Carbohydrate Research, 58 (1977) 230–234

Note

Synthesis of 2,6-dideoxy-α-L-*lyxo*- and 2,6-dideoxy-α-L-*arabino*-hexopyranosyl halides

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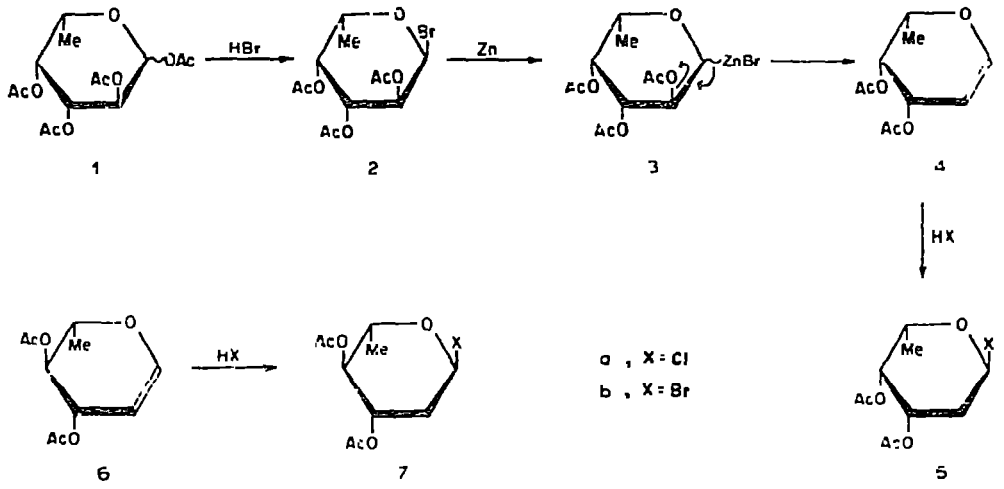
(Received December 17th, 1976; accepted for publication, January 3rd, 1977)

Anthracycline antibiotics have as their sugar components the amino sugars daunosamine and rhodosamine, either alone or in combination with deoxy sugars, or a deoxy sugar and a ketose. 2,6-Dideoxy-L-*lyxo*-hexose ("2-deoxy-L-fucose") is found in the antibiotics cinerubin A (ref. 1) and the rhodomycin complex[2], and may be considered to be an oxygen analog of the amino sugars daunosamine and rhodosamine present in all anthracycline antibiotics. Synthetic anthracyclines having aglycons linked to 3-amino-2,3,6-trideoxyhexopyranoses of the L-*lyxo* and L-*arabino* configurations have shown antibiotic and antineoplastic activities, suggesting that their oxygen analogs, namely, 2,6-dideoxy-L-*lyxo*- and 2,6-dideoxy-L-*arabino*-hexose, when linked to anthracycline aglycons may possibly form glycosides possessing biological activity. Thus, 2,6-dideoxy-L-*lyxo*-hexopyranosyl halides (**5a** and **5b**) and 2,6-dideoxy-L-*arabino*-hexopyranosyl halides (**7a** and **7b**) could, for example, be linked either to anthracycline aglycons or to anthracycline antibiotics to give, in the second case, disaccharide-type anthracycline analogs.

The aim of this work was to synthesize the glycosyl halides of 2,6-dideoxy-L-*lyxo*- and 2,6-dideoxy-L-*arabino*-hexose from readily available starting-materials. A review of the literature revealed that several 2-deoxyglycopyranosyl halides have been prepared from the corresponding acetylated glycals by the action of hydrogen halides[3,4]. The acetylated glycals required, namely di-*O*-acetyl-L-fucal (**4**) and di-*O*-acetyl-L-rhamnal (**6**) were prepared by Reichstein and Iselin[5,6]; tetra-*O*-acetyl-L-fucose (**1**) and tetra-*O*-acetyl-L-rhamnose were separately treated with hydrogen bromide to give the bromides, which were treated with zinc in acetic acid to afford the desired **4** and **6**. However, when this procedure was repeated with tetra-*O*-acetyl-L-fucose, the desired compound **4** was obtained in a yield of 15% instead of the 33% reported[5]. It was therefore decided to monitor the reaction by t.l.c., and then to change the experimental conditions in order to optimize the yield. We found that raising the temperature to 0° during the addition of the glycosyl bromide increased the yield of **4** to 40%. The higher temperature seems to shift the equilibrium in favor of the carbanion elimination and to decrease the competing, nucleophilic substitution



of the bromide by the acetate ion and other nucleophiles. Compound **4** was obtained crystalline after vacuum distillation of the product. On treatment of **4** with hydrogen chloride or hydrogen bromide, the desired halides, namely, 3,4-di-*O*-acetyl-2,6-dideoxy-α-L-*lyxo*-hexopyranosyl chloride (**5a**) and bromide (**5b**) were obtained in quantitative yields. Although these compounds were syrups, they gave satisfactory analyses, and could be converted into anthracycline glycosides[7].

Di-*O*-acetyl-L-rhamnal (**6**) was obtained by Iselin and Reichstein's method[6] in 83% yield, and on treatment with hydrogen chloride or bromide, it afforded crystalline 3,4-di-*O*-acetyl-2,6-dideoxy-α-L-*arabino*-hexopyranosyl chloride (**7a**) and bromide (**7b**) in theoretical yields.

Halides **5a**, **5b**, **7a**, and **7b** were found to be anomerically pure and in the α-L configuration: this was established by n.m.r spectroscopy, and confirmed by their high, negative rotation. The 100-MHz, n.m.r. spectra of the bromides, **5b** and **7b**, shown in Fig. 1, were quite similar to those of the corresponding chlorides (**5a** and **7b**), except that the chemical shift of the anomeric protons of the chlorides were less deshielded, and were shifted by 40 Hz towards higher field. The splitting of the anomeric-proton signal in the spectra of all of the halides prepared is characteristic of equatorial protons coupled by the axial and equatorial protons attached to C-2, with $J_{1,2}$ 3–4 Hz and $J_{1,2'} = 1$ Hz. The $^1C_4$(L) conformation of the compounds was apparent in the coupling of H-4 in the spectra of halides **7a** and **7b**, where H-3, H-4, and H-5 are all axial; the signal appeared as a triplet having the large coupling-constant of 10 Hz. In the spectra of halides **5a** and **5b**, where H-4 is equatorial and flanked by two axial protons, the coupling constant was only ~4 Hz.

EXPERIMENTAL

General. — Melting points were determined with a Kofler block and are uncorrected. Nuclear magnetic resonance spectra were recorded with a Varian HA-100

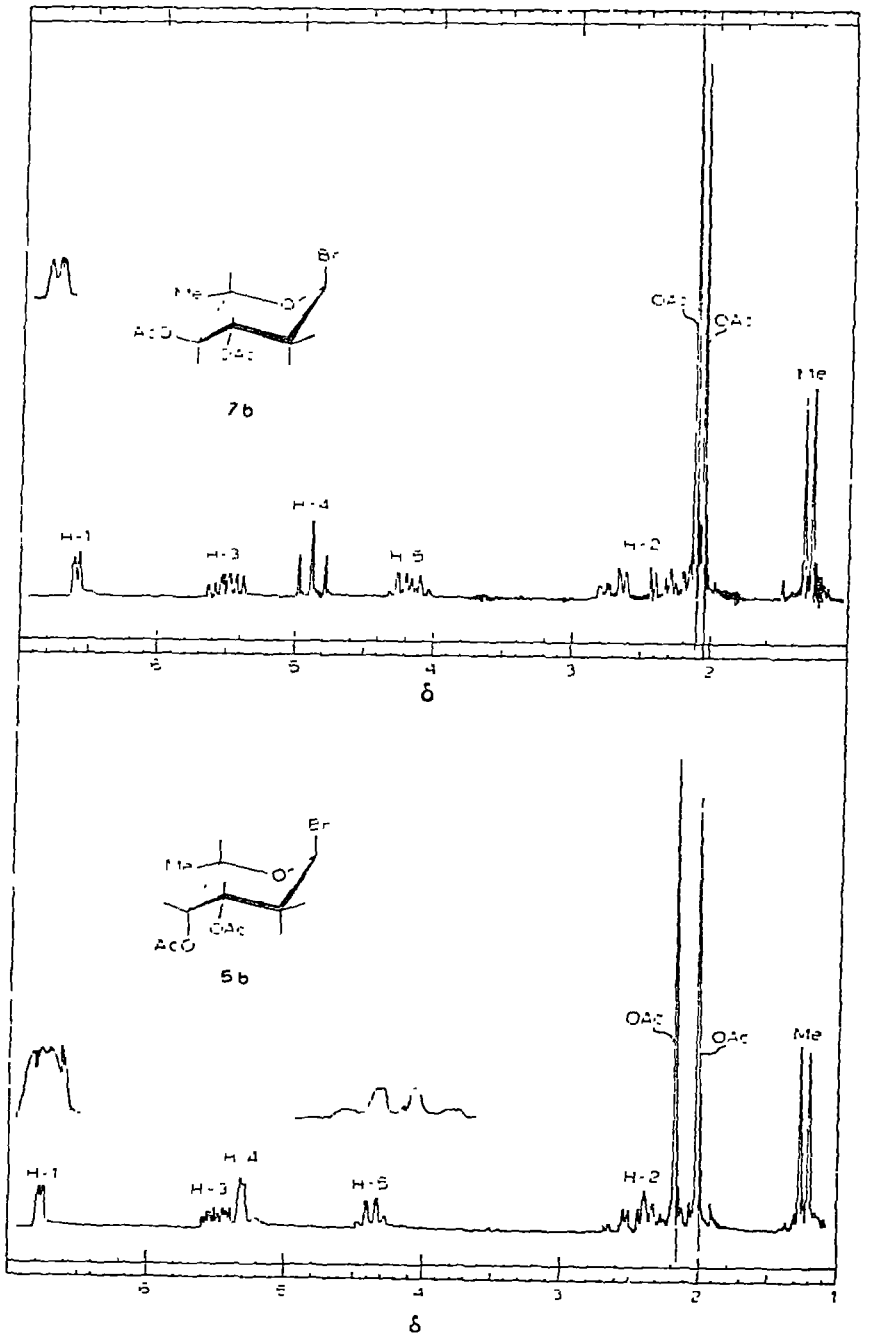


Fig. 1. N.m.r. spectra (100 MHz) of 2,6-dideoxy-α-L-*arabino*-hexopyranosyl bromide (*7b*) and 2,6-dideoxy-α-L-*lyxo*-hexopyranosyl bromide (*5b*).

spectrometer, and infrared spectra with a Perkin–Elmer 621 spectrophotometer. Optical rotations were measured on a Bendix series 1100 polarimeter in calibrated cells. Microanalyses were performed in the Department of Chemistry and Chemical Engineering Microanalytical Laboratory by Miss Pat Smiley with a Perkin–Elmer 240 elemental analyzer.

*1,5-Anhydro-3,4-di-*O*-acetyl-1,2,6-trideoxy-*L*-lyxo-hex-1-enitol* (*di-*O*-acetyl-*L*-*fucal*) (**4**). — Compound **4** was prepared by a modification of a procedure developed by Iselin and Reichstein[5]. L-Fucose (Pfanstiehl Laboratories; 20 g) was suspended in pyridine (75 ml) to which acetic anhydride (75 ml) was slowly added. The mixture was stirred for two days, and then poured into a separatory funnel containing ice, kept for 15 min, and extracted with chloroform; the extract was washed with sodium hydrogencarbonate, dried (sodium sulfate), and evaporated to a syrup. To remove the pyridine remaining, the product was co-distilled with toluene several times. The resulting L-fucose tetraacetate (**1**) was treated with hydrogen bromide in acetic acid for 2 h, and the glycosyl bromide (**2**) was slowly treated with activated zinc dust (20 g) suspended in 50% acetic acid containing sodium acetate. The temperature was kept at 0° until all of the bromide had been added, and then lowered to −10° for 2 h. The cold mixture was filtered, the filtrate extracted with chloroform, and the extract washed with potassium hydrogencarbonate, dried (sodium sulfate), and evaporated under diminished pressure to a syrup. Di-*O*-acetyl-L-fucal distilled at 70°/0.6 torr, and crystallized on standing, m.p. 48–50°, lit.[5] m.p. 47–49).

*3,4-Di-*O*-acetyl-2,6-dideoxy-α-L-lyxo-hexopyranosyl chloride* (**5a**). — Compound **4** (2 g) was dissolved in benzene (75 ml), and 25 ml of the benzene was distilled off, to remove traces of water. A stream of dry hydrogen chloride was passed into the dried solution, which was stirred for 5 min at room temperature, and then evaporated to a syrup under diminished pressure (bath temp. below 35°). The remaining acid was removed by co-distillation with benzene (four 40-ml portions); the resulting syrup (yield 2.3 g) could not be crystallized; $[\alpha]_D^{20}$ −215° (*c* 0.25, chloroform); ν_{max}^{KBr} 1740 (OAc) and 570 cm^{-1} (C–Cl).

Anal. Calc. for $C_{10}H_{15}ClO_5$: C, 47.91; H, 6.03. Found: C, 47.64; H, 5.91.

*3,4-Di-*O*-acetyl-2,6-dideoxy-α-L-lyxo-hexopyranosyl bromide* (**5b**). — Compound **4** (2 g) was dissolved in benzene (75 ml), and 25 ml of the benzene was distilled off, to remove any trace of water. A stream of dry hydrogen bromide was passed into the dried benzene solution, which was processed as described for **5a**, giving a syrup (yield 2.70 g) that could not be crystallized; $[\alpha]_D^{20}$ −190° (*c* 0.27, chloroform), ν_{max}^{KBr} 1740 (OAc) and 520 cm^{-1} (C–Br).

Anal. Calc. for $C_{10}H_{15}BrO_5$: C, 40.70; H, 5.12. Found: C, 40.52; H, 5.32.

*3,4-Di-*O*-acetyl-2,6-dideoxy-α-L-*arabino*-hexopyranosyl chloride* (**7a**). — Di-*O*-acetyl-L-rhamnal[6] (**6**) (2 g) was dissolved in benzene (50 ml), and 20 ml of the benzene was distilled off to remove any traces of water. A stream of dry hydrogen chloride was passed into the dried benzene solution, which was processed as described for **5a**, affording crystals. These were recrystallized from 1:1 isopropyl ether–cyclohexane

(20 ml), yield 1.9 g, m.p. 90°, $[\alpha]_D^{20}$ −120° (*c* 0.3, chloroform); ν_{max}^{KBr} 1740 (OAc) and 570 cm^{-1} (C–Cl).

Anal. Calc. for $C_{10}H_{17}ClO_5$: C, 47.91; H, 6.03. Found: C, 47.95; H, 6.05.

*3,4-Di-O-acetyl-2,6-dideoxy-α-*L-arabino-*hexopyranosyl chloride* (**7b**). — Di-*O*-acetyl-L-rhamnal[6] (**6**) (2 g) was dissolved in benzene (50 ml), and 20 ml of the benzene was distilled off to remove any traces of water. A stream of dry HBr was passed into the dried benzene solution, which was processed as described for **5a**, giving crystals. These were recrystallized from 1:1 isopropyl ether–cyclohexane (20 ml), yield 2.2 g, m.p. 82–83°, $[\alpha]_D^{20}$ −115° (*c* 0.3, chloroform); ν_{max}^{KBr} 1760 (OAc) and 540 cm^{-1} (C–Br).

Anal Calc. for $C_{10}H_{15}BrO_5$: C, 40.70; H, 5.12. Found: C, 40.80; H, 5.13.

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