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SYNTHESIS OF GLYCOSYL ISOCYANIDES

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Abstract—Substitution of benzylated or methylated glycopyranosyl and furanosyl bromides with silver cyanide gives rise to glycosylisocyanides as main products. The isocyanide structure is ascertained by physical (^{13}C NMR, IR) and by chemical methods (hydrolysis, isomerisation to nitriles).

Substitution of glycosyl halides with metallic cyanides is a general route to glycosyl nitriles which in turn are good precursors in the synthesis of C-nucleosides.[1-3] The reaction is generally performed with mercuric cyanide and the two isomeric nitriles are obtained in yields ranging from 30% to 60% in both the pyranosyl and the furanosyl series.[3-7]

When the substitution is performed with silver cyanide on a halogenosugar having a participating group in the C-2 position, such as 2,3,4,6 - tetra - O - acetyl - α - D - glucopyranosyl bromide, the reaction occurs quite differently and the main product is 3,4,6 - tri - O - acetyl - 1,2 - O - (1 - cyanoethylidene) - α - D - glucopyranose[8] and not, as previously stated,[9] 2,3,4,6 - tetra - O - acetyl - D - glycosyl cyanide. Very recently, this reaction has been reinvestigated and two isomeric 2,3,4,6 - tetra - O - acetyl - D - glucopyranosyl isocyanides have been isolated in low yields together with the main cyanoethylidenic compound.[10]

The formation of 1-isocyano sugars was previously suspected as an intermediate during the reaction of 2,3,5 - tri - O - benzylarabinofuranosyl bromide with silver cyanide[3] and was confirmed in the course of preliminary studies in our laboratory in a communication[11] concerning benzylated halogeno sugars. These studies have now been extended to other series and definitive proof for the isocyanide structure are given in the present paper.

Very recently, when this paper was in preparation, glucosyl isocyanides have been obtained via dehydration of the corresponding N-formyl glucopyranosyl amines.[12]

RESULTS AND DISCUSSION

Nucleophilic attack of the ambident cyanide ion[13,14] on alkyl halides can lead either to nitriles or isocyanides. Better yields of isocyanides are obtained with silver cyanide (via metal-isocyanide complexes) whilst mercuric cyanide leads almost exclusively to alkyl nitriles.[15,16] The results obtained in the substitution of glycosyl halides are in good agreement with those obtained with alkyl halides. Mercuric cyanide leads to glycosyl nitriles[3-7] whilst silver cyanide leads to isocyanides[3,10,11] or to products derived from isocyanides. Our reinvestigation of the reaction of 2,3,4,6 - tetra - O - acetyl - α - D - glucopyranosyl bromide with silver cyanide in boiling xylene seems indeed, to indicate that the cyanoethylidenic compound obtained as main product could, in fact, be derived from the isocyanide intermediate, as proposed by Coxon *et al.*,[8] since the last isocyanides are transformed in part into cyanoethylidenic compounds when treated in the same conditions.

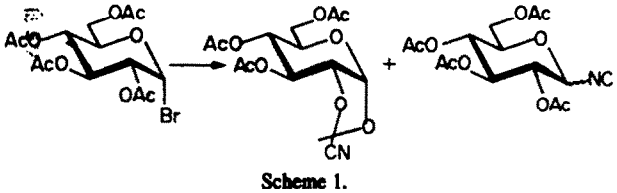
On the other hand, isomerisation of alkyl isocyanides to nitriles occurring at temperature higher than 140°[17,18a] was probably also observed by Acton *et al.*[3] with the hypothetical glycosyl isocyanide at the same temperature (refluxing xylene). The substitution of 2,3,4,6 - tetra - O - acetyl - α - D - glucopyranosyl bromide with silver cyanide at elevated temperature (140°) is therefore complicated by isomerisation (leading to nitriles) and rearrangement (leading to ethylidenic compounds) before further decomposition of the reaction products and does not constitute a good access to the glycosyl isocyanides.

(A) *Synthesis of* 1-*isocyano sugars*

As pointed out in our earlier communication[11] the substitution of glycopyranosyl bromides with silver cyanide in the benzylated series leads to isocyanides and occurs at room temperature. The higher reactivity of the etherified glycosyl bromides as compared with the esterified ones allows an extension of this reaction to the methylated glycosyl bromides as well as to the benzylated and methylated furanosyl bromides, as is illustrated in Table 1.

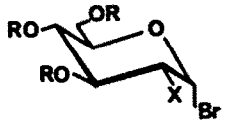
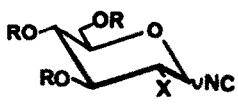
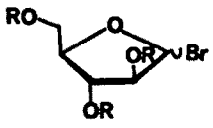
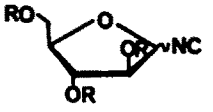
The yields and times of reaction are strongly dependent on the solvent used and on the reactivity of the glycosyl halide engaged in the substitution. The best results obtained in aprotic solvents of medium polarity such as dichloromethane are recorded in Table 1. In non polar solvents the reaction is slow except for the very reactive compounds **2**, **7**, **8**. In polar solvents, such as nitromethane, the reaction occurs about twice as fast as in dichloromethane but the yields are lower, due to the formation of byproducts.

The rates of reaction are directly related to the ease of formation of the anomeric oxocarbenium ion and



Scheme 1.

Table 1. Syntheais of isocyanides starting from glycosyl halides. Reactions are performed at room temperature in dichloromethane unless otherwise stated

Starting material	Time of reaction (hours)	Yield of isocyanides [a] (percent)		
				
		α		β
1 R= Bn X= OBn	36	9a	30	9b 45
2 R= Bn X= H	0.25 [b]	10a	80	10b -
3 R= Bn X= Br	48	11a	15	11b 70
4 R= Bn X= Cl	170	12a	20	12b 40
5 R= Me X= OMe	17	13a	35	13b 45
6 R= Ac X= OAc	1 [c]	14a	10	14b 12
				
		α		β
7 R= Bn	3 [d]	15a	40	15b 8
8 R= Me	3 [d]	16a	38	16b 7

[a] Yields at complete disappearance of the starting material.

[b] Reaction performed in toluene. The lack of reproducibility of this experiment recently claimed by Nolte *et al.*[12] is probably due to difficulties in the synthesis of the starting glycosyl bromide requiring a careful control of the amount of hydrogen bromide added. In our hands this reaction performed many times is very clean and leads to one main compound only, the structure of which is ascertained by both NMR and IR spectra.

[c] Reaction performed in refluxing xylene according to Martin-Lomas *et al.*[10]

[d] Reaction performed in ether.

decrease with increasing electronegativity of the C-2 substituent (H > OBn > Br > Cl). This result is confirmed by the inertness of 3,4,6 - tri - O - benzyl - 2 - chloro - 2 - deoxy - α - D - glucopyranosyl chloride towards substitution with silver cyanide. Elimination products only (1,6 - anhydro - 3,4 - di - O - benzyl - 2 - chloro - 2 - deoxy - β - D - glucopyranose **24** and 3,4,6 - tri - O - benzyl - 2 - chloro - 1,2 - dideoxy - D - *arabino* - hex - 1 - enopyranose) are formed when the reaction is carried out at 80°. This lack of reactivity towards substitution can be attributed to the difficulty of extraction of the anomeric Cl atom which is increased by the inductive effect of the C-2 substituent. The substitution of the highly reactive furanosyl bromides **7** and **8** needs ether as solvent in order that the reaction occurs at a convenient rate but, because of the low solubility of silver cyanide in ether, the yields are low.

The β-anomeric isocyanides are formed preferentially because of the shielding effect of the leaving bromine atom on the α-side of the molecule but these products anomerise in the reaction mixture and the percentage of the α-anomeric isocyanides increases during the course of reaction. This increase is very fast with the more reactive glycosyl bromides **2**, **7**, **8** and therefore the β-isocyanides are very difficult to observe in these cases.

The anomeric equilibration was tested with compound **13** in dichloromethane at room temperature and in the presence of silver cyanide. Starting from pure β compound **13b**, an equilibrium is reached via an isocyanide-silver cyanide complex after 7 days. The intermediate complex can be observed, as in the case of the isocyanide synthesis, by IR spectrometry (broad peak near 2190 cm^{-1}). The ratio at equilibrium (about **13a**:**13b** = 3:1) indicates that although the N atom in the isocyanide is in a positively charged environment[19] no reverse anomeric effect[20] is observed.

(B) *Identification of* 1-*isocyano sugars*

(a) *Spectroscopic methods.* Spectrometric differences between nitriles and isocyanides occur in the stretching frequencies of the C≡N bond in infrared spectroscopy and in the chemical shifts of the carbon of the functional group in ^{13}C NMR.

The ^{13}C NMR chemical shifts for the sp carbon of alkyl nitriles appear at 112–126 ppm and for isocyanides at 156–158 ppm.[21] In the glycosyl nitriles the chemical shifts are of the same order (114.5–117 ppm) as in the alkyl series.[22]

In our previous communication[11] the resonance of the carbons of isocyanides was assumed to coalesce with that of the quaternary carbon of the benzyl groups (139 ppm) since we observed no other signal in this region. However our recent observations in the methylated series indicate that this assumption was wrong. In effect, the signal of the isocyanide carbon is of low intensity but the observed chemical shifts (**13a**, 163.8; **13b**, 162.3 ppm) are in good agreement with that of the isocyano-carbon reported by Martin-Lomas *et al.* (164.4 ppm)[10] and Nolte *et al.* (166.1 and 165.1 ppm).[12]

The IR C≡N stretching frequencies constitute the main spectroscopic difference between nitriles and isocyanides; they are respectively around 2250 cm^{-1} and 2150 cm^{-1} in alkyl series.[23] The C≡N stretching signals are not detectable in the spectra of glycosyl nitriles;[8] however a sharp intensive band in the region 2120–2150 cm^{-1} is observed in the spectra of glycosyl isocyanides. The precise frequency of this band is directly related to the anomeric configuration of the isocyanide: α-anomer $\nu(N \cong C)$ 2123–2129; β-anomer $\nu(N \cong C)$ 2141–2146 cm^{-1}. The data listed in Table 2 indicate that these stretching frequencies may be used in order to determine the configuration of any glycosyl isocyanide.

(b) *Chemical transformations.* Chemical proof confirm the isocyanide structure of compounds **9** to **16**. Acid hydrolysis of cyanides leads to acids whilst that of isocyanides leads to N-alkyl formamides and then to primary amines.[24] The hydrolysis of the benzylated isocyanides **9** to **12** gives rise to the N-glycosyl formamides **17** to **20** in almost quantitative yields with retention of the anomeric configuration. Dehydration of the formamides **17** to **20** with phosphorus oxychloride[28] gives isocyanides **9** to **12** back.

The hydrolysis performed under more drastic conditions results in the breaking of the anomeric N–C bond and leads to the formation of the corresponding reducing carbohydrates.

The isomerisation of isocyanides to nitriles occurs at 140° and above.[17,18a] This isomerisation is also observed for compounds **9** and **13**. In the case of compound **9**, the formation of by-products of elimination reactions competes with the isomerisation (i.e. **23** from **9**). With compound **10**, elimination only occurs at 110° and leads to 3,4,6 - tri - O - benzyl - D - glucal. The fragile compounds **11**, **15** and **16** decompose between 110° and 140° whilst for compound **12** elimination occurs only in boiling xylene and the glucosane **24** is obtained in low yield.

The isomerisation isocyanide⇌nitrile has been carefully studied for compound **13** because in this case no side reactions occur. Both the anomeric isocyanides **13a** and **13b** upon refluxing in xylene solution gave the anomeric mixtures of glycosyl cyanides **22a** and **22b**. The α-anomer **13a** leads to a mixture of thermostable nitriles of **22a** + **22b** (4:1) in 24 hr whilst the β-anomer **13b** yields a similar mixture (3:2) in 65 hr. Anomerisation of the starting glycosyl isocyanides is also observed in the course of this isomerisation thereby explaining the lack of stereoselectivity of this rearrangement which, in the case of alkyl isocyanides, occurs with retention of configuration.[26]

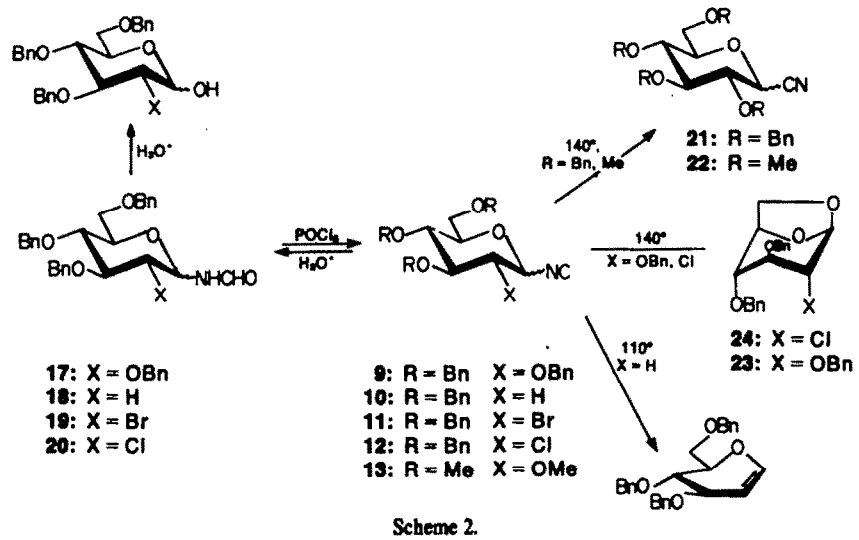
CONCLUSION

Substitution of benzylated or methylated glycosyl bromides with silver cyanide constitutes a good synthesis of the corresponding glycosyl isocyanides. The reaction which probably occurs with Walden inversion, is accompanied by anomerisation and good yields of mixtures of α–β glycosyl isocyanides are therefore obtained. Infrared spectrometry is useful in determination of the anomeric configurations of glycosyl isocyanides, the N≅C stretching frequency of both anomers being quite different. In the case of methylated isocyanides, their

Table 2. IR N≅C stretching frequencies in glycosyl isocyanides (recorded on a Perkin–Elmer 225 IR spectrometer)

	anomeric configuration	glycosyl isocyanides							
		9	**10**	**11**	**12**	**13**	**14**	**15**	**16**
−N≅C stretch frequencies (cm^{-1})	a (α)	2124.5	2123	2123	2123	2126	2129	2125	2127
	b (β)	2141.5	-	2143	2142	2144.5	2145.5	-	-

[a]Data reported by Nolte *et al.*[12] for α and β anomers of 2,3,4,6 - tetra - O - benzyl - D - glucopyranosideisocyanide are respectively 2124 ± 1 cm^{-1} and 2142 ± 1 cm^{-1}.



Scheme 2.

thermal isomerisation to the corresponding nitriles represents a possible synthesis of glycosyl nitriles.

Glycosyl isocyanides constitute a new class of potentially reactive carbohydrates: α-metallation[27] could give access to C-glycosides or C-nucleosides; α-additions, cycloadditions, or the use of isocyanides in peptide synthesis[18b] could be the main use of isocyanides.

EXPERIMENTAL

M.ps are determined in capillary tubes with Büchi apparatus and are not corrected. Optical rotations are determined with a Perkin Elmer 141 polarimeter. IR spectra are recorded with Perkin Elmer 225 and Perkin Elmer 237 spectrometers. ^{1}H NMR are recorded using Varian A-60 and Varian HA-100 spectrometers (internal Me_4Si), ^{13}C NMR spectra with a Varian XL-100 spectrometer operating at 25.2 MHz (internal Me_4Si). Column chromatographies are performed on silica gel Merck (230–400 mesh).

Glycosyl bromides **1** *to* **8**. Glycosyl bromides **1** and **7** were prepared by displacement of the corresponding *p*-nitrobenzoate derivatives with HBr in a mixture of dichloromethane and toluene 5:1. After removal of the insoluble material, the filtrate was used without further purification.

Compounds **5** and **8** were obtained by substitutions of the corresponding anomeric acetates with HBr in toluene. After careful evaporation of the acid formed during the reaction the products were used without further purification.

Compound **2** and **3** were obtained from 3,4,6 - tri - O - benzyl - D - glucal respectively by addition of HBr or Br_2 according to the procedures already described.[11,28]

Compound **4** was obtained from the corresponding glycosyl chloride[29] via the classical route using the epimeric glycosyl acetate subsequently treated with HBr. Except for compound **6**, the glycosyl bromides **1** to **8** were very reactive and unstable derivatives and had to be used immediately after synthesis and carefully protected from moisture.

Glycosyl isocyanides **9** *to* **13**, **15**, **16**. To the freshly prepared glycosyl bromide (2 mmoles) dissolved in 20 ml dry solvent (Table 1) 1 g of molecular sieves (4 Å) and 1.34 g freshly prepared AgCN (10 mmoles) was added. The mixture was kept in the dark and magnetically stirred for the time indicated in Table 1 and then filtered, evaporated to dryness and chromatographed on silica gel; eluent-ether: benzene: hexane 1:2:2, (benzylated compounds); ethyl acetate: hexane 1:2 (methylated compounds); the respective yields are given in Table 1.

2,3,4,6 - *Tetra* - O - *benzyl* - D - *glucopyranosyl isocyanide* **9a**, **9b**. Prepared from **1** (dichloromethane, 36 hr, yield: 75%). Compounds **9a** and **9b** were separated in low yield because of their neighbouring R_f.

Compound **9a**: oily material (Found: C, 75.95; H, 6.31; N, 2.39. $C_{35}H_{35}O_5N$ requires: C, 76.48; H, 6.42; N, 2.55%). $[\alpha]_D^{26}$ +52.4° (*c* 3.6, $CHCl_3$); IR: ν_{max} 2124.5 cm^{-1}; NMR (CD_3COCD_3): 5.63 (1, d, H-1, $J_{1,2}$ 3.6 Hz).

Compound **9b**: oily material (Found: C, 76.04; H, 6.38; N, 2.58. $C_{35}H_{35}O_5N$ requires: C, 76.48; H, 6.42; N, 2.55%). $[\alpha]_D^{26}$ +22.5° (*c* 2.5, $CHCl_3$); IR: ν_{max} 2141.5 cm^{-1}; NMR (CD_3COCD_3): 4.5–5.0 (9, m, H_1 + benzylic CH_2).

3,4,6 - *Tri* - O - *benzyl* - 2 - *deoxy* - α - D - arabino - *hexopyranosyl isocyanide* **10a**. Prepared from **2** (toluene, 15 min, yield: 80%) oily material (Found: C, 75.51; H, 6.73; N, 2.84. $C_{28}H_{29}O_4N$ requires: C, 75.82; H, 6.59; N, 3.16%). $[\alpha]_D^{21}$ +64° (*c* 1.4, $CHCl_3$); IR: ν_{max} 2123 cm^{-1}; NMR (CD_3COCD_3): 5.48 (1, dd, H-1, $J_{1,2}$ 3.4 Hz; $J_{1,2}$ 1.5 Hz).

3,4,6 - *Tri* - O - *benzyl* - 2 - *bromo* - 2 - *deoxy* - D - *glucopyranosyl isocyanide* **11**. Prepared from **3** (dichloromethane, 48 hr, yield: 85%). Compounds **11a** and **11b** were not separable—oily material (Found: C, 64.37; H, 5.44; N, 2.49. $C_{28}H_{28}O_4NBr$ requires: C, 64.37; H, 5.40; N, 2.68%); IR: ν_{max} 2123, 2143 cm^{-1}, NMR (CD_3COCD_3): 5.60 (0.2, d, H-1 (**11a**), $J_{1,2}$ 3.5 Hz) 5.14 (0.8, d, H-1 (**11b**), $J_{1,2}$ 8.7 Hz).

3,4,6 - *Tri* - O - *benzyl* - 2 - *chloro* - 2 - *deoxy* - D - *glucopyranosyl isocyanide* **12**. Prepared from **4** (dichloromethane, 7 days, yield: 60%). Compounds **12a** and **12b** were not separable—oily material (Found: C, 70.43; H, 5.90; N, 2.81. $C_{28}H_{28}O_4NCl$ requires: C, 70.95; H, 5.95; N, 2.96%); IR: ν_{max} 2123, 2142 cm^{-1}; NMR (CD_3COCD_3): 5.62 (0.3, d, H-1 (**12a**), $J_{1,2}$ 3.9 Hz) 5.09 (0.6, d, H-1 (**12b**), $J_{1,2}$ 8.4 Hz).

2,3,4,6 - *Tetra* - O - *methyl* - D - *glucopyranosyl isocyanide* **13a**, **13b**. Prepared from **5** (dichloromethane, 17 hr, yield: 80%). Compounds **13a** and **13b** were easily separated on a silica gel column (eluent-ethyl acetate: hexane 1:1). **13a**: oily material (Found. C, 54.00; H, 7.86; N, 5.56. $C_{11}H_{19}O_5N$ requires: C, 53.86; H, 7.81; N, 5.71%); $[\alpha]_D^{20}$ +28.1° (*c* 1.8, $CHCl_3$); IR: ν_{max} 2123 cm^{-1}; NMR (C_6D_6) 4.96 (1, d, H-1, $J_{1,2}$ 4.5 Hz); ^{13}C NMR (CD_3COCD_3) 163.8 (N ≡ C).

Compound **13b** white needles, m.p. 85°–86° (petroleum ether); (Found: C, 53.69; H, 7.79; N, 5.51. $C_{11}H_{19}O_5N$ requires: C, 53.86; H, 7.81; N, 5.71%); $[\alpha]_D^{20}$ +28.1° (*c*, 1.8, $CHCl_3$); IR: ν_{max} 2144.5 cm^{-1}, NMR (C_6D_6) 4.03 (1, d, H-1, $J_{1,2}$ 8.2 Hz); ^{13}C NMR (CD_3COCD_3) 162.3 (N ≡ C).

2,3,5 - *Tri* - O - *benzyl* - α - D - *arabinofuranosyl isocyanide* **15a**. Prepared from **7** (ether, 3 hr, yield: 48%). Compound **15a** was always contaminated by **15b** (<5%)—oily material (Found: C, 74.22; H, 6.26; N, 3.14. $C_{27}H_{27}O_4N$ requires: C, 75.50; H, 6.34; N, 3.26%); $[\alpha]_D^{20}$ +49° (*c* 0.5, $CHCl_3$); IR: ν_{max} 2125 cm^{-1}; NMR (CD_3COCD_3) 5.52 (1, s, H-1).

2,3,5 - *Tri* - O - *methyl* - α - D - *arabinofuranosyl isocyanide* **16a**. Prepared from **8** (ether, 3 hr, yield 45%). Compound **16a** was always contaminated by a small amount of **16b** (<5%)—oily material (Found: C, 53.91; H, 7.49; N, 6.89. $C_9H_{15}O_4N$ requires: C, 53.72; H, 7.51; N, 6.96%); $[\alpha]_D^{20}$ +73° (*c* 0.5, $CHCl_3$); IR: ν_{max} 2127 cm^{-1}; NMR (CD_3COCD_3) 5.38 (1, s, H-1).

Hydrolysis of isocyanides **9** *to* **12**. The same experimental

procedure was used in all cases. Isonitrile (1.0 mmole) in ether (10 ml) was reacted for 3 hr at room temp with 2.5 N HCl (5 ml). After extraction, neutralization and evaporation a quantitative yield of a mixture of anomeric N-formyl glycosylamine was obtained (**17** to **20**). In each case it was possible to separate the β-compound by fractional crystallization from ether (except for **18a**).

N - *Formyl* - 2,3,4,6 - *tetra* - O - *benzyl* - β - D - *glucopyranosylamine* **17b**. Prepared from **9** and separated in low yield (15%) from **17a**, m.p. 138° from ether. (Found: C, 73.93; H, 6.59; N, 2.48. $C_{35}H_{37}O_6N$ requires: C, 74.07; H, 6.52; N, 2.47%); $[\alpha]_D^{21}$ −10.0° (*c* 2.2, $CHCl_3$); IR: ν_{max} 3280 cm^{-1} (NH), 1680 cm^{-1} (C=O), 1540 cm^{-1} (C–N); NMR (CD_3COCD_3) 8.25 (1, m, CHO) 7.9 (1, m, NH) 4.6 to 5.0 (9, m, CH_2 + H-1). The mixture enriched with **17a** showed the anomeric proton at 6.0 (1, dd, $J_{1,2}$ 4.0 Hz, $J_{1,NH}$ 8.8 Hz).

N - *Formyl* - 3,4,6 - *tri* - O - *benzyl* - 2 - *deoxy* - α - D - arabino-*hexopyranosylamine* **18a** was obtained from **10** in almost quantitative yield—oily material. (Found: C, 72.60; H, 6.84; N, 2.99. $C_{28}H_{31}O_5N$ requires: C, 72.86; H, 6.77; H, 3.03%); $[\alpha]_D^{20}$ +62° (*c* 2.6, $CHCl_3$); IR: ν_{max}: 3300 cm^{-1} (N–H), 1680–1705 cm^{-1} (C=O), 1535 cm^{-1} (C–N); NMR (C_6D_6) 8.15 (1, m, CHO) 8.0 (1, m, NH) 5.94 (1, m, H-1).

N - *Formyl* - 3,4,6 - *tri* - O - *benzyl* - 2 - *bromo* - 2 - *deoxy* - β - D - *glucopyranosylamine* **19b**. This unstable compound was obtained in low yield (12%) from **11**, due to difficult separation from **19a**, m.p. 127° dec from ether. (Found: C, 61.20; H, 5.77; N, 2.43. $C_{29}H_{30}O_5NBr$ requires: C, 62.22; H, 5.55; N, 2.59%); $[\alpha]_D^{20}$ +47.5° (*c* 2.3, $CHCl_3$); IR: ν_{max} 3295 cm^{-1} (NH), 1675 cm^{-1} (C=O) 1530 cm^{-1} (C–N) NMR (CD_3COCD_3) 8.25 (1, m, CHO); 7.91 (1, m, NH) 5.3 (1, m, H-1).

N - *Formyl* - 3,4,6 - *tri* - O - *benzyl* - 2 - *chloro* - 2 - *deoxy* - β - D - *glucopyranosylamine* **20b** was obtained from **12** after fractional crystallization (yield 19%) from ether, m.p. 123° from ether. (Found: C, 67.82; H, 6.00; N, 2.74. $C_{28}H_{30}O_5NCl$ requires: C, 67.81; H, 6.05; N, 2.82%); $[\alpha]_D^{20}$ +36° (*c* 3.6, $CHCl_3$); IR: ν_{max} 3290 cm^{-1} (NH), 1680 cm^{-1} (C=O), 1525 cm^{-1} (C–N); NMR (CD_3COCD_3) 8.3 (1, m, CHO) 7.9 (1, m, NH) 5.4 (1, m, H-1).

Dehydration of formamides **17** *to* **20**. The formamide **17** to **20** (2 mmoles) dissolved in pyridine (10 ml) was treated for 30 mn at 60° with $POCl_3$ (4 mmoles) and then for 1 hr at room temp. The mixture was poured onto ice and then extracted with $CHCl_3$, neutralized and evaporated. The isocyanide **9** to **12** was recovered in a 60% yield.

Thermal treatment of isocyanides **9** *to* **13**. 2-Deoxyglycosyl isocyanide **10a** (443 mg, 1 mmole) was refluxed in toluene (25 ml) for 5 hr. After complete disappearance of the starting material, the mixture was chromatographed on silica gel. The only product recovered was 3,4,6 - tri - O - benzyl - D - glucal (229 mg, yield 55%) identical with the product previously prepared.[29]

2,3,4,6 - *Tetra* - O - *benzyl* - α - D - *glucopyranosyl cyanide* **21**. The isocyanide **9** (1 g, 1.8 mmole) was refluxed in xylene for 15 hr. After evaporation, the oily material was chromatographed on silica gel (eluent—ether:benzene:hexane, 1:2:2). Compound **21** (300 mg, yield 30%) was thus isolated together with the elimination product **23** identical with the product isolated by Zemplen *et al.* by direct benzylation of 1,6 - anhydro - β - D - glucopyranose,[30] yield 15% (120 mg), **21**—oily material. (Found: C, 76.68; H, 6.51; N, 2.42. $C_{35}H_{35}O_5N$ requires: C, 76.48; H, 6.42; N, 2.55%); $[\alpha]_D^{25}$ +36.3° (*c* 5.3, $CHCl_3$); NMR (CD_3COCD_3) 5.21 (1, d, H-1, $J_{1,2}$ 4.2 Hz).

2,3,4,6 - *Tetra* - O - *methyl* - D - *glucopyranosyl cyanide* **22a**, **22b**. The isocyanide **13b** (1 g, 4.1 mmoles) was refluxed in xylene (6 ml) for 65 hr. The mixture thus obtained was chromatographed on a silica gel column (eluent—ethyl acetate:hexane, 1:1) and compounds **22b** (380 mg, yield 38%) and **22a** (570 mg, 57%) were successively separated.

Compound **22a**—oily material. (Found: C, 53.75; H, 7.89; N, 5.76. $C_{11}H_{19}O_5N$ requires: C, 53.86; H, 7.81; N, 5.71%); $[\alpha]_D^{23}$ +120° (*c* 1.1, $CHCl_3$); NMR (C_6D_6) 4.6 (1, d, H-1, $J_{1,2}$ 4.6 Hz).

Compound **22b**—white needles, m.p. 88°–89° from petroleum ether. (Found: C, 54.10; H, 7.85; N, 5.68. $C_{11}H_{19}O_5N$ requires: C, 53.86; H, 7.81; N, 5.71%); $[\alpha]_D^{20}$ +36.2° (*c* 1.1, $CHCl_3$); NMR (C_6D_6), no anomeric proton separated from other protons.

Isomerisation of isocyanide **13a** for 24 hr under similar conditions (140°) afforded **22a** and **22b** in yields of 76% and 19%.

In the case of **11** and **12** no isomerisation was observed and decomposition or elimination products were formed. Starting from **12**, **24** separated in low yield (10%), and was similar to that obtained during the reaction of 3,4,6 - tri - O - benzyl - 2 - chloro - 2 - deoxy - α - D - glucopyranosyl chloride with AgCN (see below).

Reaction of 3,4,6 - *tri* - O - *benzyl* - 2 - *chloro* - 2 - *deoxy* - α - D - *glucopyranosyl chloride with silver cyanide*. The dichloro compound (1 g, 2.1 mmoles) was refluxed in toluene (10 ml) with 2 g AgCN (14.9 mmoles) for 5 hr. After filtration and evaporation, the mixture was chromatographed on silica gel (eluent—ether:benzene:hexane, 1:2:2) and two compounds were recovered, **25** (400 mg; yield 43%) and **24** (300 mg; yield 40%).

3,4,6 - *Tri* - O - *benzyl* - 2 - *chloro* - 1,2 - *dideoxy* - D - arabino-*hex* - 1 - *enopyranose* **25**—oily material. (Found: C, 71.55; H, 6.16. $C_{27}H_{28}O_4Cl$ requires: C, 71.75; H, 6.24%); $[\alpha]_D^{20}$ +11.8° (*c* 0.5, $CHCl_3$); IR: ν_{max} 1655 cm^{-1}; NMR (CD_3COCD_3) 6.48 (1, s, H-1).

1,6 - *Anhydro* - 3,4 - *di* - O - *benzyl* - 2 - *chloro* - 2 - *deoxy* - β - D - *glucopyranose* **24**—oily material. (Found: C, 66.64; H, 5.95; Cl, 9.96. $C_{20}H_{21}O_4Cl$ requires: C, 66.57; H, 5.86; Cl, 9.83%); $[\alpha]_D^{20}$ +14.5° (*c* 0.5, $CHCl_3$); NMR (CD_3COCD_3) 5.44 (1, dd, H-1, $J_{1,2}$ 1.4 Hz, $J_{1,3}$ 0.9 Hz) 4.03 (1, dd, H-6', $J_{5,6'}$ 1.3 Hz, $J_{6,6'}$ 7.5 Hz) 3.64 (1, dd, H-6, $J_{5,6}$ 6.0 Hz).

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