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A SYNTHESIS OF 3-AMINO-3-DEOXY-L-LYXOSE

J. S. BRIMACOMBE,
Chemistry Department, The University, Dundee DD1 4HN (Great Britain)

A. M. MOFTI*, AND M. STACEY
Chemistry Department, The University, P. O. Box 363, Birmingham 15 (Great Britain)

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ABSTRACT

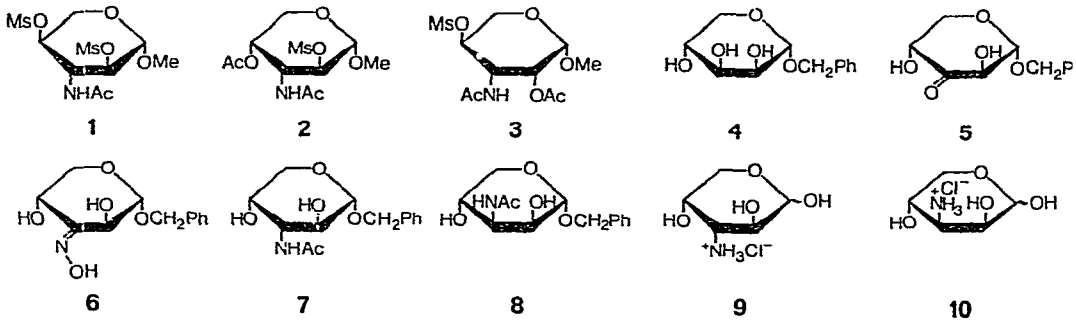
The title amino sugar has been synthesised from 1,2:5,6-di-*O*-isopropylidene-α-D-gulofuranose (**13**). Oxidation of this diacetal with acetic anhydride and methyl sulphoxide afforded the ketone **14**, which was converted into 3-acetamido-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-gulofuranose (**16**) by sequential oximation, reduction, and acetylation. Application of a conventional chain-shortening sequence to the amide **16** gave 3-acetamido-3-deoxy-1,2-*O*-isopropylidene-β-L-lyxofuranose (**19**), which yielded the syrupy amino sugar hydrochloride **20** following hydrolysis with hydrochloric acid.

INTRODUCTION

Whereas the stereoisomeric 3-amino-3-deoxypentoses having the D(L)-*ribo*[1–4], -*xylo*[3,5], and -*arabino*[4] configurations have been synthesised, there is no route leading to the isomeric *lyxo* compounds. Baker and Schaub[2] found that solvolysis of methyl 3-acetamido-3-deoxy-2,4-di-*O*-methanesulphonyl-β-L-xylopyranoside (**1**) gave, after acetylation, a monosulphonate which could be either the D-arabinose derivative (**2**) or the L-lyxose derivative (**3**). Although the structure of the monosulphonate was not established, the structure **2** seems more likely when comparison is made with the solvolysis of methyl 3-acetamido-3,6-dideoxy-2,4-di-*O*-methanesulphonyl-α-L-glucopyranoside[6], and when the generally low reactivity of C-2 sulphonates is taken into consideration.

We have previously attempted[7] to synthesize 3-amino-3-deoxy-D-lyxose (**10**) from benzyl α-D-lyxopyranoside (**4**) by the route outlined. The lyxoside **4** is oxidised catalytically[8] in the *1C*(D) conformation (**11**) at the axial C-3 hydroxyl group to give the ketone **5**, which was converted into the oxime **6** by treatment with hydroxylamine at pH 4. Catalytic hydrogenation of the oxime gave, after *N*-acetylation, a mixture of the two possible glycosaminides **7** and **8**, from which the amino sugars **9** and **10**, respectively, were liberated by hydrolysis with hydrochloric acid. One of the amino

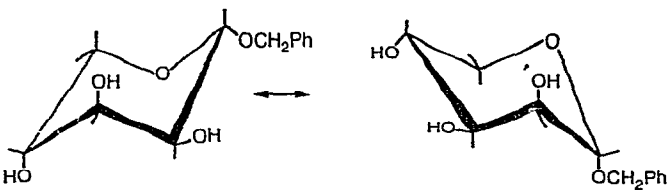
*Present address: Chemistry Department, The University, Dundee DD1 4HN, Great Britain.



1 2 3 4 5

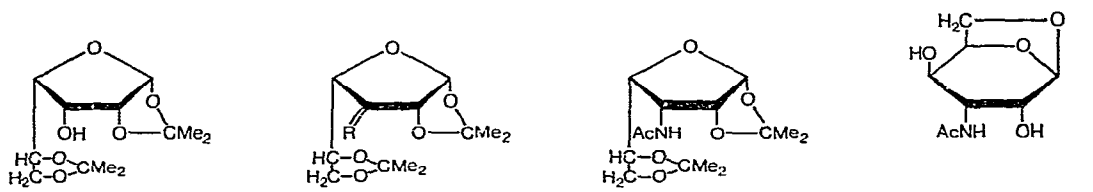
6 7 8 9 10

sugars was shown to be chromatographically indistinguishable from 3-amino-3-deoxy-L-arabinose hydrochloride[4], but, unfortunately, their separation could not be achieved satisfactorily by ion-exchange chromatography[9].



11 *1C*(D) 12 *C1*(D)

Our interest in synthesizing 3-amino-3-deoxy-L (or D)-lyxose was revived during attempts to prepare certain 3,5-diamino sugars. One of the ways used to introduce the 3-amino group utilized the oximation of a diacetal ketone such as **14**, which is readily prepared by recent oxidation procedures[10]. Such procedures are attractive because the fused, bicyclic system in these compounds would be expected to exert a major influence on the stereochemistry of the product resulting, for example, from the reduction of the oxime **15**. Moreover, the ease of removal of the exocyclic acetal group permits chain-shortening sequences to be performed on the resulting monoacetal. A synthesis of 3-amino-3-deoxy-L-lyxose was devised along these lines.



13 14 R=O 15 R=NOH 16 17

18 19 20 21

1,2:5,6-Di-*O*-isopropylidene-α-D-gulofuranose (**13**), which is available[11] in three steps from the isomeric D-glucose diacetal, was oxidised to the crystalline ketone **14** with acetic anhydride and methyl sulphoxide[12]; this oxidation has also been accomplished[13] by using a catalytic quantity of ruthenium dioxide in the presence of sodium periodate[14]. A crystalline oxime **15** was formed on treatment of **14** with hydroxylamine hydrochloride in ethanolic pyridine, and it was reduced stereospecifically either with lithium aluminium hydride or with hydrogen over Adams' catalyst to give, after acetylation, 3-acetamido-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-gulofuranose (**16**).

The identity of **16** followed from the observations that its n.m.r. spectrum and physical constants {m.p. 141.5–142.5°, $[\alpha]_D$ −45° (*c* 1, chloroform)} differed from those of the diastereoisomeric 3-acetamido-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-galactofuranose[15] {m.p. 157.5–159°, $[\alpha]_D$ −12° (*c* 1, chloroform)} and from its conversion into the known[16] 3-acetamido-1,6-anhydro-3-deoxy-β-D-gulopyranose (**17**) following acid hydrolysis and *N*-acetylation of the resulting amine. The stereospecificity of these reductions is not surprising; the reactions are subject to kinetic control and, clearly, the reagent's approach is more favoured from the *exo*-side of the bicyclo[3.3.0]octane ring-system.

Partial hydrolysis of the diacetal **16** with 70% acetic acid gave the diol **18**, which successive treatments with aqueous sodium periodate and sodium borohydride converted into 3-acetamido-3-deoxy-1,2-*O*-isopropylidene-β-L-lyxofuranose (**19**). Subsequent hydrolysis of **19** with dilute hydrochloric acid yielded 3-amino-3-deoxy-L-lyxose hydrochloride (**20**) as a chromatographically homogeneous syrup; our previous experiments[7] suggested that this hydrochloride might be crystalline but we have been unable to crystallise it in the present case. Peracetylation of **20** gave an amorphous tetraacetate **21**, which had mass and n.m.r. spectra in accord with the structure assigned.

EXPERIMENTAL

Thin-layer chromatography (t.l.c.) was performed on Kieselgel G (Merck) with detection by vanillin–sulphuric acid[17]. Infrared spectra for solids were routinely recorded on Nujol mulls with a Perkin–Elmer 125 spectrometer; the spectra were consistent with the structures assigned. N.m.r. spectra were usually measured on solutions in *ca.* 10% deuteriochloroform, with tetramethylsilane as internal reference, using either a Perkin–Elmer R-10 or a Perkin–Elmer R-14 spectrometer. Solvents were removed by evaporation at *ca.* 40°.

1,2:5,6-Di-O-isopropylidene-α-D-xylo-hexofuranos-3-ulose (**14**). — A solution of the D-gulose diacetal[11] **13** (1 g) in a mixture of methyl sulphoxide (11.5 ml) and acetic anhydride (7.5 ml) was set aside for 18 h at room temperature, during which time complete oxidation had occurred. Removal of the solvents afforded a brown syrup which was distilled (b.p. 110°/0.1 mmHg). The distillate crystallised on standing and was recrystallised from light petroleum (b.p. 40–60°) to give the ketone **14** (0.73 g),

m.p. 73–74.5°, $[\alpha]_D$ +15° (*c* 2, chloroform), ν_{max} 1765 cm^{-1} (C=O) (Found: C, 55.8, H, 7.0. $C_{12}H_{18}O_6$ calc.: C, 55.8; H, 7.0%). Slessor and Tracey[13] have since recorded m.p. 76–77°, $[\alpha]_D$ −58.5° (*c* 0.4, water), for this compound prepared by oxidation of **13** with ruthenium tetroxide; the optical rotation is presumably that of the hydrated form[13].

*1,2:5,6-Di-*O*-isopropylidene-α-*D*-xylo-hexofuranos-3-ulose oxime* (**15**). — To a solution of the ketone **14** (0.5 g) in ethanol (10 ml) was added hydroxylamine hydrochloride (1 g) followed by pyridine (10 ml), and the solution was heated for 2 h under gentle reflux. The solution was cooled, the solvents were removed, and the residue was extracted with chloroform (100 ml) which was washed with aqueous cadmium chloride (10 ml) and water (20 ml), and dried ($MgSO_4$). The solvent was removed, and the residue was recrystallised from ether–light petroleum (b.p. 40–60°) to give the oxime **15** (0.3 g), m.p. 145–147°, $[\alpha]_D$ +55° (*c* 1, chloroform), ν_{max} 1650 cm^{-1} (oxime) (Found: C, 52.5; H, 6.9; N, 4.8. $C_{12}H_{19}NO_6$ calc.: C, 52.7; H, 7.0; N, 5.1%). N.m.r. data: τ 4.11 (1-proton doublet, $J_{1,2}$ 4 Hz, H-1); 4.75 (1-proton doublet, $J_{1,2}$ 4 Hz, H-2); 8.43, 8.54, and 8.62 (singlets, 12 protons, intensity ratios 1:1:2, 2 CMe_2 groups); 1.63 (broad singlet, oximino H).

*3-Acetamido-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-*D*-gulofuranose* (**16**). — (*a*) *By reduction of* **15** *with lithium aluminium hydride.* A solution of the oxime (0.4 g) in dry tetrahydrofuran (50 ml) containing lithium aluminium hydride (0.4 g) was heated under reflux for 3 h, and t.l.c. (hexane–ethyl acetate, 1:1) then showed that all of the starting material had reacted. Ethyl acetate (30 ml) and water (0.7 ml) were added to decompose the excess of reagent, the mixture was heated for 10 min and filtered, and the filtrate was concentrated. The residue was taken up in dry methanol (5 ml) and treated with acetic anhydride (0.5 ml) for 1 h at room temperature. Removal of the solvent, with repeated additions of toluene, and chromatography on silica gel (elution with ethyl acetate) gave the amide **16** (0.2 g), m.p. 141.5–142.5° (from chloroform–light petroleum, b.p. 60–80°), $[\alpha]_D$ −45° (*c* 1, chloroform), ν_{max} 1673, 1525 cm^{-1} (NHAc) (Found: C, 55.8; H, 7.5; N, 4.5. $C_{14}H_{23}NO_6$ calc.: C, 55.8; H, 7.7; N, 4.65%). N.m.r. data: τ 4.15 (1-proton doublet, J ~4 Hz, H-1); 5.35 (1-proton multiplet, H-2); 7.95 (3-proton singlet, NAc); and 8.36, 8.57, and 8.63 (singlets, 12 protons, intensity ratios 1:1:2, 2 CMe_2 groups).

(*b*) *By hydrogenation of* **15** *over platinum.* The oxime (0.18 g) in butyl alcohol (5 ml) containing suspended platinum oxide (0.1 g) was shaken with a slight overpressure of hydrogen for 30 h at room temperature, whereupon the catalyst was filtered off through a Celite pad and washed thoroughly with methanol. The combined filtrate and washings were evaporated, and the residue was acetylated, as described in (*a*), to give **16** (0.1 g), m.p. and mixed m.p. 141–142°, $[\alpha]_D$ −45° (*c* 1, chloroform).

*3-Acetamido-1,6-anhydro-3-deoxy-β-*D*-gulopyranose* (**17**). — A sealed tube containing the diacetal **16** (30 mg) in 2M hydrochloric acid (3 ml) was immersed in a boiling-water bath for 10 h, after which time the hydrolysate was evaporated to dryness with repeated additions of ethanol and toluene. The resulting syrup was dissolved in methanol (2 ml), silver acetate (60 mg) and acetic anhydride (0.2 ml)

were added, and the mixture was set aside overnight at room temperature. The suspension was heated under reflux for a few minutes and filtered with the aid of a Celite pad, and the solvents were removed. Chromatography of the residue on silica gel (elution with acetone–ethyl acetate, 1:1) afforded the anhydro sugar **17** (13 mg), m.p. 201–203° (from acetone–ether), $[\alpha]_D$ +83 ±1° (*c* 0.4, methanol); lit.[16] m.p. 203–204°, $[\alpha]_D$ +81 ±3° (*c* 1.8, methanol).

*3-Acetamido-3-deoxy-1,2-*O*-isopropylidene-α-*D*-gulofuranose* (**18**). — A solution of the diacetal **16** (0.23 g) in 70% acetic acid (8 ml) was kept at room temperature for 12 h, after which time the solvents were removed; t.l.c. (ethyl acetate–methanol, 6:1) indicated that small proportions of starting material and the free acetamido sugar were present as well as the monoacetal. Chromatography on silica gel (elution with ethyl acetate–methanol, 4:1) gave pure **18**, m.p. 146–147° (from methanol–ether), $[\alpha]_D$ +14° (*c* 1, methanol) (Found: C, 50.6; H, 7.3; N, 5.3. $C_{11}H_{19}NO_6$ calc.: C, 50.6; H, 7.3; N, 5.3%).

*3-Acetamido-3-deoxy-1,2-*O*-isopropylidene-β-*L*-lyxofuranose* (**19**). — A solution of the diol **18** (0.2 g) in water (2 ml) was treated for 90 min at room temperature with sodium metaperiodate (0.2 g) dissolved in a small quantity of water. Methanol (30 ml) was added, and the solution was kept at 0° for 3 h and then filtered. Removal of the solvents left a colourless syrup which was dissolved in 80% aqueous ethanol (5 ml) and treated with sodium borohydride (0.1 g) for 2 h at room temperature. Water (2 ml) and ethyl acetate (3 ml) were added, and cations were removed by stirring the solution with Amberlite IR-120(H^+) resin. The filtered mixture was concentrated to dryness several times in the presence of methanol. Chromatography on silica gel (elution with ethyl acetate–methanol, 7:1) gave **19** (0.15 g), m.p. 166–167° (from ethyl acetate containing a little hexane), $[\alpha]_D$ −5° (*c* 1, methanol), ν_{max} 1650, 1550 cm^{-1} (NHAc) (Found: C, 52.0; H, 7.7; N, 5.9. $C_{10}H_{17}NO_5$ calc.: C, 51.9; H, 7.4; N, 6.1%). N.m.r. data (D_2O): τ 4.03 (1-proton doublet, $J_{1,2}$ 4 Hz, H-1), 7.98 (3-proton singlet, NAc), 8.42 and 8.65 (3-proton singlets, CMe_2).

*3-Amino-3-deoxy-*L*-lyxose hydrochloride* (**20**). — The acetal **19** (0.1 g) in M hydrochloric acid (4 ml) was heated for 18 h on a boiling-water bath, after which time the solution was concentrated, with repeated additions of water, and decolourised. Evaporation of the solvent gave the amino sugar hydrochloride **20** (*ca.* 80 mg), $[\alpha]_D$ −24 ±3° (*c* 0.5, water), as an essentially chromatographically homogeneous syrup which could not be induced to crystallise. On paper chromatograms irrigated with ethyl acetate–pyridine–water–acetic acid (5:5:3:1), **20** had R_G 0.94, whereas 3-amino-3-deoxy-L-arabinose hydrochloride[4] had R_G 0.76; both compounds gave a positive reaction to ninhydrin.

Acetylation of **20** with acetic anhydride and pyridine, followed by chromatography on silica gel (elution with ethyl acetate), gave an amorphous tetraacetate **21**, $[\alpha]_D$ +5° (*c* 0.5, chloroform); n.m.r. data: τ 7.85, 7.87, 7.95 (3-proton singlets, 3 OAc groups), 8.06 (3-proton singlet, NAc). The mass spectrum of **21** contained a weak molecular ion peak at *m/e* 317.

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