Carbohydrate Research, 106 (1982) 239–245
Elsevier Scientific Publishing Company, Amsterdam – Printed in The Netherlands

Note

The allyl and benzyl glycosides of D-erythrose

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(Received October 9th, 1981; accepted for publication, December 10th, 1981)

D-Erythrose (**1**), first described by Wohl[1], has been prepared by a variety of methods. Perhaps the most commonly used procedure[2] involves the hydrolysis of 2,4-*O*-ethylidene-D-erythrose (**2**), a compound that has also been used to prepare derivatives of **1** and as an intermediate for the synthesis of higher sugars[3]. Despite the extensive literature concerning the preparation of **1** and the chemistry of **2**, the reactivity of **1**, itself, has received scant attention. Glycosidation studies, for example, have been limited to the preparation of the methyl furanosides[4–6].

A recent program at this laboratory concerning an investigation of the organoleptic properties of various sugars and derived compounds has included an interest in **1** and its compounds. For the preparation of derivatives of D-erythrofuranose bearing acid- or base-labile substituents at C-2 and C-3, the allyl and benzyl erythrofuranosides seemed to be suitable starting compounds, as benzyl and allyl ethers may be cleaved under neutral conditions. Hydrogenolysis readily cleaves benzyl glycosides[7], and Gigg and his associates have shown that the isomerizing step of deallylation may be effected by a rhodium catalyst[8,9]. Subsequent cleavage of the resulting isopropenyl group is then achieved with mercury salts[10,11].

Glycosidation of **1** with allyl alcohol–hydrogen chloride gave the expected glycosidic mixture, which was fractionally distilled *in vacuo* to give the two syrupy, allyl glycosides in 10:1 ($\beta:\alpha$) ratio. The β glycoside (**3**) was purified by conversion into the crystalline dibenzoate (**7**) followed by saponification and distillation *in vacuo*. The α glycoside (**5**) was characterized as its crystalline di-*p*-nitrobenzoate (**6**).

When glycoside **3** was esterified with one equivalent of *p*-nitrobenzoyl chloride in pyridine, the 3-*p*-nitrobenzoate (**4**) was obtained. Its facile preparation in good yield constitutes a route to the preparation of 2-*O*-substituted derivatives of **1**. The ester group was assigned at C-3 by n.m.r. spectroscopy.

Glycosidation of **1** with benzyl alcohol–benzaldehyde–hydrogen chloride gave the expected pair of anomeric benzyl glycosides and, in addition, a mixture of the *S* and *R* acetal isomers of benzyl 2,3-*O*-benzylidene-β-D-erythroside. Separation of the benzyl α,β-D-erythroside mixture was effected *via* *p*-nitrobenzoylation. Fractional

0008-6215/82/0000–0000/S 02.75,

crystallization, assisted by silica-gel chromatography, effected quantitative separation of the two di-*p*-nitrobenzoates. The separated esters were obtained in a ratio of 10:1 ($\beta:\alpha$). Saponification gave the pure glycosides. Benzyl β-D-erythroside (**12**) was further characterized as its 2,3-dibenzoate (**14**) and as its 2,3-carbonate (**16**). Benzoylation of benzyl α,β-D-erythroside (**9**) gave crystalline benzyl α,β-D-erythroside 2,3-dibenzoate (**15**), which could not be fractionally crystallized to afford the pure anomers. Silica-gel column chromatography of the mixed, benzylidenated benzyl glycosides gave a quantitative separation of benzyl 2,3-*O*-(*S*)- (**17**) and -(*R*)- (**18**)-benzylidene-β-D-erythrosides. N.m.r. assignments of the benzylidene acetal configurations for the two acetal isomers were based on proton-resonance shift principles established for 1,3-dioxolanes[12] and analogous 2,3-*O*-benzylidene derivatives of **1** and 1,4-anhydroerythritol[13,14]. The *R* configuration was assigned to **18**, the isomer formed in higher yield, in which the phenyl ring occupies the *endo* orientation and H-2, H-3, and the acetal methine proton signals are shifted to higher field.

This investigation has shown that glycosidation of **1** with allyl or benzyl alcohol–hydrogen chloride gives the anomeric glycosides in each case in the ratio of 10:1 ($\beta:\alpha$). A number of characterizing derivatives of the glycosides have been prepared. Some are possible intermediates for the preparation, via glycoside cleavage, of useful derivatives of **1** in its reducing form.

EXPERIMENTAL

General methods. — Evaporations were performed under diminished pressure (water aspirator unless otherwise stated) and melting points are uncorrected. The allyl alcohol was redistilled. The benzyl alcohol was supplied commercially as a practical grade. It contained an unspecified percentage of benzaldehyde. The pyridine was anhydrous, the activated charcoal was Darco* G-60 (ICI United States, Wilmington, DE), and the petroleum ether had b.p. 35–60°. The 1,4-dioxane was rendered peroxide-free by distilling it from stannous chloride immediately before use. The same packing (60–200 mesh) of the silica gel (J. T. Baker Chemical Co., Phillipsburg, NJ) column (3 × 65 cm) was used repeatedly. Before each use it was conditioned as follows: all solvent in the column from the previous separation was drained and the packing was dried by drawing air through it. Ethanol–water (1:1) was then allowed to percolate through the column. This solvent was subsequently displaced with acetone. When the eluate was water-free, the acetone was displaced with the solvent to be used for the separation. If the packing was not preconditioned in this manner, its resolving power was diminished with successive usage. N.m.r. spectra were recorded at 100 MHz with a Varian HA spectrometer, with tetramethylsilane as the internal standard. Esterification mixtures were processed as follows: the cooled mixture was poured into saturated sodium hydrogencarbonate (200–500 mL). After 2–3 h, the

*The mention of firm names or trade products does not imply that they are endorsed or recommended by the U.S. Department of Agriculture over other firms or similar products not mentioned.

mixture was extracted with chloroform and water was distilled from the extract until all chloroform and pyridine had been removed. The resulting aqueous suspension was reextracted with chloroform, and the extract was filtered and evaporated to give the crude ester.

D-*Erythrose* (**1**). — A modification of the method of Rappaport and Hassid[2] was used as follows: to a solution of sodium metaperiodate (53.24 g) in water (670 mL) at 5° (ice bath) was added, portionwise, an intimate mixture of 4,6-*O*-ethylidene-D-glucose (23.83 g) and sodium hydrogencarbonate (19.06 g). When the vigorous reaction had subsided, the mixture was removed from the bath, kept for several hours at room temperature, and then evaporated (bath ≯45°) to near-dryness. The residue was extracted with abs. ethanol. The extracts were filtered and evaporated (bath ≯45°) to a syrup that was dissolved in ethyl acetate. Filtration and evaporation gave amorphous **2** (16.7 g), which was dissolved in 0.05M sulfuric acid (500 mL). The solution was vigorously steam-distilled (100°) for 15 min and then made neutral with barium carbonate. The solution was evaporated to a residue that was dissolved in abs. ethanol (1400 mL). The solution was treated with activated charcoal (10 g), filtered, and evaporated to give crude, syrupy **1** (11.5 g).

*Allyl α,β-*D-*erythrosides*. — The foregoing syrup was dissolved in allyl alcohol (600 mL) containing 0.1% by weight of anhydrous hydrogen chloride. After 22 h the optical rotation became constant ($[\alpha]_D^{20}$ −0.77° [3 min] → −1.86° [22 h], 1-dm tube). Neutralization with sodium hydrogencarbonate was followed by filtration and evaporation to a syrup that was extracted with warm benzene. After several h, the extract was filtered and evaporated to give the crude, syrupy glycoside mixture (12.3 g). Distillation [b.p. 86–130° (bath)/5 mm] gave allyl α,β-D-erythrosides (10.2 g, 55% yield), a colorless, mobile syrup.

A portion (6.64 g) of the foregoing distillate was fractionally distilled to give allyl α-D-erythroside (**5**, 0.45 g), b.p. 95–97° (bath)/5 mm, n^{28} 1.4745, $[\alpha]_D^{20}$ +120° (*c* 2, ethanol), and **3** (4.48 g)*, b.p. 107–109° (bath)/5 mm, n^{28} 1.4760, $[\alpha]_D^{20}$ −134° (*c* 2, ethanol).

Allyl α-D-*erythroside 2,3-di-*p-*nitrobenzoate* (**6**). — To a solution of **5** (0.202 g) in pyridine (5 mL) was added *p*-nitrobenzoyl chloride (0.705 g). The mixture was heated for 1 h at 90° (bath) and then processed as previously described. The crude ester was extracted with boiling heptane and the extract was filtered hot. The filtrate was evaporated to give a semicrystalline residue. Two recrystallizations from 60% ethanol gave **6** (0.35 g, 60% yield), m.p. 80°, $[\alpha]_D^{20}$ −10° (*c* 1, ethyl acetate).

Anal. Calc. for $C_{21}H_{18}N_2O_{10}$: C, 55.0; H, 4.0; N, 6.1. Found: C, 55.2; H, 4.4; N, 6.3.

*Allyl β-*D-*erythroside 2,3-dibenzoate* (**7**). — To a solution of **3** (3.21 g) in pyridine (25 mL) was added benzoyl chloride (10 mL), and the mixture was heated for 1 h at 90° (bath). Processed as before, the mixture yielded a syrup that was dissolved in heptane. The turbid solution was filtered and evaporated to a syrup that was dissolved

*On prolonged storage, the distilled product hardened to a clear, glassy solid.

in boiling 50% ethanol. The solution was filtered hot, chilled, seeded, and refrigerated for 16 h. Two recrystallizations of the crystalline product from 50% ethanol gave **7** (5.4 g, 73% yield), m.p. 50°, $[\alpha]_D^{20}$ −87° (*c* 1.5, ethyl acetate).

Anal. Calc. for $C_{21}H_{20}O_6$: C, 68.5; H, 5.5. Found: C, 68.5; H, 5.8.

To a solution of **7** (5 g) in methanol (100 mL) was added barium hydroxide octahydrate (4.3 g). The resulting mixture was kept for 6 days at room temperature and then filtered and the filtrate evaporated to a residue that was extracted with acetone. Evaporation of the filtered extract gave a syrup (2.013 g) that was distilled to give pure, syrupy **3** (1.625 g), b.p. 125–127° (bath)/5 mm, n^{30} 1.4742, $[\alpha]_D^{20}$ −155° (*c* 2, ethanol).

*Allyl β-*D*-erythroside 3-*p*-nitrobenzoate* (**4**). — To a solution of **3** (3.158 g) in pyridine (100 mL) was added *p*-nitrobenzoyl chloride (4.026 g) (1.1 equiv.). The mixture was heated for 45 min at 90° (bath), and then processed conventionally. The crude monoester, admixed with diester, was extracted with boiling water (7 × 250 mL), each extract being filtered hot. The cooled, combined filtrates were extracted with chloroform and the extract was evaporated to a crystalline residue. Recrystallization from 1:4 (v/v) ethyl acetate–heptane gave **4** (2.575 g), m.p. 133–134°, $[\alpha]_D^{20}$ −108° (*c* 0.6, ethyl acetate); ^{1}H-n.m.r. (in acetone-d_6): δ 8.34 (s, 4, aromatic), 5.9 (m, 1, $-CH_2CH{=}CH_2$), 5.56 (m, 1, H-3), 5.37 (m, 1, H-1), 5.14 (m, 2, $-CH_2CH{=}CH_2$), and 4.1 (m, $-CH_2CH{=}CH_2$, H-2,-4,-4′). The assignment of the *p*-nitrobenzoyl group to O-3 is based upon the resonance of the downfield proton, which gave a complex multiplet because of coupling with both protons at C-4 as well as with H-2.

Anal. Calc. for $C_{14}H_{15}NO_7$: C, 54.4; H, 4.9; N, 4.5. Found: C, 54.6; H, 5.2; N, 4.8.

From the mother liquor could be obtained a second crop, as follows: evaporation gave a residue that was dissolved in ethyl acetate (500 mL). The solution was treated with activated charcoal (1 g), filtered, and the filtrate evaporated to a crystalline residue which, recrystallized as before, gave additional **4** (0.231 g), m.p. 134°; total yield. 2.806 g (46%).

*Allyl β-*D*-erythroside 2,3-di-*p*-nitrobenzoate* (**8**). — (*a*) *From* **4**. To a solution of **4** (0.314 g) in pyridine (5 mL) was added *p*-nitrobenzoyl chloride (0.372 g) and the mixture was heated for 1 h at 90° (bath). Processed as before, the mixture yielded the crude diester, which was extracted with boiling heptane and the extract filtered hot. Evaporation gave a crystalline residue that was recrystallized from 50% ethanol to give **8** (0.442 g, 97% yield), m.p. 127–128°, $[\alpha]_D^{20}$ −63.5° (*c* 1.2, ethyl acetate).

Anal. Calc. for $C_{21}H_{18}N_2O_{10}$: C, 55.0; H, 4.0; N, 6.1. Found: C, 55.1; H, 4.1; N, 6.0.

(*b*) *From allyl α,β-*D*-erythroside*. To a solution of crude allyl α,β-D-erythroside (0.218 g) in pyridine (5 mL) was added *p*-nitrobenzoyl chloride (0.753 g). The mixture was heated for 1 h at 90° (bath) and processed as before. The crude, semicrystalline ester was extracted with boiling heptane and the extract cooled to 50° and rapidly filtered. Evaporation gave a crystalline residue which, recrystallized once

from 50% ethanol and once from 70% ethanol, gave **8** (0.373 g, 60%), m.p. and mixed m.p. with product of (*a*), 127–128°.

Glycosidation of **1** *with benzyl alcohol.* — A suspension of **1** (14.4 g) in benzyl alcohol (750 mL) containing 0.1–0.2% by weight of anhydrous hydrogen chloride was stirred vigorously with powdered Drierite (24 g) for 24 h, whereupon the optical rotation remained constant $[\alpha]_D^{20}$ −2.67°, 1-dm tube). The mixture was made neutral with sodium hydrogencarbonate, filtered, and the filtrate evaporated (bath 90°, 7 mm). The syrup remaining was extracted with benzene to separate unreacted **1**. Filtration and evaporation gave a syrup that was steam-distilled (100°) to remove residual benzyl alcohol. There remained an aqueous, syrupy suspension. On cooling, the mixture was filtered. The filtrate was evaporated to give crude, syrupy benzyl α,β-D-erythroside (**9**) (16.7 g, 66% yield). The syrup separated by the filtration solidified on standing. It consisted of the two acetal isomers of benzyl 2,3-*O*-benzylidene-β-D-erythroside. A portion of **9** was freed of minor impurities by passage through the silica-gel column, development being with 3:1 (v/v) petroleum ether–acetone.

p-*Nitrobenzoylation of* **9**. *Separation of anomeric glycosides.* — To a solution of column-purified **9** (2.20 g) in pyridine (100 mL) was added *p*-nitrobenzoyl chloride (7.7 g). The mixture was kept for two days at room temperature and then it was heated for 1.5 h at 80–90° (bath). Processed conventionally, the mixture yielded a crude crystalline product that, after 3 recrystallizations from abs. ethanol, gave benzyl β-D-erythroside 2,3-di-*p*-nitrobenzoate (**10**, 3.35 g), m.p. 115.5–116.5°, $[\alpha]_D^{20}$ −100° (*c* 1.5, ethyl acetate).

Anal. Calc. for $C_{25}H_{20}N_2O_{10}$: C, 59.1; H, 4.0; N, 5.5. Found: C, 59.0; H, 4.1; N, 5.5.

Evaporation of the mother liquors gave a solid that contained residual **10** plus another compound, as revealed by t.l.c. when 2:3 (v/v) ethyl acetate–heptane was the irrigating solvent. This second product was readily separated *via* silica-gel column chromatography with the same irrigating solvent, thus giving syrupy benzyl α-D-erythroside 2,3-di-*p*-nitrobenzoate (**11**, 0.42 g), $[\alpha]_D^{20}$ +7.0° (*c* 2, ethyl acetate). An additional amount (0.81 g) of **10** was also separated. Thus the ratio of the separated glycosidic esters was 10:1 (β:α).

^{1}H-N.m.r. data for **11**: δ 8.1 (m, 13, aromatic), 5.86 (m, 1, H-3), 5.55 (d, 1, $J_{1,2}$ 4.5 Hz, H-1), 5.30 (dd, 1, $J_{2,3}$ 6 Hz, H-2), 4.73 (AB quartet, 2, *J* 12 Hz, OCH_2-aromatic), 4.48 (dd, 1, $J_{3,4}$ 5.5, $J_{4,4'}$ 10.5 Hz, H-4), and 4.23 (dd, 1, $J_{3,4'}$ 3 Hz, H-4').

Benzyl β-D-erythroside (**12**). — A solution of **10** (0.49 g) in methanol (200 mL) that was saturated with respect to barium hydroxide octahydrate was kept for 3 days at room temperature and then carbonated with Dry Ice and evaporated. The residue was extracted with acetone, and the extract was filtered and evaporated to dryness. The residue was dissolved in benzene, filtered, and evaporated to give syrupy **12** (0.15 g), $[\alpha]_D^{20}$ −144° (*c* 1.5, benzene); ^{1}H-n.m.r.: δ 7.28 (s, 5, aromatic), 5.00 (d, 1, $J_{1,2}$ 1.5 Hz, H-1), 4.54 (AB quartet, 2, *J* 12 Hz, O-CH_2-aromatic), 4.34 (m, 1, H-3), 4.04 (m, 2, H-2, H-4), and 3.76 (dd, 1, $J_{3,4'}$ 4, $J_{4,4'}$ 10 Hz, H-4').

Benzyl α-D-erythroside (**13**). — The same processing of **11** (0.37 g) gave syrupy

13 (0.07 g), $[\alpha]_D^{20}$ +96° (*c* 0.7, benzene); ^{1}H-n.m.r.: δ 7.32 (s, 5, aromatic), 5.02 (d, 1, $J_{1,2}$ 4 Hz, H-1), 4.69 (AB quartet, *J* 12 Hz, OCH_2-aromatic), and 4.02 (m, 4, H-2,-3,-4,-4').

*Benzyl β-*D*-erythroside 2,3-dibenzoate* (**14**). — To a solution of **12** (0.15 g) in pyridine (5 mL) was added benzoyl chloride (0.5 mL). The mixture was heated for 1 h at 80–90° (bath) and then processed conventionally to give the crude dibenzoate which, twice recrystallized from ethanol–water, gave **14** (0.25 g, two crops) m.p. 79.5°, $[\alpha]_D^{20}$ −122° (*c* 0.5, benzene).

Anal. Calc. for $C_{25}H_{26}O_6$: C, 71.8; H, 5.3. Found: C, 71.8; H, 5.3.

*Benzyl α,β-*D*-erythroside 2,3-dibenzoate* (**15**). — To a solution of **9** (16.7 g) in pyridine (150 mL) was added benzoyl chloride (37 mL). The mixture was heated for 1.5 h at 90° (bath) and then processed conventionally to give the crude, crystalline dibenzoate which was extracted with hot heptane (1600 mL). Cooled to room temperature, the extract was filtered and the filtrate evaporated to a syrup that, on seeding and evaporation, crystallized to a solid mass. Recrystallization from 93% ethanol (165 mL) gave a product having m.p. 75–79°. Further recrystallization did not change the m.p. Examination of the product by t.l.c. [19:1 (v/v) petroleum ether–acetone] revealed the presence of two compounds, one preponderant.

Anal. Calc. for $C_{25}H_{26}O_6$: C, 71.8; H, 5.3. Found: C, 71.8; H, 5.4.

*Benzyl β-*D*-erythroside 2,3-carbonate* (**16**). — To a solution of **12** (0.88 g) in 1,4-dioxane (5 mL) was added methyl chloroformate (10 mL). The mixture was kept at 5° (ice bath) and, as the solution was vigorously stirred, a solution of triethylamine (5 mL) in benzene (30 mL) was added, dropwise, during 35 min. After further stirring for 2 h at 5°, an excess of sodium hydrogencarbonate was added to decompose the excess of chloroformate. After 1.5 h, the mixture was extracted with benzene and the extract filtered and evaporated to a syrup that was dissolved in ethanol (20 mL). Upon addition of water, and seeding, crystalline **16** was obtained (0.66 g, 67% yield), m.p. 65.5–66°, $[\alpha]_D^{20}$ −167° (*c* 2, ethyl acetate).

Anal. Calc. for $C_{12}H_{12}O_5$: C, 61.0; H, 5.1. Found: C, 61.1; H, 5.2.

*Benzyl 2,3-*O*-(*S*)-(**17**) and -(*R*)-(**18**)-benzylidene-β-*D*-erythroside.* — Examination of the crude, solid mixture of the benzylidene acetals of benzyl 2,3-*O*-benzylidene-β-D-erythroside by t.l.c. with 24:1 (v/v) petroleum ether–acetone as irrigating solvent revealed the presence of two components. Two recrystallizations from 70% ethanol and three from abs. ethanol gave pure **18**. Silica-gel column chromatography of the residue from the mother liquor with the foregoing irrigating solvent gave an additional amount of **18**; total yield 4.14 g, m.p. 92–93°, $[\alpha]_D^{20}$ −160° (*c* 2.4, ethyl acetate); ^{1}H-n.m.r. ($CDCl_3$): δ 7.40 (m, two phenyl rings), 5.76 (s, benzylidene methine), 5.29 (s, H-1), 4.89 (qd, $J_{2,3}$ 6.5, $J_{3,4}$ 0.5, $J_{3,4}$ 3.2 Hz, H-3), 4.69 (d, H-2), 4.61 (q, CH_2), 4.21 (m, H-4), and 3.99 (dd, $J_{4,4'}$ 10.5 Hz, H-4').

Anal. Calc. for $C_{18}H_{18}O_4$: C, 72.5; H, 6.1; mol. wt., 298. Found: C, 72.5; H, 6.4; mol. wt., 280.

Also separated by the silica-gel column was **17** (2.62 g). Recrystallized from 70% ethanol, it had m.p. 69–70°, $[\alpha]_D^{20}$ −137° (*c* 2, ethyl acetate); ^{1}H-n.m.r. ($CDCl_3$):

δ 7.33 (m, two phenyl rings), 6.01 (s, benzylidene methine), 5.27 (s, H-1), 4.96 (qd, $J_{2,3}$ 5.5, $J_{3,4}$ 0.5, $J_{3,4'}$ 3.5 Hz, H-3), 4.73 (d, H-2), 4.59 (q, CH_2), 4.19 (m, H-4), and 4.01 (dd, $J_{4,4'}$ 10.8 Hz, H-4').

ACKNOWLEDGMENTS

The author thanks L. W. Tjarks for the n.m.r. data, and D. Weisleder and W. E. Dick for assistance in their interpretation.

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