Note

Synthesis of tetrazoles from acylated aldononitriles.
Part I. Synthesis of tetrazoles from penta-*O*-acyl-D-galactononitriles

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Synthesis of 5-alkyl- and 5-aryl-tetrazoles from acid nitriles has been widely studied. Mihina and Herbst[1] described the synthesis of 5-substituted tetrazoles by the reaction of nitriles with hydrazoic acid in benzene or alcohol for 96–120 h at 110–150° in a sealed tube. Behringer and Kohl[2] and Lieber *et al.*[3] prepared tetrazoles under less drastic conditions by boiling a solution of the nitrile in benzene or tetrahydrofuran with aluminum azide under reflux. Finnegan *et al.*[4] introduced other solvents and azides for these syntheses, particularly the use of the nitrile in *N,N*-dimethylformamide with ammonium or lithium azide formed *in situ* from a mixture of sodium azide and ammonium or lithium chloride.

We now describe the extension of this reaction to acylated aldononitriles in order to prepare tetrazoles having a polyhydroxyalkyl chain on C-5. In some instances, the reaction was unsatisfactory because of the lability of the particular aldononitrile to long heating in the reaction medium. However, the reaction conditions described by Finnegan *et al.*[4] could be applied with good results (66% yield) to penta-*O*-benzoyl-D-galactononitrile, giving 5-(D-*galacto*-pentabenzoyloxypentyl)tetrazole (**2**), but no such product could be obtained from penta-*O*-acetyl-D-galactononitrile.

However, we have found that the reaction of the acylated aldononitriles with prepared ammonium azide in *N,N*-dimethylformamide proceeds to completion at 25–35°. Under these conditions, 5-(D-*galacto*-pentaacetoxypentyl)tetrazole (**1**) was obtained in 51% yield from penta-*O*-acetyl-D-galactononitrile, and **2** in 95% yield from penta-*O*-benzoyl-D-galactononitrile. Deacylation of both **1** and **2** with sodium methoxide gave 5-(D-*galacto*-pentahydroxypentyl)tetrazole (**3**).

Synthesis of tetrazoles from other per-*O*-acylaldononitriles, and of derivatives of these compounds having potential pharmacological properties, are in progress in our laboratory.

EXPERIMENTAL

*5-(*D*-galacto-Pentaacetoxypentyl)tetrazole* (**1**). — Penta-*O*-acetyl-D-galactononitrile[5] (5 g) was dissolved in *N,N*-dimethylformamide (25 ml), and ammonium azide* (1.2 g) was added. The mixture was kept at room temperature (25–35°) with occasional shaking until the ammonium azide had completely dissolved (24–48 h). The reaction was monitored by t.l.c.; the nitrile had all reacted after 5–7 days. The solution was evaporated *in vacuo* (bath temp. $<50°$), and the residue was dissolved in water (30 ml). Compound **1** (2.85 g; 51%) was crystallized on scratching, and recrystallized from water, affording needles of m.p. 100–102°, $[\alpha]_D^{20}$ +32.8° (*c* 0.85, chloroform).

Anal. Calc. for $C_{16}H_{22}N_4O_{10}$: C, 44.65; H, 5.15; N, 13.02. Found: C, 44.20; H, 5.58; N, 12.85.

5-(D-galacto-*Pentabenzoyloxypentyl*)*tetrazole* (**2**). — *Method A.* The technique just described was applied to penta-*O*-benzoyl-D-galactononitrile[6] (5 g). After evaporation of the reaction mixture and dissolution of the residue in ethanol (30 ml), compound **2** (5.1 g; 95%) was isolated as needles. Recrystallization from ethanol gave needles having m.p. 163–165°, $[\alpha]_D^{26}$ +5.76° (*c* 0.83, chloroform).

Anal. Calc. for: $C_{41}H_{32}N_4O_{10}$: C, 66.48; H, 4.32; N, 7.56. Found: C, 66.22; H, 4.69; N, 7.40.

Method B. To a solution of penta-*O*-benzoyl-D-galactononitrile[6] (11 g) in *N,N*-dimethylformamide (50 ml) were added sodium azide (3.64 g) and ammonium chloride (3.0 g), and the mixture was heated during 10 h at 110°, and cooled. Water (100 ml) was added, and the mixture was stirred for several hours until a solid was obtained; this was filtered off, washed with water, and recrystallized from ethanol. Compound **2** (7.7 g; 65.9%) was obtained, having the same physical properties as for the compound prepared by Method A.

5-(D-galacto-*Pentahydroxypentyl*)*tetrazole* (**3**). — To a solution of compound **1** (1 g) in methanol (50 ml) was added some sodium methoxide, and the solution was kept for 24 h at room temperature. It was neutralized with Zeo Karb 225, the suspension was filtered, and the filtrate was evaporated; the residue (0.45 g; 90%) crystallized from water as rectangular plates, m.p. 218–220°, $[\alpha]_D^{26}$ +12.8° (*c.* 0.96, water).

By the same procedure, **3** was obtained from **2** in similar yield.

Anal. Calc. for $C_6H_{12}N_4O_5$: C, 32.73; H, 5.49; N, 25.45. Found: C, 33.00; H, 5.62; N, 25.35.

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*Ammonium azide was prepared by heating a mixture of ammonium chloride (12.47 g), sodium azide (15.61 g), and *N,N*-dimethylformamide (20 ml) at 110°. The sublimed product crystallized from methanol as needles (11.6 g; 82.8%).

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