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The Preparation of Some Cyanoethyl Derivatives of Glucose

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The preparations of the following crystalline substances, required for the purposes of partial cyanoethylation studies are described: 3-*O*-(2-cyanoethyl)-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose, 3-*O*-(2-cyanoethyl)-D-glucose, 6-*O*-(2-cyanoethyl)-1,2:3,5-di-*O*-methylene-α-D-glucofuranose, 6-*O*-(2-cyanoethyl)-D-glucose, methyl 4,6-*O*-benzylidene-2-*O*-(2-cyanoethyl)-α-D-glucopyranoside, 2-*O*-(2-cyanoethyl-D-glucose, methyl 4,6-*O*-benzylidene-3-*O*-(2-cyanoethyl)-α-D-glucopyranoside, methyl 3-*O*-(2-cyanoethyl)-α-D-glucopyranoside and methyl 4,6-*O*-benzylidene-2,3-di-*O*-(2-cyanoethyl)-α-D-glucopyranoside.

In connection with partial cyanoethylation studies on glucosides some mono-(2-cyanoethyl) ethers of glucose were required as reference materials. 1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranose and 1,2:3,5-di-*O*-methylene-α-D-glucofuranose [1] were chosen as suitable intermediates for the syntheses of 3-*O*- and 6-*O*-(2-cyanoethyl)-D-glucose, respectively.

Danilov and Lopatenok [2] and also Carter [3] have reported that cyanoethyl cellulose on treatment with sodium in liquid ammonia yields a cellulose with some deoxyglucose residues combined in the chain molecules in addition to suffering the more expected cleavage of the cyanoethyl groups to yield the unsubstituted anhydroglucose units. This reaction does not appear to have been investigated with simple compounds. In order to study the reaction, it was thought desirable to have, in addition to the two cyanoethyl derivatives of the two acetals described above, some partially cyanoethylated glucopyranosides. For this purpose methyl 4,6-*O*-benzylidene-α-D-glucopyranoside was chosen as a suitable starting material.

Crystalline 3-*O*-(2-cyanoethyl)-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose was prepared as described by Corbett [4] who obtained this compound as a syrup. Mild acid hydrolysis gave crystalline 3-*O*-(2-cyanoethyl)-D-glucose. It showed upward mutarotation indicating that it crystallised as the β-derivative.

1,2:3,5-Di-*O*-methylene-α-D-glucofuranose [1] on treatment with acrylonitrile under the same conditions as those used for the di-*O*-isopropylidene derivative

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gave the crystalline 6-*O*-(2-cyanoethyl) derivative. This on careful acid hydrolysis and recycling of incompletely hydrolysed material gave crystalline 6-*O*-(2-cyanoethyl)-D-glucose. This showed downward mutarotation indicating that it crystallised as the α-derivative. Some degradation of the cyanoethyl groups occurred during the hydrolyses.

Partial cyanoethylation of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside followed by column chromatography and fractional crystallisation gave the crystalline 2-*O*-, 3-*O* and 2,3-di-*O*-(2-cyanoethyl) ethers, the latter in two crystalline modifications. The yields were rather low due to the number of steps involved in the fractionations, and also to the rather low degree of substitution obtained in the reaction.

Acid hydrolysis of methyl 4,6-*O*-benzylidene-2-*O*-(2-cyanoethyl)-α-D-glucopyranoside yielded crystalline 2-*O*-(2-cyanoethyl)-D-glucose. It showed upward mutarotation indicating that it crystallised as the β-derivative.

Mild acid hydrolysis of methyl 4,6-*O*-benzylidene-3-*O*-(2-cyanoethyl)-α-D-glucopyranoside yielded crystalline methyl 3-*O*-(2-cyanoethyl)-α-D-glucopyranoside. Further hydrolysis yielded crystalline 3-*O*-(2-cyanoethyl)-D-glucose, identical with the material prepared as described above.

The 2-*O*-, 3-*O*- and 6-*O*-(2-cyanoethyl) ethers of glucose had the same mobilities on paper electrophoresis in germanate buffer [5] as the corresponding mono-*O*-methyl ethers of glucose. This confirmed the structures assigned to the 2-cyanoethyl ethers.

EXPERIMENTAL

All melting points are corrected. Evaporations were carried out under reduced pressure at a bath temperature below 40°.

Chromatography. Paper: Whatman No. 1. Solvent: Butanol-ethanol-water 10:3:5. Ascending thin layer chromatography [6]. Absorbent: Kieselgel G nach Stahl, E. Merck AG. Solvents: A. Benzene-ethyl ether 2:1. B. Ethyl acetate-ethyl ether 2:1.

Paper electrophoresis. Paper. Whatman No. 3MM. Buffer: 0.05 M germanate buffer at pH 10.7.[5]

The spots on the thin layer chromatograms were located with iodine vapour, those on the papers with *p*-anisidine hydrochloride for reducing sugars and with silver nitrate-sodium hydroxide for the glucosides.

3-O-(2-Cyanoethyl)-1,2:5,6-di-O-isopropylidene-α-D-glucofuranose. 1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranose (165 g) was cyanoethylated as described by Corbett [4]. Unreacted starting material was recovered by crystallisation from benzene solution and cyanoethylated again. By recycling starting material a syrup (77.4 g) was finally obtained which on thin layer chromatography using solvent A appeared to contain only a small amount of starting material and a faster, major, spot. The syrup was added to the top of a silicic acid column (Mallinckrodt silicic acid, AR, 100 mesh, activated by heating at 180° overnight, 10 × 100 cm). The column was irrigated with solvent A. The syrupy, first, fraction collected (38.5 g) crystallised. Recrystallisation from light petroleum (40–60°) gave crystals (28.8 g) with m.p. 58–60°, unchanged on further recrystallisations from isopropyl ether. $[\alpha]_D^{20}$ −35° (*c*, 1.2 in chloroform). (Found: C 57.7 H 7.39 N 4.59; O 30.6. Calc. for $C_{15}H_{23}NO_6$: C 57.5; H 7.40, N 4.47; O 30.6).

3-O-(2-Cyanoethyl)-D-glucose. 3-*O*-(2-Cyanoethyl)-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (4.0 g) was hydrolysed in 0.2 N sulphuric acid (200 ml) at 100° for 30 min. The solution was neutralised with Dowex 3 (free base), filtered and concentrated to a syrup (3.2 g) which crystallised on stirring with acetone. Recrystallisation from ethanol gave crystals (2.3 g) with m.p. 142–144°, $[\alpha]_D^{20}$ + 18° (5 min) → + 29° (25 min) → + 48° (final, 24 h; *c*, 1.1 in water). (Found: C 46.5; H 6.49; N 6.09; O 41.5. Calc. for $C_9H_{15}NO_6$: C 46.3; H 6.48; N 6.01; O 41.2).

6-O-(2-Cyanoethyl)-1,2:3,5-di-O-methylene-α-D-glucofuranose. 1,2:3,5-Di-*O*-methylene-α-D-glucofuranose [1] (50.9 g) was treated with acrylonitrile (20.5 ml) and sodium methoxide (1.5 g) in dry dioxan (65 ml) with stirring for 19 h at 60°. The mixture was neutralised with N sulphuric acid and concentrated to dryness. The residue was extracted with chloroform, the chloroform solution was filtered and concentrated to dryness. The syrup (57.0 g) on thin layer chromatography using solvent A contained an appreciable amount of starting material. Chromatography on a silicic acid column as described above, using solvent A, gave a syrup (20.5 g) which crystallised. Recrystallisation from light petroleum (40–60°) gave crystals (11.6 g) m.p. 47–48.5°, $[\alpha]_D^{20}$ + 34° (*c*, 1.5 in chloroform). (Found: C 51.7; H 6.01; N 5.35; O 37.7. Calc. for $C_{11}H_{15}NO_6$: C 51.4; H 5.88; N 5.45; O 37.3).

6-O-(2-Cyanoethyl)-D-glucose. 6-*O*-(2-Cyanoethyl)-1,2:3,5-di-*O*-methylene-α-D-glucofuranose (4.0 g) was hydrolysed by heating with N sulphuric acid (200 ml) at 100° for 2 h. The mixture was neutralised with Dowex 3 (free base), filtered and concentrated to a syrup (3.9 g). Paper chromatography indicated a faster spot, presumably a monomethylene derivative, in addition to the expected 6-*O*-(2-cyanoethyl)-D-glucose. Starting material was not developed by the spray reagents used. Hydrolysis for more than 2 h produced some compounds with chromatographic mobilities lower than that of glucose. The syrup was dissolved in water and the aqueous solution extracted continuously with chloroform overnight. Paper chromatography indicated that only 6-*O*-(2-cyanoethyl)-D-glucose remained in the aqueous phase. This on concentration gave a syrup (0.5 g). The chloroform extract was concentrated to dryness and hydrolysed as above. Further recycling of the chloroform extracts gave an accumulation of syrup (1.8 g) which consisted of the presumed 6-*O*-(2-cyanoethyl)-D-glucose together with some degradation products. The syrup was extracted with ethanol, dark-coloured insoluble material was removed by filtration and the filtrate was concentrated to a syrup which crystallised from acetone. Recrystallisation from acetone gave crystals (0.4 g) with m.p. 129–131° (transition at 121–123°), $[\alpha]_D^{20}$ + 80° (7 min) → + 61° (50 min) → + 48° (24 h final; *c*, 0.9 in water). (Found: C 46.5; H 6.45; N 6.10; O 41.3. Calc. for $C_9H_{15}NO_6$: C 46.3; H 6.48; N 6.01; O 41.2).

Methyl 4,6-O-benzylidene-2,3-di-O-(2-cyanoethyl)-α-D-glucopyranoside. Methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (10 g) was treated with acrylonitrile (3.5 ml) and sodium methoxide (2 g) in dry dioxan (40 ml) at room temperature with stirring for 24 h. Precipitation occurred after 2h. Thin layer chromatography (solvent B) indicated a low degree of conversion to 2-cyanoethyl ethers. Acrylonitrile (6.5 ml) was added and the reaction was allowed to proceed for another 24 h. The mixture was neutralised with 2 N sulphuric acid, when the precipitate, apart from sodium sulphate, dissolved. The solution was filtered and concentrated to a crystalline mixture. Thin layer chromatography using solvent B indicated four spots of which three had faster mobility than that of the starting material. The separation of the two intermediary, presumed, mono-(2-cyanoethyl) ethers was poor. By fractional crystallisation from isopropyl ether, chromatographically pure starting material (2.0 g) was obtained, and also a crystalline mixture (2.3 g) of starting material and the di-*O*-(2-cyanoethyl) ether and another crystalline mixture (1.0 g) containing mainly starting material with only small amounts of each of the other three components. The remaining mother liquor was added to the top of a silicic acid column (7 × 70 cm) and eluted with solvent B. The last fraction to be eluted, starting material, (1.05 g, m.p. 168–169.5°) was pure, the other fractions eluted contained the di-*O*-(2-cyanoethyl) and the two mono-(2-cyanoethyl) ethers in varying proportions. Methyl 4,6-*O*-benzylidene-2,3-di-*O*-(2-cyanoethyl)-α-D-glucopyranoside (0.79 g) was obtained from the first fractions by fractional crystallisation from isopropyl ether. Two crystalline modifications, identical on thin layer chromatography in solvent B, were found, one with m.p. 108–110°, $[\alpha]_D^{20}$ + 58° (*c*, 1.0 in chloroform), the othe rwith m.p. 126–127°, $[\alpha]_D^{20}$ + 58° (*c*, 1.2 in chloroform). (Found for the compound with m.p. 108–110°: C 61.9; H 6.20; N 7.15; O 24.9. Calc. for $C_{20}H_{24}N_2O_6$: C 61.8; H 6.23; N 7.21; O 24.7). The lower-melting modification on recrystallisation from isopropyl ether and seeding with the higher-melting modification gave crystals with m.p. 126–127° undepressed on admixture with the modification with m.p. 126–127°, $[\alpha]_D^{20}$ + 58° (*c*, 0.9 in chloroform). (Found: C 61.9; H 6.47; N 7.10; O 24.7. Calc.: as above). The two crystalline modifications had almost identical IR spectra in potassium bromide pellets.

Methyl 4,6-O-benzylidene-2-O-(2-cyanoethyl)-α-D-glucopyranoside and 2-O-(2-cyanoethyl)-D-glucose. The above fractional crystallisations of the fractions obtained from the silicic acid column gave crystals (0.32 g) with m.p. 145–146° $[\alpha]_D^{20}$ + 77° (*c*, 0.7 in

chloroform) (Found: C 61.0; H 6.13; N 4.21; O 28.7. Calc. for $C_{17}H_{21}NO_6$: C 60.9; H 6.31; N 4.18; O 28.6). Hydrolysis of a small amount of the compound with 8 % sulphuric acid at 100° for 4 h, neutralisation with barium carbonate, filtration and concentration gave a syrup which on paper chromatography gave a major spot with R_F value higher than that of glucose and some minor spots with R_F values less than that of glucose. On paper electrophoresis only one spot which, like 2-*O*-methylglucose was immobile,[5] was observed.

The 2-*O*-(2-cyanoethyl)-D-glucose crystallised from ethanol (62 mg, from 300 mg methyl 4,6-*O*-benzylidene-2-*O*-(2-cyanoethyl)-*a*-D-glucopyranoside), m.p. 173.5—180°. The recrystallised substance had m.p. 177.5—180.5°, $[\alpha]_D^{20}$ + 24° (6 min) → + 38° (30 min) → + 53° (24 h final; *c* 0.4 in water) (Found: C 46.7; H 6.63; N 5.92; O 41.4. Calc. for $C_9H_{15}NO_6$: C 46.3; H 6.48; N 6.01; O 41.2).

Methyl 4,6-O-benzylidene-3-O-(2-cyanoethyl)-a-D-glucopyranoside. From the above fractional crystallisations, crystals (0.91 g), m.p. 155—157°, $[\alpha]_D^{20}$ + 87° (*c*, 1.1 in chloroform) were obtained. (Found: C 61.1; H 6.30; N 4.20; O 28.7. Calc. for $C_{17}H_{21}NO_6$: C 60.9; H 6.31; N 4.18; O 28.6). On hydrolysis as described above the material gave a major spot with R_F similar to that of 2-*O*-(2-cyanoethyl)-D-glucose and some minor spots with low R_F values. Paper electrophoresis [5] gave a single spot with the same mobility as that of 3-*O*-methylglucose. On seeding an ethanolic solution of the material with a crystal of 3-*O*-(2-cyanoethyl)-D-glucose crystals were obtained with m.p. 141—145° unchanged on admixture with the above authentic material.

Methyl 3-O-(2-cyanoethyl)-a-D-glucopyranoside. Methyl 4,6-*O*-benzylidene-3-*O*-(2-cyanoethyl)-*a*-D-glucopyranoside (1.0 g) was dissolved in acetone (5.2 ml) and water (1.8 ml), N hydrochloric acid (0.2 ml) was added and the solution was refluxed for 4 h. After neutralisation with Dowex 3 (free base), filtration and concentration to a small volume, the solution was diluted with water. Benzaldehyde was extracted with hexane, the aqueous layer was filtered through active carbon and concentrated to a syrup (0.65 g). Immediate crystallisation occurred on stirring with benzene. Recrystallisation from ethanol-benzene yielded crystals (0.61 g), m.p. 114.5—115.5° $[\alpha]_D^{20}$ + 132° (*c*, 1.2 in water). (Found: C 48.5; H 6.71; N 5.77; O 38.7. Calc. for $C_{10}H_{17}NO_6$: C 48.6; H 6.93; N 5.67; O 38.8).

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