Note

Selective action of acetylating agents on 1-amino-1-deoxy-D-erythritol and its derivatives

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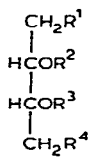
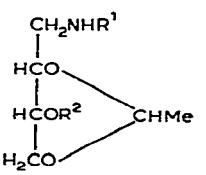
Per-*O*-substituted derivatives of 1-amino-1-deoxy-D-erythritol (**1**) were required for the extension of earlier work[1]. In order to avoid *N*-acylation during esterification of **1**, the basicity of the amino group may be decreased by temporary derivatisation with benzyloxycarbonyl chloride or, alternatively, by protonation[1,8] with a strong acid. Thus, the hydrobromide of the tribenzoate of **1** was obtained by treating 2,3,4-tri-*O*-benzoyl-1-(benzyloxycarbonyl)amino-1-deoxy-D-erythritol[1] with hydrogen bromide. However, benzoylation of the toluene-*p*-sulphonic acid salt of **1** in pyridine resulted[2] in both *N*- and *O*-benzoylation. We now describe an extension of this work to the acetyl analogues, where different behaviour was found.

Treatment with acetic anhydride–pyridine converted 1-(benzyloxycarbonyl)-amino-1-deoxy-D-erythritol[1] into the triacetate **2**, which reacted with hydrogen bromide in glacial acetic acid to form 2,3-di-*O*-acetyl-1-amino-4-bromo-1,4-dideoxy-D-erythritol hydrobromide (**3**). The structure of **3** was confirmed by its conversion into 2,3-di-*O*-acetyl-1,4-dibromo-1,4-dideoxyerythritol (**4**) on treatment with nitrosyl bromide. Replacement of a primary acetoxyl group by bromine also occurs when hydrogen bromide reacts with glycerol triacetate[3] or with D-glucose penta-acetate[4]. This lability of the acetoxyl group contrasts with the stability of the primary benzoyloxy group in the benzoate analogue of **2** in the presence of hydrogen bromide[1].



1 $R^1 = NH_2$; $R^2 = R^3 = H$; $R^4 = OH$
2 $R^1 = NHCO_2CH_2Ph$; $R^2 = R^3 = Ac$; $R^4 = OAc$
3 $R^1 = NH_3Br$; $R^2 = R^3 = Ac$; $R^4 = Br$
4 $R^1 = R^4 = Br$; $R^2 = R^3 = Ac$
5 $R^1 = NH_3SO_3C_6H_4Me(p)$; $R^2 = R^3 = Ac$; $R^4 = OAc$



6 $R^1 = R^2 = H$
7 $R^1 = Ac$; $R^2 = H$
8 $R^1 = R^2 = Bz$

In an examination of the alternative approach, *O*-acetylation of a protonated form of **1** was explored. Although acetyl bromide acts as a selective *O*-acetylating

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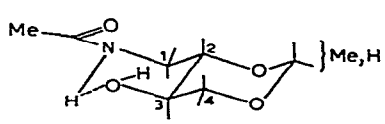
agent for 2-amino-2-deoxy-D-glucose hydrochloride[5], it reacted with the hydrobromide or toluene-*p*-sulphonic acid salt of **1** to form **3**. This may also involve bromine displacement of an initially formed primary acetoxyl group. Eventually, the required 2,3,4-tri-*O*-acetyl-1-amino-1-deoxy-D-erythritol toluene-*p*-sulphonic acid salt (**5**) was obtained by dissolving the toluene-*p*-sulphonic acid salt of **1** in hot acetic anhydride. After deamination of **5**, it was possible to isolate pure erythritol.

The necessity for protonation of the amino group with a strong acid in order to avoid *N*-acetylation was demonstrated by the action of hot acetic anhydride on 1-amino-1-deoxy-2,4-*O*-ethylidene-D-erythritol (**6**) which gave 1-acetamido-1-deoxy-2,4-*O*-ethylidene-D-erythritol (**7**).

An attempt to achieve peracetylation of **6** by treatment with cold acetic anhydride–pyridine also gave **7**. However, benzoyl chloride–pyridine converted **6** into the peracylated 1-benzamido-3-*O*-benzoyl-1-deoxy-2,4-*O*-ethylidene-D-erythritol (**8**). Compound **6** was further characterized as its oxalic acid salt.

The resistance of the hydroxyl group in **7** to acetylation under experimental conditions that cause per-*O*-acetylation of the toluene-*p*-sulphonic acid salt of **1**, as well as under pyridine catalysis, is apparently anomalous. Selective esterification of certain cyclic carbohydrates has been ascribed[6] to the formation of intramolecular hydrogen bonds that could enhance[7] the nucleophilicity of hydroxyl groups. The present case of a non-reactive hydroxyl group may be accounted for by a lowered nucleophilicity of the hydroxyl oxygen atom which could be achieved by hydrogen-bond acceptance.

A Dreiding model shows that **7** could adopt a chair conformation having the bulky substituents at C-2 and C-3 oriented equatorially. The amide linkage was assigned the *trans* configuration as expected for a non-cyclic, amide structure, and as indicated[8] by the presence of an amide II band in the i.r. spectrum. By rotation about the exocyclic bonds, it was found that the nearest approach of N to O-3 was 2.4 Å, which is well within the distance[9] for an N-H...O hydrogen bridge. Formation of this hydrogen bond would involve chelation to a puckered, six-membered ring in a "quasi-chair" conformation **9**, which could contribute to the stabilisation of **7** to acetylation by strengthening the hydrogen bond and consequently diminishing the nucleophilicity of O-3. The i.r. absorption frequencies for **7** in chloroform solution indicate considerable hydrogen-bonding of the functional groups.



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EXPERIMENTAL

Pyridine was dried over potassium hydroxide. Light petroleum (b.p. 60–80°) was used. Evaporations were performed *in vacuo*. Benzene solutions of acylation

products prepared in pyridine were washed twice with hydrochloric acid (4%), with water, with 4% aqueous sodium hydrogen carbonate, and finally with water. T.l.c. was performed on Camag Silica Gel D-5 (development distance 10 cm, unless otherwise stated) and descending paper chromatography on Whatman No. 1 paper, using (*a*) ethyl acetate–cyclohexane (1:1), or (*b*) butyl alcohol–ethanol–water[10] (9:1:10); detection was by (*c*) iodine vapour, (*d*) ninhydrin[11], and (*e*) naphthoresorcinol–phosphoric acid[12]. Optical rotations were obtained with a Bellingham polarimeter Model A by using 1-dm cells. I.r. spectra were determined with a Perkin–Elmer grating spectrophotometer Model 337, for chloroform solutions (1.2%) with a pathlength of 0.5 mm. The mass spectrum was obtained on an Atlas CH4 spectrometer. Melting points were determined in a Buchi oil-bath apparatus.

2,3,4-Tri-O-acetyl-1-(benzyloxycarbonyl)amino-1-deoxy-D-erythritol (**2**). — Acetic anhydride (42.5 ml, 0.45 mole) was added dropwise to a cooled and stirred solution of 1-(benzyloxycarbonyl)amino-1-deoxy-D-erythritol[1] (25.5 g, 0.1 mole) in pyridine (250 ml). After 18 h, most of the pyridine was evaporated, and the concentrate was poured into water (2 l). The crystals that separated were filtered off and dissolved in benzene. This solution was washed, dried ($CaCl_2$), and concentrated to a syrup, which was crystallised from ethanol (75 ml) to give **2** (29.7 g), m.p. 76.5°. A second crop was obtained from the mother liquor; m.p. 76° (2.3 g; total yield 85%). Treatment with Norit in chloroform, followed by two recrystallisations from chloroform–light petroleum and a final recrystallisation from ethanol, yielded **2**, m.p. 76°, $[\alpha]_D$ *ca.* 0° (*c* 11, chloroform), R_F 0.36 [t.l.c., (*a*), (*c*)].

Anal. Calc. for $C_{18}H_{23}NO_8$ (381): C, 56.68; H, 6.08; N, 3.67. Found: C, 56.93; H, 6.22; N, 3.87.

2,3-Di-O-acetyl-1-amino-4-bromo-1,4-dideoxy-D-erythritol hydrobromide (**3**). — (*a*) Acetyl bromide (12 ml, 0.16 mole) was added dropwise to a stirred suspension of 1-amino-1-deoxy-D-erythritol toluene-*p*-sulphonic acid salt[13] (8.79 g, 0.03 mole) in glacial acetic acid (40 ml); the salt dissolved immediately. Ether (200 ml, dried over sodium) was then added, and the mixture was stored for 18 h in a refrigerator. The product (5 g), m.p. 164–166°, was then filtered off. A second crop (4.2 g; total yield, 88%) was obtained by the addition of more ether. Two recrystallisations of the first crop from methanol–ether raised the m.p. to 168°. However, crystals of m.p. 171–172° were obtained by adding more ether to the final mother liquor, and they were recrystallised from the same solvents to give material having m.p. 176°, $[\alpha]_D^{25}$ −11° (*c* 1, methanol); R_F [(*b*), (*d*)] 0.33 (t.l.c.) and 0.40 (paper); i.r. (KBr) data: 2920 (NH_3^+ stretch), 2680 (NH_3^+), 2600 (NH_3^+), 1955 (NH_3^+), 1745 (C=O), 1600 (NH_3^+), 1380 (CH_3), 1237 (C–O), 1216 (CH_2Br), and 1040 cm^{-1} (O–CH).

Anal. Calc. for $C_8H_{15}Br_2NO_4$ (349): C, 27.53; H, 4.22. Found: C, 27.58; H, 4.39.

(*b*) A solution of **6**[13] (4.4 g, 0.03 mole) in hydrobromic acid (20%, 220 ml) was boiled for 30 min with bubbling of nitrogen through the solution, and then concentrated. The concentrate was treated with acetyl bromide (8.9 ml, 0.12 mole), and the product was isolated as detailed in (*a*); m.p. 162–165°, R_F [(*b*), (*d*)] 0.40 (paper).

(*c*) A solution of **2** (3.8 g, 0.01 mole) in hydrogen bromide-saturated glacial acetic acid (15 ml) was kept for 2 days at room temperature. The product, isolated as described in (*a*), had m.p. 162–165°, R_F [(*b*), (*d*)] 0.40 (paper). The product contained halide anion (silver nitrate).

2,3-Di-O-acetyl-1,4-dibromo-1,4-dideoxyerythritol (**4**). — Sodium nitrite (0.8 g, 12 mmoles) was added portionwise to a stirred and cooled solution of **3** (1 g, 2.9 mmoles) in hydrogen bromide-saturated acetic acid (9 ml). The next day, the reaction mixture was poured into water, and the deposit formed was crystallised from methanol to give **4**, m.p. 136.5–137°; lit.[14] m.p. 137°; $[\alpha]_D$ *ca.* 0° (*c* 2.3, chloroform).

2,3,4-Tri-O-acetyl-1-amino-1-deoxy-D-erythritol toluene-p-sulphonic acid salt (**5**). — The toluene-*p*-sulphonic acid salt[13] of **1** (20.5 g, 0.07 mole) was dissolved in acetic anhydride (70 ml, 0.74 mole) by gentle heating. On spontaneous cooling, crystals appeared. The next day methanol (28 ml) was added to decompose excess of anhydride, and, after a further 18 h, the solvents were evaporated and the residue was crystallised from methanol–ether to give **5** (6.2 g, 21%), m.p. 162–163°; starting material was recovered from the mother liquor. Recrystallisation from the same solvents yielded material having m.p. 163–163.5°, $[\alpha]_D^{24}$ −9.7° (*c* 0.8, methanol); i.r. (KBr) data: 3010–2965 (NH_3^+), 1750 (C=O), 1600 (NH_3^+), 1495 (NH_3^+), 1370 (acetate CH_3), 1215 (C–O, SO_3), 1190 (SO_3), 1128 (S-ring), 1040 (O–CH_2, SO_3), 1014 (ring), 819 (*p*-substituted ring), 691, and 573 cm^{-1}.

Anal. Calc. for $C_{17}H_{25}NO_9S$ (419): C, 48.80; H, 6.01; S, 7.65. Found: C, 48.80; H, 6.01; S, 7.54.

To a cooled solution of **5** (4.2 g, 0.01 mole), glacial acetic acid (4.8 ml, 0.08 mole), and sodium bromide (3.09 g, 0.03 mole) in water (40 ml), a solution of sodium nitrite (1.38 g, 0.02 mole) in water (10 ml) was added dropwise during 1 h. After a further 45 min, gas evolution ceased, and the reaction mixture was extracted with chloroform. The combined extracts were washed with water, aqueous sodium hydrogen carbonate (8%), and water, dried ($CaCl_2$), and concentrated to a syrup that was then dissolved in ethyl acetate. Light petroleum was added to turbidity, and the mixture was stored for several months at ambient temperature. The resulting crystals had m.p. and mixture m.p. with authentic erythritol 119°.

Bis-(1-amino-1-deoxy-2,4-O-ethylidene-D-erythritol) oxalic acid salt. — An ethereal solution of oxalic acid was added to an ethanolic solution of **6**[13]. The resulting salt, recrystallised from methanol–ether, had m.p. 209–210°, $[\alpha]_D^{25}$ −48.5° (*c* 0.8, water); violet colour with spray (*d*).

Anal. Calc. for $C_{14}H_{28}N_2O_{10}$ (384): C, 43.74; H, 7.34; N, 7.29. Found: C, 43.50; H, 7.60; N, 7.59.

1-Acetamido-1-deoxy-2,4-O-ethylidene-D-erythritol (**7**). — (*a*) Dissolution of **6**[13] (7.35 g, 0.05 mole) in acetic anhydride (19 ml, 0.2 mole) was effected by gentle heating. After 6.5 h at ambient temperature, t.l.c. (*b*) showed the absence of starting material (*d*) and the appearance of one product (*c*). Methanol was added, and, the next day, the solution was concentrated, and the residue was crystallised from methanol–ether to give **7** (5.15 g, 55%), m.p. 157–158°, $[\alpha]_D^{24}$ −47° (*c* 1, methanol);

R_F 0.65 (t.l.c., developed (*b*) to 5.4 cm, (*c*), (*e*)); i.r. data: ($CHCl_3$) 3430 with shoulder at 3330 (OH and NH), 1660 (C=O), 1520 (CNH), 1370, and 1390 cm^{-1} (identical with the frequencies for 2,3-diacetamido-4-hydroxypentane[15]); (Nujol or KBr) 3400 and 3230 (OH and NH), 3080 (CNH overtone), 1615 (C=O), and 1585 cm^{-1} (CNH) (frequency shifts characteristic for transformation of an amido-alcohol to a more-associated form in the solid state[16]).

The material showed no inflection for acetic acid on potentiometric titration. It did not react with ninhydrin, nor did it release nitrogen with nitrous acid (Van Slyke determination).

Anal. Calc. for $C_6H_{12}NO_3(CH_3CO)$ (189): C, 50.78; H, 7.99; N, 7.40; acetyl, 7.9. Found: C, 50.64; H, 7.76; N, 7.40; acetyl, 7.6.

The mass spectrum contained a strong peak for $(M+1)^+$ at 190, (*cf.* Ref. 17).

(*b*) Acetic anhydride (14.3 ml, 0.15 mole) was added dropwise to a solution of **6**[13] (7.35 g, 0.05 mole) in pyridine (70 ml). The next day, water was added, and the solution was concentrated. Traces of pyridine were removed by azeotropic distillation with water, and the water by azeotropic distillation with benzene. The R_F of this crude product was identical with that of **7** prepared in (*a*). A methanolic solution of the residue was treated with Norit, ether was added, and the mixture was cooled to give **7** (2.4 g, 25%), m.p. 156.5–157°, mixture m.p. with sample (*a*) 157–157.5°; i.r. (Nujol) identical with sample (*a*).

*1-Benzamido-3-*O*-benzoyl-1-deoxy-2,4-*O*-ethylidene-*D*-erythritol* (**8**). — Benzoyl chloride (18 ml, 0.15 mole) was added dropwise to a cooled and stirred solution of **6**[13] (7.35 g, 0.05 mole) in pyridine (70 ml). The next day, water (3 ml) was added, most of the pyridine was evaporated, and the concentrate was poured into iced water (300 ml). A benzene solution (80 ml) of the precipitate obtained was washed, dried ($MgSO_4$), boiled twice with Norit, and concentrated. Crystallisation of the residue from benzene–light petroleum gave a product (7 g, 40%) having m.p. 131°. Further treatment with Norit and two recrystallisations from the same solvents gave **8**, m.p. 131–132°, $[\alpha]_D^{29}$ −77.5° (*c* 1, chloroform); i.r. data: ($CHCl_3$) 3435 (NH), 2975, 2855, 1722 (benzoate C=O), 1670 (amide C=O), 1515 (CNH), 1310 (CNH), 1260 (benzoate C–O), and 1113 cm^{-1} (O–CH); (Nujol) 3300 (NH), 1715 (benzoate C=O), 1630 (amide C=O), 1530 (CNH), 1314 (CNH), 1260 (benzoate C–O), 1136 and 1120 cm^{-1} (O–CH).

Anal. Calc. for $C_{20}H_{21}NO_5$ (355): C, 67.59; H, 5.96; N, 3.94. Found: C, 67.65; H, 5.97; N, 3.96.

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