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Note

The synthesis of methyl 3-amino-2,3,6-trideoxy-α-L-*arabino*-hexopyranoside, a structural analog of daunosamine

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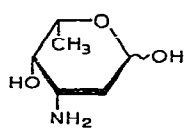
Adriamycin and daunorubicin are members of an important group of naturally occurring antibiotics that exhibit a wide spectrum of antitumor activity[1,2]. However, the chemotherapy of these clinically useful antibiotics is often complicated by undesirable cardiac toxicity[3]. Chemical modifications in the structures of these antibiotics are expected to produce analogs having less toxicity and more activity.

Daunosamine (3-amino-2,3,6-trideoxy-L-*lyxo*-hexose, **1**) is the amino sugar moiety common to adriamycin and daunomycin[4,5]. The syntheses of daunosamine[6] and *N*-benzoyl-D-daunosamine[7] have been reported. The preparation of methyl 3-amino-2,3,6-trideoxy-α-L-*arabino*-hexopyranoside (**4b**), the 4-epimer of **1**, is reported here. Methyl 2,6-dideoxy-3-*O*-*p*-tolylsulfonyl-α-L-*arabino*-hexopyranoside (**2**) was prepared from L-rhamnose according to procedures in the literature[6]. The method of Jarý *et al.*[8] was used to effect the conversion of **2** into methyl 3,4-anhydro-2,6-



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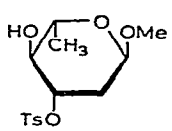

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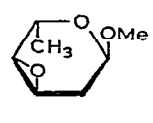

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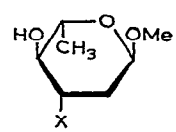

4a, X = N_3
4b, X = NH_2
4c, X = NH_2·HCl
4d, X = NHAc
4e, X = NHBz

dideoxy-α-L-*ribo*-hexopyranoside (**3**). Treatment of the epoxide **3** with sodium azide gave methyl 3-azido-2,3,6-trideoxy-α-L-*arabino*-hexopyranoside (**4a**). Opening of the epoxide **3** at C-3 by azide to give mainly **4a** is consistent with the work of Goodman *et al.*[6]. The azide **4a** was catalytically hydrogenated[9] to afford methyl 3-amino-2,3,6-trideoxy-α-L-*arabino*-hexopyranoside (**4b**). Characterization of the amino sugar **4b** was accomplished by preparing its hydrochloride salt **4c** and the *N*-acetyl (**4d**) and *N*-benzoyl (**4e**) derivatives.

EXPERIMENTAL

General. — Melting points were determined with a Fisher–Johns melting-point apparatus and are corrected. The elemental analyses were performed by Enviro Analytical Laboratory, Knoxville, Tennessee. A Beckman IR-33 spectrophotometer was used for recording the infrared (i.r.) spectra of the compounds.

*Methyl 3-azido-2,3,6-trideoxy-α-*L*-*arabino*-hexopyranoside* (**4a**). — To a warm (60°), stirred solution of methyl 2,6-dideoxy-3-*O*-*p*-tolylsulfonyl-α-L-*arabino*-hexopyranoside[5] (**2**, 140 g, 443 mmoles) in absolute ethanol (1.5 litres) containing phenolphthalein as indicator, was added, portionwise, a saturated solution of sodium hydroxide in absolute ethanol until a pink coloration persisted for 10 min. The mixture was cooled to 10°, and the precipitated sodium *p*-toluenesulfonate was removed by filtration. The filtrate was made neutral with 4M hydrochloric acid, and mixed with sodium azide (79.3 g, 1.22 moles), ammonium chloride (47.4 g, 886 mmoles), and water (10 ml). The suspension was boiled under reflux with stirring for 4 h, cooled, evaporated to dryness under diminished pressure, and the residue extracted with ether. The extracts were dried ($MgSO_4$) and evaporated to dryness *in vacuo*, giving 73.0 g (88.1%) of **4a** as an oil; this was purified by dry-column chromatography on silica gel with chloroform as the eluant; yield of analytically pure material 35.0 g (42.5%, based on **2**); $[\alpha]_D^{25.5}$ −131.8° (*c* 0.50, chloroform); ν_{max}^{neat} 3440, 2925, 2890, 2100, 1440, 1360, 1350, 1300, 1245, 1200, 1175, 1115, 1070, 1040, 970, and 900 cm^{-1}; n.m.r. ($CDCl_3$): δ 4.70 (m, 1, H-1), 3.55 (m, 3, H-3,4,5), 3.30 (s, 3, OCH_3), 3.20 (s, 1, O*H*), 1.90 (m, 2, H-2), and 1.30 (d, 3, *J* 6.5 Hz, CH_3).

Anal. Calc. for $C_7H_{13}N_3O_3$: C, 44.91; H, 7.00; N, 22.45; O, 25.64. Found: C, 44.81; H, 6.98; N, 22.35; O, 25.94.

*Methyl 3-amino-2,3,6-trideoxy-α-*L*-*arabino*-hexopyranoside* (**4b**). — A mixture of **4a** (1.0 g, 5.3 mmoles), 10% palladium-on-charcoal catalyst (0.2 g), and methanol (300 ml) was hydrogenated[9] for 3 h at room temperature. The initial hydrogen pressure was 2.8 $kg.cm^{-2}$. The catalyst was removed by filtration, and the filtrate was evaporated to dryness under diminished pressure to give 650 mg (75%) of **4b** as a colorless solid, m.p. 128–130°. Recrystallization from methanol–ether afforded an analytical sample, m.p. 132–133°; $[\alpha]_D^{26}$ −145.1° (*c* 0.61, methanol); ν_{max}^{Nujol} 3320, 3295, 3120, 2980–2830, 1585, 1450, 1375, 1300, 1225, 1210, 1180, 1130, 1115, 1060, 1040, 1020, 970, 900, 820, and 750 cm^{-1}; n.m.r. ($CDCl_3$): δ 4.58 (d, 1, *J* 3 Hz, H-1), 3.45 (m, 1, H-5), 3.20 (s, 3, OCH_3), 2.80 (m, 2, H-3,4), 2.48 (m, 3, NH_2 and O*H*), 1.80 (m, 2, H-2), and 1.20 (d, 3, *J* 6 Hz, CH_3).

Anal. Calc. for $C_7H_{15}NO_3$: C, 52.16; H, 9.38; N, 8.69; O, 29.78. Found: C, 52.28; H, 9.52; N, 8.52; O, 30.03.

*Methyl 3-amino-2,3,6-trideoxy-α-*L*-*arabino*-hexopyranoside hydrochloride* (**4c**). — A solution of conc. hydrochloric acid in anhydrous ether was added dropwise to a solution of **4b** (0.5 g, 3 mmoles) in anhydrous ether (100 ml) until it became acidic. Filtration of the resulting, white precipitate afforded 550 mg (90%) of **4c**, m.p. 194–196° (dec.). Recrystallization from ethanol–ether gave an analytical sample,

m.p. 196–198° (dec.), $[\alpha]_D^{25}$ −115.5° (*c* 0.5, methanol); ν_{max}^{Nujol} 3360, 3320, 2960–2860, 1600, 1525, 1460, 1375, 1210, 1120, 1060, 970, and 900 cm^{-1}.

Anal. Calc. for $C_7H_{16}ClNO_3$: C, 42.53; H, 8.16; Cl, 17.94; N, 7.08. Found: C, 42.57; H, 8.12; Cl, 18.03; N, 7.20.

*Methyl 3-acetamido-2,3,6-trideoxy-α-*L-arabino-*hexopyranoside* (**4d**). — Acetic anhydride (1.0 ml, 9.8 mmoles) was added to a cold (0°), stirred solution of **4b** (1.0 g, 6.2 mmoles) in methanol (50 ml)[9]. The solution was stirred for 3 h at 0–5°, evaporated to dryness under diminished pressure, and the residue triturated with petroleum ether (b.p. 30–60°), to give 1.0 g (90%) of **4d**; m.p. 156–158°. An analytical sample, m.p. 159–160°, $[\alpha]_D^{25}$ −148.0° (*c* 0.4, methanol), was prepared by recrystallization from ethanol–ether; ν_{max}^{Nujol} 3280, 2960–2820, 1640, 1525, 1455, 1370, 1340, 1295, 1270, 1240, 1145, 1120, 1100, 1035, 1010. 970, 910, and 850 cm^{-1}.

Anal. Calc. for $C_9H_{17}NO_4$: C, 53.19; H, 8.43; N, 6.89. Found: C, 53.41; H, 8.37; N, 7.05.

*Methyl 3-benzamido-2,3,6-trideoxy-α-*L-arabino-*hexopyranoside* (**4e**). — Benzoyl chloride (1.0 ml, 7 mmoles) was added dropwise to a cold (0°), stirred solution of **4b** (0.5 g, 3 mmoles) in methanol (50 ml). After being stirred for 2 h at 0–5°, the solution was evaporated to dryness under diminished pressure, the residue triturated with petroleum ether (b.p. 30–60°), and the resulting solid recrystallized twice from methanol–ether to give 490 mg (60%) of **4e** as colorless crystals, m.p. 204–206°, $[\alpha]_D^{25}$ −92.0° (*c* 0.52, methanol); ν_{max}^{Nujol} 3400, 3280, 2960–2840, 1625, 1540, 1450, 1370, 1325, 1110, 1050, 1040, 960, 910, and 680 cm^{-1}.

Anal. Calc. for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.22; N, 5.28. Found: C, 63.59; H, 7.08; N, 5.22.

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