, 2 mmoles) in *N,N*-dimethylformamide (20 ml) was refluxed for 1.5 h. The reaction mixture was worked up as described in (*a*) above. Two recrystallisations from benzene–light petroleum yielded **3** (95 mg, 11%), m.p. 135–136°; mixture m.p. with **4** 100°; R_F 0.46; $[\alpha]_D^{29}$ +51° (*c* 1); i.r. data (Nujol) 3420 weak (hydroxyl), 1720, 1250, and 1115 cm^{-1} (benzoate); lit.[2] values for the enantiomorph: m.p. 135–136°, $[\alpha]_D^{25}$ −56.2° (*c* 5, chloroform).

Anal. Calc. for $C_{25}H_{22}O_7$ (434): C, 69.11; H, 5.10. Found: C, 69.12; H, 5.13.

The same product was obtained when the reaction was performed with the addition of water (0.3% in *N,N*-dimethylformamide).

Benzoylation of **3** (50 mg) was performed as described for **4**, yielding **2** (59 mg, 96%), m.p. 185°; mixture m.p. with authentic[4] **2**, 188–189°.

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REFERENCES

1 I. Ziderman and E. Dimant, *J. Org. Chem.*, 32 (1967) 1267.
2 D. C. MacDonald, H. O. L. Fischer, and C. E. Ballou, *J. Amer. Chem. Soc.*, 78 (1956) 3720.
3 A. Kampf, A. Felsenstein, and E. Dimant, *Carbohyd. Res.*, 6 (1968) 22.
4 H. Ohle and G. A. Melkonian, *Ber.*, 74B (1941) 291.
5 E. Tommila, *Acta Chem. Scand.*, 20 (1966) 923.
6 N. Kornblum and R. K. Blackwood, *J. Amer. Chem. Soc.*, 78 (1956) 4037.
7 S. J. Angyal and T. S. Stewart, *Proc. Chem. Soc.*, (1964) 331.
8 P. W. Kent, K. R. Wood, and V. A. Welch, *J. Chem. Soc.*, (1964) 2493.
9 A. Klemer, *Ber.*, 96 (1963) 634.
10 D. Waldi, in E. Stahl (Ed.), *Thin Layer Chromatography*, Springer-Verlag, Berlin, 1965, pp. 486–487.