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Note

Synthesis of aldopyranosyl cyanides

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Use of the cyano group, added *via* the Kiliani or cyanohydrin synthesis as a one-carbon, chain-extending unit, has a long history in carbohydrate chemistry. The same reaction has been used to prepare branched-chain sugars[1,2]. However, the preparation of glycosyl cyanides has been limited, even though they have an obvious utility in the preparation of *C*-glycosyl compounds, particularly after equivalence of the cyano group with the formyl group had been demonstrated[3].

Reaction of per-*O*-acylated aldopentofuranosyl halides with metal cyanides, most frequently mercuric cyanide, gives good yields of aldofuranosyl cyanides[4]. In the hexopyranose series, only β-D-galactopyranosyl cyanide has been efficiently prepared[5,6]. Recent reports of the use of trimethylsilyl cyanide for this purpose indicate facile exchange of a hemiacetal ester group for a cyano group[7,8], and an elimination–addition reaction of glycals in the presence of catalytic amounts of Lewis acids[9].

We now report the synthesis of hitherto unknown aldopyranosyl cyanides obtained by dehydration of the corresponding amides. Some 3,4,5,7-tetra-*O*-acetyl-2,6-anhydroheptonamides* are available by photochemical addition of formamide to 2,3,4,6-tetra-*O*-acetyl-hex-1-enitols[10,11]. The carbamoylation has been studied in detail, and the configuration of all photoadducts has been established[12,13].

3,4,5,7-Tetra-*O*-acetyl-2,6-anhydro-D-*glycero*-D-*ido*-heptonamide (**1**), 3,4,5,7-tetra-*O*-acetyl-2,6-anhydro-D-*glycero*-D-*talo*-heptonamide (**2**), 3,4,5,7-tetra-*O*-acetyl-2,6-anhydro-D-*glycero*-L-*gluco*-heptonamide (**3**), and 3,4,5,7-tetra-*O*-acetyl-2,6-anhydro-D-*glycero*-L-*altro*-heptonamide were dehydrated to give good yields of glycopyranosyl cyanides having the α-D-*gluco* (**4**), α-D-*manno* (**5**), α-D-*galacto* (**6**), and β-D-*talo* configurations, respectively. *N*-(Chloromethylene)-*N*-methylmethanaminium chloride (chloromethylenedimethylforminium chloride), generated *in situ* from

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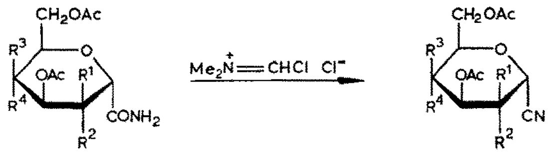
*The starting compounds are named as amides of anhydroaldonic acids. The dehydration products are named as glycosyl cyanides, in accordance with a tradition well established in carbohydrate literature.



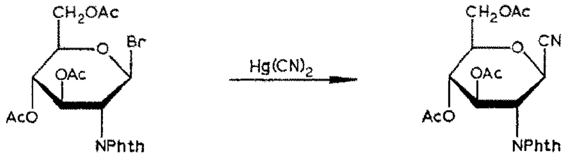
1 R^1 = H, R^2 = OAc, R^3 = H, R^4 = OAc 4

2 R^1 = OAc, R^2 = H, R^3 = H, R^4 = OAc 5

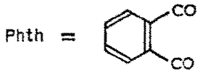
3 R^1 = H, R^2 = OAc, R^3 = OAc, R^4 = H 6

N,*N*-dimethylformamide and oxalyl chloride[14-16], was used as the dehydrating agent.

In part because of neighboring-group participation, replacement of the halogen atom of per-*O*-acylated aldosyl halides by cyanide ion is a complex process giving only products having 1,2-*trans* geometry, in poor yield[6]. We investigated the reactions of cyanide ion with 3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl bromide[17,18] with mercuric cyanide in acetonitrile, with and without addition of a quaternary ammonium salt to the reaction mixture, because this derivative of 2-amino-2-deoxy-D-glucose has a nonparticipating group at C-2, so that a stable 1,2-*trans* glycosyl halide can be prepared, and because 2-acetamido-2-deoxy-α-D-glucopyranosyl cyanide was the desired goal. In all cases, only one cyanide, identified by ^{1}H-n.m.r. spectroscopy as that having the β-D configuration, was obtained in poor yield, indicating that more than neighboring-group participation is involved in determining the configuration of the product. This finding is an extension of the results of Akiya and Osawa[17] and of Lemieux *et al.*[18], *viz.*, that both compound **7** and its α anomer give, in high yield, glycosides with 1,2-*trans* geometry, even though there is no evidence of orthoester formation.



7 8



For none of the glycopyranosyl cyanides could the characteristic C≡N stretching band be found in the infrared spectrum recorded for either a pellet or a Nujol mull. This phenomenon, noted previously[5,6], is still unexplained.

EXPERIMENTAL

General. — Melting points were determined with a Thomas–Hoover Uni-melt apparatus and are uncorrected. Optical rotations were determined with a Bendix ETL-NPL automatic polarimeter. Infrared spectra were recorded with a Perkin–Elmer 297 infrared spectrophotometer. ^{1}H-N.m.r. spectra were recorded, for solutions in deuteriochloroform (internal standard, tetramethylsilane), with a Nicolet NT-200, 200-MHz spectrometer.

Amide dehydration; general procedure. — To a solution of *N,N*-dimethylformamide (0.19 mL, 2.4 mmol) in dry acetonitrile (5 mL) stirred at 0° under argon was added oxalyl chloride (0.20 mL, 2.3 mmol) (white precipitate appears); this was followed by a solution of a 3,4,5,7-tetra-*O*-acetyl-2,6-anhydro-D-heptonamide (0.75 g, 2 mmol) in acetonitrile (2 mL). The reaction mixture became homogeneous on complete addition of the heptonamide solution. Dry pyridine (0.36 mL, 4.4 mmol) was added, and stirring was continued for 15 min. The mixture was then diluted with dichloromethane (60 mL), washed with saturated brine containing 1% of HCl (2 × 20 mL), dried (magnesium sulfate), and evaporated, to yield a colorless oil which was purified by chromatography on a column of silica gel 60 (Merck; 230–400 mesh) with 2:1 (v/v) light petroleum–ethyl acetate.

*2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl cyanide* (**4**). — Yield 67%; m.p. 112°, $[\alpha]_D$ +76° (*c* 1.0, CH_2Cl_2); ^{1}H-n.m.r.: δ 2.0, 2.3 (4 s, 12 H, 4 AcO), 4.09 (m, 1 H, H-5), 4.24 (2 pd, $J_{5,6}$ 2.0, $J_{5,6'}$ 4.5, $J_{6,6'}$ 13.0 Hz, 2 H, H-6,6′), 5.04 (d, $J_{2,3}$ 9.5 Hz, 1 H, H-2), 5.09 (t, $J_{3,4} = J_{4,5} = 9.5$ Hz, 1 H, H-4), 5.12 (s, 1 H, H-1), and 5.46 (t, $J_{2,3} = J_{3,4} = 9.5$ Hz, 1 H, H-3).

Anal. Calc. for $C_{15}H_{19}NO_9$: C, 50.42; H, 5.36; N, 3.92. Found: C, 50.53; H, 5.27; N, 3.78.

*2,3,4,6-Tetra-*O*-acetyl-α-D-mannopyranosyl cyanide* (**5**). — Yield 75%; m.p. 149–150°, $[\alpha]_D$ −28° (*c* 1.0, CH_2Cl_2); ^{1}H-n.m.r.: δ 2.01, 2.06, 2.12, 2.26 (4 s, 12 H, 4 AcO), 3.71 (m, 1 H, H-5), 4.21 (m, $J_{5,6}$ 2.5, $J_{5,6'}$ 5.5, $J_{6,6'}$ 14.8 Hz, H-6,6′), 4.61 (d, $J_{1,2}$ 1.6 Hz, 1 H, H-1), 5.05 (pd, $J_{2,3}$ 3.5, $J_{3,4}$ 10.0 Hz, H-3), 5.26 (t, $J_{3,4} = J_{4,5} =$ 10.0 Hz, 1 H, H-4), and 5.63 (pd, 1 H, H-2).

Anal. Calc. for $C_{15}H_{19}NO_9$: C, 50.42; H, 5.36; N, 3.92. Found: C, 50.61; H, 5.32; N, 3.85.

*2,3,4,6-Tetra-*O*-acetyl-α-D-galactopyranosyl cyanide* (**6**). — Yield 87%; m.p. 97°, $[\alpha]_D$ +120° (*c* 1.0, CH_2Cl_2); ^{1}H-n.m.r.: δ 2.02, 2.08, 2.16 (3 s, 12 H, 4 AcO), 4.13 (m, 2 H, H-6,6′), 4.32 (pt, $J_{5,6} = J_{4,5} = 1.5$ Hz, $J_{5,6'}$ 6.5 Hz, 1 H, H-5), 5.15–5.35 (m, 3 H, H-1,2,3), and 5.54 (m, $\Sigma J \sim 5$ Hz, H-4).

Anal. Calc. for $C_{15}H_{19}NO_9$: C, 50.42; H, 5.36; N, 3.92. Found: C, 50.59; H, 5.47; N, 3.88.

*2,3,4,6-Tetra-*O*-acetyl-β-D-talopyranosyl cyanide.* — Yield 81%; m.p. 118°, $[\alpha]_D$ −2° (*c* 1.0, CH_2Cl_2); ^{1}H-n.m.r.: δ 2.01, 2.08, 2.16, 2.23 (4 s, 12 H, 4 AcO), 3.97 (pt, $J_{5,6} = J_{4,5} = 1.6$ Hz, $J_{5,6'}$ 6.2 Hz, 1 H, H-5), 4.20 (d, 2 H, H-6,6′), 4.66 (d, 1 H, H-4), 5.12 (t, $J_{1,2} = J_{2,3} = 3.7$ Hz, 1 H, H-2), 5.32 (d, 1 H, H-1), and 5.49 (bs, 1 H, H-3).

Anal. Calc. for $C_{15}H_{19}NO_9$: C, 50.42; H, 5.36; N, 3.92. Found: C, 50.67; H, 5.32; N, 3.90.

3,4,6-Tri-O-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl cyanide (**8**). — 3,4,6-Tri-*O*-acetyl-2-deoxy-2-phthalimido-*β*-D-glucopyranosyl bromide[18] (**7**; 0.996 g, 2 mmol) was dissolved in dry acetonitrile (10 mL). Mercuric bromide (0.758 g, 3 mmol) was added, and the mixture was stirred in a tightly stoppered flask for 48 h at room temperature, and evaporated under diminished pressure. The residue was dissolved in chloroform (20 mL), and the solution was successively washed with 1:1 (v/v) water–conc. ammonia (4 × 10 mL) and water (2 × 10 mL), and evaporated. Chromatography of the residue on a column of silica gel with 2:1 (v/v) light petroleum–ethyl acetate gave **8**; yield 0.107 g (12%). Recrystallization was effected from hexane–ethyl acetate; m.p. 178°, $[\alpha]_D$ +78° (*c* 1.0, CH_2Cl_2); ^{1}H-n.m.r.: δ 1.88, 2.05, 2.15 (3 s, 9 H, 3 AcO), 3.90 (pq, $J_{5,6}$ 2.3, $J_{5,6'}$ 4.7, $J_{4,5}$ 10.0 Hz, 1 H, H-5), 4.24 (2 pd, $J_{6,6'}$ 12.7 Hz, 2 H, H-6,6'), 4.67 (t, $J_{1,2} = J_{2,3} =$ 10.5 Hz, 1 H, H-2), 5.20 (pd, $J_{3,4}$ 9.5 Hz, 1 H, H-4), 5.38 (d, 1 H, H-1), and 5.75 (pd, 1 H, H-3).

Anal. Calc. for $C_{21}H_{20}NO_9$: C, 56.75; H, 4.55; N, 6.30. Found: C, 56.91; H, 4.66; N, 6.32.

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