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Note

Daunosamine derivatives suitable for the synthesis of anthracycline analogs and disaccharides

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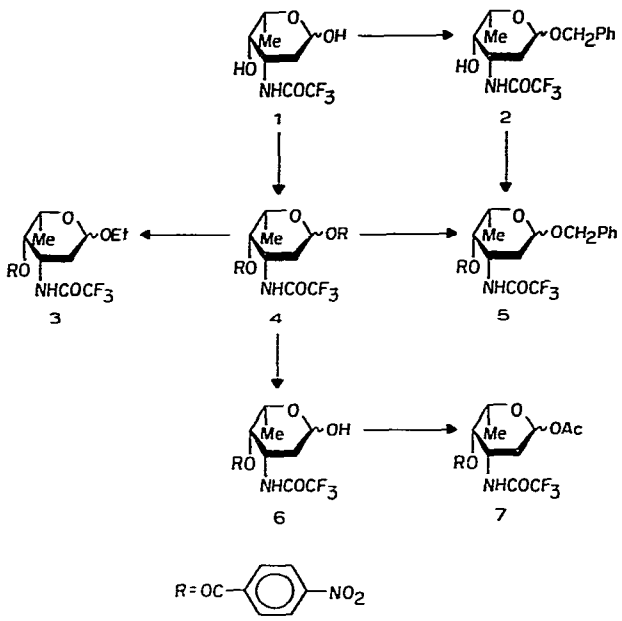
Daunosamine, the sugar component of the anti-tumor anthracycline antibiotics daunorubicin[1], adriamycin[2], and carminomycin[3], has been used in the preparation of anthracycline antibiotics and their analogs. The method of linkage most commonly employed has been to allow the glycosyl halide to react with the anthracyclinone[4–8]. However, the glycosyl halide of daunosamine lacks stability, and is difficult to prepare in large quantities. A better approach for the synthesis of anthracycline analogs is to treat daunosamine esters with the anthracyclinone in the presence of a Lewis-acid catalyst[9].

The present work deals with the synthesis of daunosamine glycosides and esters suitable for the preparation of anthracycline analogs[1]. A number of partially protected daunosamine derivatives suitable for the preparation of daunosamine-containing disaccharides were also prepared. These daunosamine derivatives have O-4 free, to allow reaction thereof with glycosyl halides, and possess a benzyl group on O-1 (so that this group may later be removed by catalytic hydrogenation). Other daunosamine derivatives have been prepared that possess a free hydroxyl group on C-1.

Starting with *N*-(trifluoroacetyl)daunosamine (**1**), we obtained the benzyl glycoside **2** in crystalline form by reaction of **1** with benzyl alcohol in the presence of *p*-toluenesulfonic acid. Compound **2** has on O-1 a benzyl group that can be removed by catalytic hydrogenation after a disaccharide has been formed by reaction with a suitable glycosyl halide. It should be noted that all disaccharides thus obtained would have the daunosamine moiety as the reducing-sugar residue. Compound **2** was characterized by conversion into the 4-(*p*-nitrobenzoate) (**5**). The latter was also prepared from the known 1,4-bis(*p*-nitrobenzoate)[4] (**4**) by reaction with benzyl alcohol in the presence of *p*-toluenesulfonic acid. This method of preparing the glycosides is quite general, and is not restricted to benzyl glycosides. Thus, the reaction of the bis(*p*-nitrobenzoate) **4** with ethanol in the presence of *p*-toluenesulfonic acid yielded the ethyl glycoside (**3**). It should be noted that the glycosidations occur with yields ranging between 80% for the benzyl glycoside to 70% for the ethyl glycoside.



To prepare a daunosamine derivative having O-4 protected and O-1 free, the bis-(*p*-nitrobenzoate) **4** was subjected to acid-catalyzed hydrolysis, to give **6**, characterized by conversion into the crystalline 1-acetate **7**.

The high yields obtained during the aforementioned glycosidations, and the fact that most of the products were obtained crystalline, render the reactions useful in the synthesis of anthracycline analogs and disaccharides.

EXPERIMENTAL

General. — Melting points were determined with a Kofler block and are uncorrected. Optical rotations were measured with a Bendix series 1100 polarimeter. N.m.r. spectra were recorded with a Varian EM-360 spectrometer, with tetramethylsilane as the internal standard, and chloroform-*d* as the solvent, unless otherwise indicated. Thin-layer chromatograms were obtained on Eastman Kodak 13181 silica-gel plates. Chromatography columns were packed with Sargent-Welch SC 14608 silica gel (60–200 mesh). Microanalyses were performed in the Department of Chemistry and Chemical Engineering Microanalysis Laboratory by Mrs. S. Brotherton. Petroleum ether refers to the fraction boiling at 30–60°.

Benzyl 2,3,6-trideoxy-3-(trifluoroacetamido)-L-lyxo-*hexopyranoside* (**2**). — 2,3,6-Trideoxy-3-(trifluoroacetamido)-L-*lyxo*-hexopyranose (**1**, 0.42 g) was suspended in benzyl alcohol (5 mL), and the suspension treated with *p*-toluenesulfonic acid (15 mg). The mixture was stirred for 16 h at room temperature, and the resulting, clear solution was extracted with chloroform. The extract was washed successively with water, saturated sodium hydrogencarbonate solution, and water, and evaporated under

diminished pressure, to give a syrup, part of which (40 mg, 7%) crystallized immediately after the addition of isopropyl ether; m.p. 154–155°, $[\alpha]_D$ —87° (*c* 0.036, chloroform); n.m.r. data (acetone-d_6): δ 7.46 (*s*, 5 H, Ph), 5.44 (q, $J_{1,2a}$ 2, $J_{1,2e}$ 4 Hz, H-1), 4.78 (AB d of d, *J* 12 Hz, 2 H, benzylic CH_2), 2.28–2.05 (m, 2 H, H-2), and 1.20 (d, *J* 6 Hz, 3 H, CH_3-5). On concentration and treatment with ether and hexane, the mother liquor yielded (after 3 days at 0°) more crystalline material (anomeric mixture), which was filtered off (yield 0.21 g, 36%). On repeated, slow evaporation of the mother liquor from isopropyl ether, it, also, crystallized.

Anal. Calc. for $C_{15}H_{18}F_3NO_4$: C, 54.05; H, 5.44; N, 4.20. Found: C, 54.42; H, 5.60; N, 4.14.

*Benzyl 2,3,6-trideoxy-4-*O-(p-*nitrobenzoyl*)-*3-(trifluoroacetamido*)-L-lyxo-*hexopyranoside* (**5**). — *a.* A cooled solution of **2** (50 mg) in pyridine (2 mL) was treated with *p*-nitrobenzoyl chloride (180 mg), and stirred for 4 h at room temperature. Ice and water were added, and the mixture was extracted with chloroform. The extract was successively washed with potassium hydrogencarbonate solution and water, dried (sodium sulfate), and evaporated, and the residue was purified by column chromatography. Elution with 1 : 1 ether–petroleum ether gave the title compound, which was isolated as a homogeneous syrup (50 mg, 69%). It crystallized from ether–petroleum ether, m.p. 122–126°, $[\alpha]_D$ —137° (*c* 0.6, chloroform); n.m.r. data: δ 8.32 (*s*, 4 H, *p*-nitrobenzoyl), 7.44 (*s*, 5 H, benzylic phenyl), 6.45 (m, 1 H, NH), 5.48 (m, 1 H, H-4), 5.18 (m, 1 H, H-1), 4.70 (AB pair of doublets, *J* 12 Hz, 2 H, benzylic CH_2), 4.27 (broadened quartet, *J* 6.4 Hz, 1 H, H-5), 2.22–1.96 (m, 2 H, H-2), and 1.18 (d, *J* 6.5 Hz, 3 H, CH_3-5).

Anal. Calc. for $C_{22}H_{21}F_3N_2O_7$: C, 54.77; H, 4.35; N, 5.80. Found: C, 54.78; H, 4.12; N, 5.40.

b. Compound **4** (170 mg) was suspended in a mixture of benzene (4 mL) and nitromethane (2 mL). Benzyl alcohol (0.2 mL) and *p*-toluenesulfonic acid (10 mg) were then added, and the mixture was stirred for 4 h at room temperature. Ethyl acetate was finally added, and the solution was successively washed with sodium hydrogencarbonate solution and water, dried (sodium sulfate), and evaporated. The residue was applied to a column of silica gel, and the product was eluted with 1 : 1 ether–petroleum ether. Crystallization from ether–petroleum ether afforded the pure product (120 mg, 80%), m.p. 122–126°.

*2,3,6-Trideoxy-4-*O-(p-*nitrobenzoyl*)-*3-(trifluoroacetamido*)-L-lyxo-*hexopyranose* (**6**).–Dry HCl was passed through a cooled solution of compound **4** (210 mg) in dichloromethane (5 mL) for 15 min. The mixture was then stirred for 2 h at room temperature, and the solid was filtered off (58 mg of *p*-nitrobenzoic acid). The filtrate was evaporated, to give an amorphous residue which was purified by chromatography on silica gel. Elution with 39:1 dichloromethane–methanol removed the fast-moving, minor components (the starting materials and a trace of halide). Continued elution with the same solvent system gave amorphous **6** (60 mg, 40%), $[\alpha]_D$ — 184° (*c* 0.65, 1:1 chloroform–methanol).

Anal. Calc. for $C_{15}H_{15}F_3N_2O_7$: C, 45.91; H, 3.82; N, 7.14. Found: C, 46.02; H, 3.86; N, 7.12.

1-O-Acetyl-2,3,6-trideoxy-4-O-(p-nitrobenzoyl)-3-(trifluoroacetamido)-L-lyxo-hexopyranose (**7**). — Compound **6** (70 mg) was acetylated with acetic anhydride–pyridine in the usual way. The residue obtained on evaporation crystallized from ether–petroleum ether (yield 60 mg, 78%), m.p. 152–156°, $[\alpha]_D$ —139° (*c* 0.3, chloroform).

Anal. Calc. for $C_{17}H_{17}F_3N_2O_8$: C, 47.00; H, 3.91; N, 6.45. Found: C, 46.95; H, 3.93; N, 6.37.

Ethyl 2,3,6-trideoxy-4-O-(p-nitrobenzoyl)-3-(trifluoroacetamido)-L-lyxo-hexopyranoside (**3**). — To a solution of compound **4** (165 mg) in benzene (6 mL) and nitromethane (2 mL) were added ethyl alcohol (0.25 mL) and *p*-toluenesulfonic acid (7 mg), and the mixture was stirred for 2 h at room temperature. Ethyl acetate was then added, and the organic layer was successively washed with potassium hydrogencarbonate solution and water, dried (sodium sulfate), and evaporated, to give a syrup which was applied to a column of silica gel. Compound **3** was obtained by elution with 1:1 ether–petroleum ether, yield 90 mg (70% syrup). A small sample crystallized from ether–petroleum ether, m.p. 172–178°, $[\alpha]_D$ —97° (*c* 0.24, chloroform); n.m.r. data: δ 8.32 (s, 4 H, *p*-nitrobenzoyl), 6.43 (m, 1 H, NH), 5.42 (m, 1 H, H-4), 3.75 (q, *J* 7.5 Hz, 2 H, CH_2 of ethyl), 1.28 (d, 3 H, *J* 6.5 Hz, CH_3-5), and 1.28 (t, 3 H, *J* 7.5 Hz, CH_3 of ethyl).

Anal. Calc. for $C_{17}H_{19}F_3N_2O_7$: C, 48.57; H, 4.52; N, 6.66. Found: C, 48.54; H, 4.61; N, 6.55.

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