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THE PREPARATION OF SOME BROMODEOXY- AND DIBROMODIDEOXY-PENTONOLACTONES*

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ABSTRACT

Treatment of ammonium D-xylonate with hydrogen bromide in acetic acid yields 2,5-dibromo-2,5-dideoxy-D-lyxono-1,4-lactone (**2a**), whereas similar treatment of potassium D-arabinonate gives 5-bromo-5-deoxy-D-arabinono-1,4-lactone (**8a**) as the main product. Two isomeric 2,5-dibromo-2,5-dideoxy-1,4-lactones are also formed in minor amounts. Selective hydrogenolysis of **2a** affords 5-bromo-2,5-dideoxy-D-*threo*-pentono-1,4-lactone, while prolonged treatment results in the formation of 3-hydroxypentanoic acid. Similarly, hydrogenolysis of **8a** produces a 2,3-dihydroxypentanoic acid together with smaller amounts of 5-deoxy-D-arabinono-1,4-lactone; the latter also results from hydrogenolysis of 5-deoxy-5-iodo-D-arabinono-1,4-lactone with Raney nickel.

INTRODUCTION

Brief treatment of D-ribono- and D-lyxono-1,4-lactone with hydrogen bromide in acetic acid (HBA) was previously shown to lead to the formation of 2-bromo-2-deoxylactones with inversion of configuration at C-2. On prolonged treatment, bromine was also introduced at C-5, yielding 2,5-dibromo-2,5-dideoxylactones[1]. Thus, bromine could be introduced selectively at C-2 in the two lactones having HO-2 and HO-3 *cis*-oriented. We now report on the reaction between HBA and the salts of D-xylonic (**1**) and D-arabinonic acid (**7**), both of which have HO-2 and HO-3 *trans*-oriented.

RESULTS AND DISCUSSION

When ammonium D-xylonate (**1**) was treated with HBA for 24 h at room temperature, followed by deacetylation with methanol, the crystalline 2,5-dibromo-2,5-dideoxy-D-lyxono-1,4-lactone (**2a**) was isolated. Alternatively, the crystalline acetate **2b** could be obtained when the methanol treatment was omitted. ^{13}C-N.m.r. spectroscopy of the crude product obtained after treatment with HBA for 1 and 4 h

*Reaction of Aldonic Acids with Hydrogen Bromide, Part IV. For Part III, see ref. 1.

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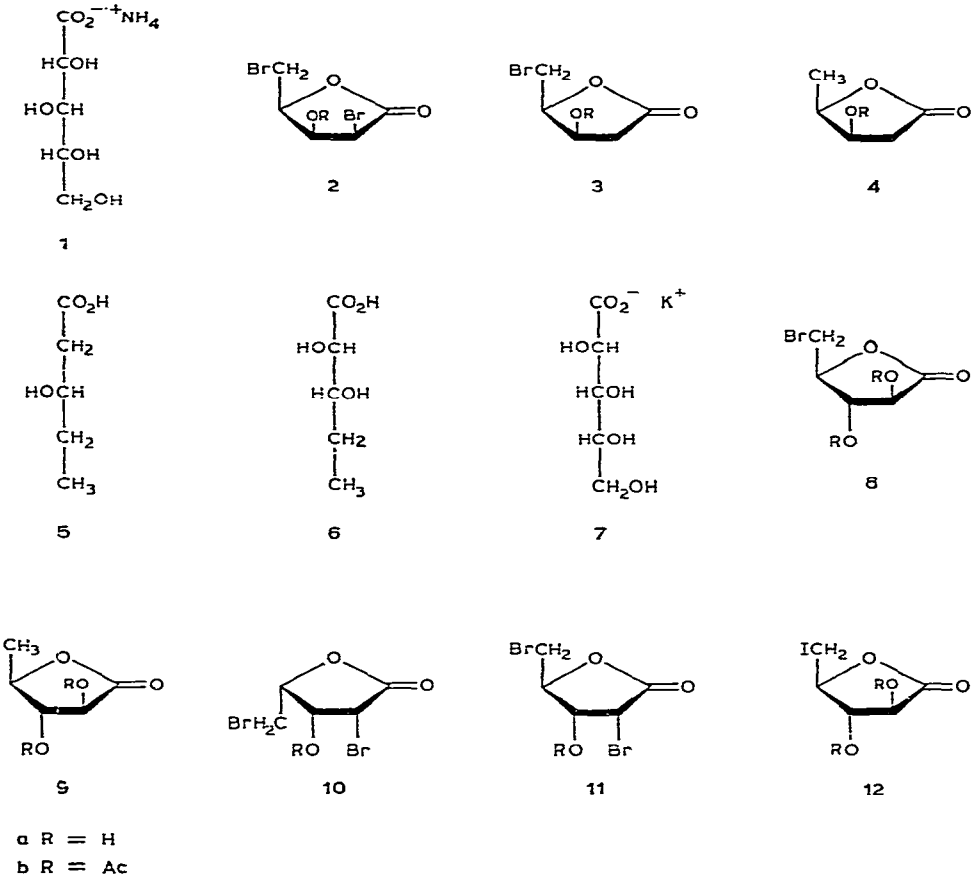

a R = H
b R = Ac

showed that **2b** was the main product present, accompanied by a 5-bromolactone and unreacted lactone; no 2-bromolactone could be detected.

Treatment of potassium D-arabinonate (**7**) with HBA for 20 h followed by deacetylation with methanol gave a complex mixture. The main product was 5-bromo-5-deoxy-D-arabinono-1,4-lactone (**8a**) isolated crystalline in ~20% yield. In addition, a mixture of 2,5-dibromo-2,5-dideoxylactones could be isolated in ~15% yield, and ^{13}C-n.m.r. spectroscopy showed that it consisted of the isomeric compounds **10a** and **11a** in the ratio of ~3:1. 2,5-Dibromo-2,5-dideoxy-L-lyxono-1,4-lactone (**10a**, 4%) was isolated crystalline. Acetylation of the material in the mother liquor afforded the corresponding acetate **10b** (6%).

After treatment of potassium D-arabinonate with HBA for 8 h, starting material was still present (^{13}C-n.m.r. spectrum), and the crude product obtained after reaction for 1 week contained the bromolactones **8b**, **10b**, and **11b** in about equal amounts. When **8a** was allowed to react with HBA for 22 h, the acetylated lactone **8b** was the sole product. Thus, the dibromolactones **10b** and **11b** must be formed directly from

D-arabinonic acid and not *via* the 5-bromo derivative **8a**. 2,3,5-Tri-*O*-acetyl-D-arabinono-1,4-lactone did not react with HBA.

The 2,5-dibromo-2,5-dideoxylactone **2a** was shown to be the 2-epimer of 2,5-dibromo-2,5-dideoxy-D-xylono-1,4-lactone[1], since both compounds gave 5-bromo-2,5-dideoxy-D-*threo*-pentono-1,4-lactone[1] (**3a**) on selective, catalytic hydrogenolysis. Furthermore, treatment of **2b** with sodium iodide in acetone and trifluoroacetic acid gave the known[1] acetate **3b**. Thus, **2** possesses the D-*lyxo* configuration.

The dibromodideoxylactone **10**, formed from **7**, was shown to be the enantiomer of **2**, since the ^{1}H- and ^{13}C-n.m.r. data for **10a** and its acetate (**10b**) were identical with those for **2a** and **2b**, and since the optical rotations of the lactones **2a** and **2b** were equal in magnitude, but opposite in sign, to those of **10a** and **10b**. The second dibromodideoxylactone (**11**) must have the D- or L-*ribo* configuration, because its ^{13}C-n.m.r. data were different from those of the other 2,5-dibromo-2,5-dideoxy-pentono-1,4-lactones[1].

Attempts at a useful synthesis of the 2,5-dideoxylactone by catalytic hydrogenolysis of **2a** were unsuccessful; the expected lactone **4a** was only a minor product, the major product being the 3-hydroxypentanoic acid **5**. A similar result was obtained when the 5-bromo-5-deoxylactone **8a** was subjected to catalytic hydrogenolysis. In this case, the expected 5-deoxylactone **9a** was also the minor product, while the 2,3-dihydroxypentanoic acid **6** was the main product.

The structure of **8a** was confirmed by its conversion into 5-deoxy-D-arabinono-1,4-lactone[2] (**9a**) *via* the 5-iodolactone **12**. The latter could be obtained from **8a** by treatment with potassium iodide; removal of the iodine from **12** was performed with Raney nickel. The enantiomeric form of **9a** was prepared by oxidative degradation of L-rhamnose, according to the method of Humphlett[3].

When aldonolactones, or salts of aldonic acids, react with HBA, the reaction probably proceeds *via* partial acetylation and subsequent formation of acetoxonium ions, which then react with bromide ions, as previously indicated[1,4]. Thus, bromine is introduced at C-2 in D-ribono-[1], D-lyxono-[1], and D-mannono-lactone[5] *via* 2,3-acetoxonium ions. When HO-2 and HO-3 are *trans*, no such ion can be formed unless the lactone ring opens. Thus, D-arabinonolactone gives mainly the 5-bromolactone **8a**, and D-galactonolactone the 6-bromo derivative[5]. Other aldono-1,4-lactones having HO-2 and HO-3 *trans*-oriented behave similarly[6]. The only exceptions are D-gluconolactone, which gives 2,6-dibromo-2,6-dideoxy-D-mannono-1,4-lactone, and D-xylonolactone discussed above. Introduction of a bromine at C-2 in these two cases, and to some extent in the case of **7**, probably involves 2,3-acetoxonium ions, which, however, can only be formed from the acyclic form of the carboxylic acids.

EXPERIMENTAL

General methods. — The solution of hydrogen bromide in acetic acid (HBA) was prepared by saturating glacial acetic acid with anhydrous hydrogen bromide at 0°. It contained ~35% of hydrogen bromide. Optical rotations were measured

with a Perkin–Elmer 141 instrument. ^{1}H-N.m.r. and ^{13}C-n.m.r. spectra were obtained on Bruker HX-90, WH-90, and HX-270 instruments. Melting points are uncorrected.

*2,5-Dibromo-2,5-dideoxy-*D*-lyxono-1,4-lactone* (**2a**). — Ammonium D-xylonate[7] (**1**, 5 g) was treated with HBA (40 mL) for 18 h at room temperature. Methanol (80 mL) was added, the solution was kept overnight and then concentrated, and water (2 × 20 mL) was evaporated from the residue. A solution of the residue in water (10 mL) was extracted with chloroform (6 × 25 mL), the chloroform solution was dried ($MgSO_4$) and concentrated, and the residue (4.8 g, 64%) was crystallised by the addition of ether, to give **2a** (2.47 g, 33%), m.p. 89–91°. Recrystallisation from ether–pentane gave a product with m.p. 92–93°, $[\alpha]_D^{20}$ +17° (*c* 2.7, ethyl acetate). N.m.r. data: ^{1}H (270 MHz, $CDCl_3$): δ 4.76 (d, 1 H, $J_{2,3}$ 4.2 Hz, H-2), 4.65 (ddd, 1 H, $J_{4,5}$ 9.0, $J_{4,5'}$ 6.0 Hz, H-4), 4.59 (dd, 1 H, $J_{3,4}$ 3.0 Hz, H-3), 3.70 (t, 1 H, $J_{5,5'}$ 10.2 Hz, H-5), and 3.63 (dd, 1 H, H-5'); ^{13}C ($CDCl_3$): 171.6 (C-1), 80.4 (C-4), 68.7 (C-3), 47.9 (C-2), and 26.1 p.p.m. (C-5).

Anal. Calc. for $C_5H_6Br_2O_3$: C, 21.92; H, 2.21; Br, 58.35. Found: C, 22.00; H, 2.22; Br, 58.21.

The mother liquor from the first crystallisation above was treated with acetic anhydride (10 mL) and a few drops of 60% aqueous perchloric acid for 30 min at room temperature. Work-up in the usual way, with crystallisation of the product from ether–pentane, gave **2b** (1.98 g, 23%), m.p. 118–120°, raising the total yield to 56%.

*3-O-Acetyl-2,5-dibromo-2,5-dideoxy-*D*-lyxono-1,4-lactone* (**2b**). — Ammonium D-xylonate[7] (**1**, 5 g) was treated with HBA (40 mL) for 18 h at room temperature. Acetic anhydride (10 mL) was added. After 2 h, a small amount of water was added and, after 1 h, dichloromethane (50 mL) was added together with more water, and the organic phase was washed three times with water, dried ($MgSO_4$), and concentrated. The residue (4.75 g, 55%) was crystallised by addition of ether, to give **2b** (3.45 g, 40%), m.p. 111–114°. Recrystallisation from dichloromethane–pentane gave a product with m.p. 121.5–122°, $[\alpha]_D^{25}$ −9° (*c* 4.6, ethyl acetate). N.m.r. data: ^{1}H (270 MHz, $CDCl_3$): δ 5.90 (dd, 1 H, $J_{3,4}$ 3.6 Hz, H-3), 4.84 (ddd, 1 H, $J_{4,5}$ 6.0 Hz, H-4), 4.82 (d, 1 H, $J_{2,3}$ 5.3 Hz, H-2), 3.64 (dd, 1 H, $J_{5,5'}$ 10.2 Hz, H-5), 3.51 (dd, 1 H, $J_{4,5'}$ 8.4 Hz, H-5'), and 2.20 (OAc); ^{13}C ($CDCl_3$): 169.5 (C-1), 168.8 (OAc), 79.2 (C-4), 69.5 (C-3), 43.4 (C-2), 26.0 (C-5), and 20.2 p.p.m. (OAc).

Anal. Calc. for $C_7H_8Br_2O_4$: C, 26.61; H, 2.55; Br, 50.58. Found: C, 26.60; H, 2.54; Br, 50.60.

Treatment of potassium D*-arabinonate* (**7**) *with HBA.* — Potassium D-arabinonate[3] (**7**, 30 g) was stirred with HBA (200 mL) for 24 h at room temperature, methanol (300 mL) was added with cooling, the solution was kept overnight and concentrated, and water was evaporated from the residue. A solution of the crude product in water (60 mL) was extracted with chloroform (10 × 25 mL), and the extract was dried ($MgSO_4$) and concentrated, leaving 6.1 g (15%) of syrupy material. A ^{13}C-n.m.r. spectrum ($CDCl_3$) showed the presence of the isomeric 2,5-dibromo-2,5-dideoxypentono-1,4-lactones **10a** [171.6 (C-1), 80.9 (C-4), 69.2 (C-3), 48.2 (C-2), and 26.5 p.p.m. (C-5)] and **11a** [171.1 (C-1), 82.1 (C-4), 70.1 (C-3), 45.7 (C-2), and 30.3

p.p.m. (C-5)] in the ratio ~2.7:1. Addition of ether gave **10a** (1.7 g, 4.2%), m.p. 91–92°, $[\alpha]_D^{25}$ −17° (*c* 3.5, ethyl acetate); the ^{1}H- and ^{13}C-n.m.r. data were identical with those of the enantiomeric form **2a**.

Anal. Calc. for $C_5H_6Br_2O_3$: C, 21.92; H, 2.21; Br, 58.35. Found: C, 21.91; H, 2.21; Br, 58.30.

Acetylation of the mother liquor with acetic anhydride and 60% aqueous perchloric acid for 30 min gave **10b** (3.0 g, 6.5%), m.p. 118–119°. Recrystallisation from dichloromethane–pentane gave a product with m.p. 119–121°, $[\alpha]_D^{25}$ +9° (*c* 2.5, ethyl acetate); the ^{1}H- and ^{13}C-n.m.r. spectra were identical with those of the enantiomeric product **2b**.

Anal. Calc. for $C_7H_8Br_2O_4$: C, 26.61; H, 2.55; Br, 50.58. Found: C, 26.71; H, 2.62; Br, 50.55.

The aqueous phase from the chloroform extraction was continuously extracted with ether for 4 h. The extract was dried (Na_2SO_4) and concentrated, and the residue (16.3 g) was crystallised from ether, to yield 6.4 g (20.6%) of **8a**, m.p. 118–124°. Continuous extraction with ether for an additional 8 h gave a syrup (2.7 g) which provided 1.6 g (5.3%) of **8a**, m.p. 106–116°, raising the total yield to 26%. Recrystallisation from ethyl acetate gave material with m.p. 126.5–129°, $[\alpha]_D^{25}$ +58° (*c* 2.8, ethyl acetate). N.m.r. data: ^{1}H (270 MHz, D_2O): δ 4.65 (d, 1 H, $J_{2,3}$ 9.5 Hz, H-2), 4.53 (m, 1 H, H-4), 4.31 (t, 1 H, $J_{3,4}$ 7.5 Hz, H-3), 3.89 (dd, 1 H, $J_{4,5}$ 3.0, $J_{5,5'}$ 12.0 Hz, H-5), and 3.73 (dd, 1 H, $J_{4,5'}$ 4.5 Hz, H-5′); ^{13}C (D_2O): 176.1 (C-1), 79.9 (C-4), 76.2 and 74.5 (C-2,3), and 31.9 p.p.m. (C-5).

Anal. Calc. for $C_5H_7BrO_4$: C, 28.46; H, 3.34; Br, 37.87. Found: C, 28.57; H, 3.32; Br, 37.82.

Treatment of **8a** *with HBA.* — The 5-bromolactone **8a** (500 mg) was treated with HBA for 22 h. Addition of acetic anhydride (2 mL) and work-up after 2 h, as described for **2b**, gave **8b** (535 mg, 77%), as seen from a ^{13}C-n.m.r. spectrum ($CDCl_3$): 169.4 (C-1), 169.0 and 167.5 (OAc), 77.6 (C-4), 74.2 and 71.9 (C-2,3), 30.6 (C-5), 20.0 and 19.7 p.p.m. (OAc). Crystallisation from ether–pentane gave material with m.p. 117–120°. ^{1}H-n.m.r. data (90 MHz, $CDCl_3$): δ 5.87 (dd, 1 H, $J_{3,4}$ 3.75 Hz, H-3), 4.82 (m, 1 H, $J_{4,5}$ 6.25 Hz, H-4), 4.78 (d, 1 H, $J_{2,3}$ 5.40 Hz, H-2), 3.64 (dd, 1 H, $J_{5,5'}$ 10.0 Hz, H-5), 3.47 (dd, 1 H, $J_{4,5'}$ 8.5 Hz, H-5′), and 2.18 (OAc).

3-O-Acetyl-5-bromo-2,5-dideoxy-D-threo-*pentono-1,4-lactone* (**3b**). — (*a*) *From* **2a**. A solution of the dibromolactone **2a** (1.0 g) in ethyl acetate (30 mL) and triethylamine (0.51 mL, 1 equiv.) was hydrogenolysed at atmospheric pressure in the presence of 5% palladium-on-carbon (200 mg). After ~20 min, one mol. equiv. of hydrogen had been consumed and the rate of uptake then decreased. The mixture was filtered and concentrated, to give the crude 2-deoxylactone **3a**, contaminated with triethylamine hydrobromide. A ^{13}C-n.m.r. spectrum was identical with that described previously[1]. Treatment with acetic anhydride (10 mL) and 60% aqueous perchloric acid (1 mL) for 30 min gave, after work-up in the usual way, 672 mg (77%) of a product that crystallised from ether–pentane, to give **3b** (568 mg, 65%), m.p. 94–96°; lit.[1]

m.p. 96–97.5°; the ^{1}H- and ^{13}C-n.m.r. spectra were identical with those described previously[1].

(*b*) *From* **2b**. The acetylated dibromolactone **2b** (1.0 g) was stirred for 22 h with acetone (15 mL) containing trifluoroacetic acid (2 mL) and sodium iodide (7 g). Dichloromethane was then added, and the mixture was washed with water, aqueous $NaHCO_3$, and aqueous $Na_2S_2O_3$, dried, and concentrated. The resulting syrup (677 mg) crystallised, to give **3b** (414 mg, 55%), m.p. 93–96°. Recrystallisation from dichloromethane–pentane gave material with m.p. 96–97°, $[\alpha]_D^{25}$ −5° (*c* 2.7, ethyl acetate); lit.[1] m.p. 96–97.5°, $[\alpha]_D^{25}$ −5.0°. The ^{1}H- and ^{13}C-n.m.r. spectra were identical with those described[1].

Catalytic hydrogenation of **2a**. — A mixture of **2a** (397 mg), ethyl acetate (15 mL), triethylamine (0.6 mL, 3 mol. equiv.), and 5% palladium-on-carbon (50 mg) was hydrogenolysed at 1 atmos. until no more hydrogen was consumed (4 h). Filtration and concentration gave a mixture of the 2,5-dideoxylactone **4a** and 3-hydroxypentanoic acid (**5**) in the ratio ~1:3, together with triethylamine hydrobromide, as seen from a ^{13}C-n.m.r. spectrum. N.m.r. data (D_2O) for **4**: 178.7 (C-1), 83.7 (C-4), 69.9 (C-3), 39.8 (C-2), and 13.8 p.p.m. (C-5); for **5** (D_2O): 180.6 (C-1), 70.9 (C-3), 43.3 (C-2), 29.8 (C-4), and 10.0 p.p.m. (C-5). The mixture was not further characterised.

Catalytic hydrogenation of **8a**. — A mixture of the 5-bromolactone **8a**, ethyl acetate (20 mL), triethylamine (0.8 mL), and 5% palladium-on-carbon (150 mg) was subjected to hydrogenation for 3 h, whereafter no more hydrogen was consumed. Filtration and concentration gave a residue that consisted of the 5-deoxylactone **9a** together with the 2,3-dihydroxypentanoic acid **6** in the ratio ~1:3 contaminated with triethylamine hydrobromide, as seen from a ^{13}C-n.m.r. spectrum. N.m.r. data (D_2O) for **9a**: 177.0 (C-1), 79.1 (C-4), 78.5 and 74.3 (C-2,3), and 17.4 p.p.m. (C-5); for **6**: 176.0 (C-1), 74.9 and 74.3 (C-2,3), 26.6 (C-4), and 10.5 p.p.m. (C-5). The mixture was not further studied.

*5-Deoxy-5-iodo-*D*-arabinono-1,4-lactone* (**12**). — A mixture of the 5-bromolactone **8a** (3.0 g), acetone (30 mL), and potassium iodide (9.0 g) was boiled under reflux for 20 h. Concentration gave a residue which was dissolved in water (30 mL) and extracted with ethyl acetate (6 × 30 mL). The organic phase was washed with aqueous sodium thiosulfate and water, dried (Na_2SO_4), and concentrated, to give a crude product (~3 g). Recrystallisation from ethyl acetate gave 2.24 g (61%) of **12**, m.p. 112–114°, $[\alpha]_D^{25}$ +55.5° (*c* 1.3, ethyl acetate). ^{13}C-N.m.r. data (D_2O): 175.7 (C-1), 79.6 (C-4), 77.8 and 74.3 (C-2,3), and 4.8 p.p.m. (C-5). Due to instability, a correct microanalysis could not be obtained.

Anal. Calc. for $C_5H_7IO_4$: C, 23.28; H, 2.73; I, 49.19. Found: C, 23.62; H, 2.76; I, 46.80.

*5-Deoxy-*D*-arabinono-1,4-lactone* (**9a**). — To a solution of the 5-iodolactone **12** (1.0 g) in ethanol (10 mL) was added calcium carbonate (1 g) and Raney nickel (excess), and the mixture was stirred for 1 h followed by filtration and evaporation. A solution of the residue in a small amount of water was extracted with ethyl acetate

(5 × 15 mL), dried (Na_2SO_4), and concentrated. The crystalline residue (235 mg, 46%) was recrystallised from ethyl acetate, to give **9a**, m.p. 120–122°, $[\alpha]_D^{25}$ +39° (*c* 1, ethyl acetate). ^{13}C-N.m.r. data (D_2O): 177.0 (C-1), 79.1 (C-4), 78.5 and 74.3 (C-2,3), and 17.4 p.p.m. (C-5).

Anal. Calc. for $C_5H_8O_4$: C, 45.45; H, 6.10. Found: C, 45.45; H, 6.07.

*5-Deoxy-*L*-arabinono-1,4-lactone.* — A solution of L-rhamnose (16.4 g) in water (36 mL) was added during 2 h to a solution of potassium hydroxide (17 g) in water (30 mL) and methanol (150 mL), which was kept at 35° whilst oxygen was passed through the mixture with vigorous stirring[3]. Work-up gave a crude product which was deionised with Amberlite IR-120 (H^+) resin and concentrated. Crystallisation from ethyl acetate–pentane gave 3.1 g (23.5%) of a product with m.p. 95–112°. Recrystallisation from chloroform raised the m.p. to 118–121°, and another recrystallisation from ethyl acetate gave the pure compound, m.p. 119–122°, $[\alpha]_D^{20}$ −39° (*c* 1.5, ethyl acetate), $[\alpha]_D^{20}$ −47° (*c* 0.8, water); lit.[2] m.p. 125°, $[\alpha]_D^{20}$ −39→ −34° (after 7 days; *c* 0.7, water).

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