562. *The Cross-linking of Cellulose and its Derivatives. Part II.*[1] *Preparation of Some New Amino-derivatives of* D-*Glucose and of* D-*Galactose.*

By W. M. Corbett.

With methanolic ammonia 6-deoxy-6-iododi-*O*-isopropylidene-D-galactose gives mainly 6-deoxydi-*O*-isopropylidene-6-methylamino-D-galactose whereas use of aqueous ammonia gives the tertiary amine with three sugar residues and use of ammonia in dioxan gives the latter and the secondary amine. 2-Aminoethyl ethers of di-*O*-isopropylidene-D-glucose and -D-galactose have been prepared from the corresponding methoxycarbonylmethyl ethers. These were converted into the amides which were then reduced to the amines. 3-Aminopropyl ethers were also prepared by reduction of the 2-cyanoethyl ethers.

In Part I [1] the addition of amines to unsaturated cellulose esters was outlined as a useful means of cross-linking cellulose and its derivatives. Such a reaction, however, can only be used if its chemistry is known in detail. Because of the impossibility of following reactions of cellulose derivatives in which only a few repeating units are involved, it is necessary to determine the details by using model compounds. That work is reported in the following paper. For the study to be complete, use of amino-derivatives of monosaccharides is essential, but only a few of these compounds have been previously reported. This paper describes the preparation of free amino-derivatives of monosaccharides by simple methods which can be applied to cellulose.

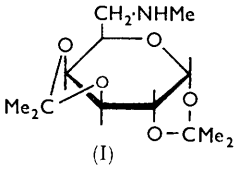
The toluene-*p*-sulphonyl group is capable of exchange by several reagents, but with ammonia it appears that formation of an anhydro-sugar intermediate is essential for high

[1] Part I, Corbett and McKay, *J. Soc. Dyers and Colourists*, in the press.

yield. Since this would impose severe restrictions in the case of cellulose derivatives, attention was turned to the replacement of iodo-groups by ammonia. 6-Deoxy-6-iododi-*O*-isopropylidene-D-galactose was studied because of its ease of preparation. Treatment with methanolic ammonia at 130° gave a syrup which was mainly 6-deoxy-1,2:3,4-di-*O*-isopropylidene-6-methylamino-D-galactose (I) contaminated with 6-amino-6-deoxydi-*O*-isopropylidene-D-galactose. The syrup gave the picrolonate of the *N*-methyl derivative in 61% yield, whereas with phenyl isocyanate the corresponding asymmetrical disubstituted urea from the free amino-derivative was obtained in 34% yield. The *N*-methyl derivative was probably formed by reaction of the hydriodide of the primary amine with the solvent. Aqueous ammonia was then used in an attempt to overcome the participation of the solvent, but the only product isolated was 6,6′,6″-nitrilotri-(6-deoxydi-*O*-isopropylidene-D-galactose), *i.e.*, the tertiary amine (II). This, together with the secondary amine analogue (III), was also isolated after reaction of ammonia in dioxan with the iodide.

A study of the reactions of 3-*O*-2′-iodoethyldi-*O*-isopropylidene-D-glucose had to be abandoned because of the low yield of 3-*O*-2′-hydroxyethyldi-*O*-isopropylidene-D-glucose obtained by reaction of 2-chloroethanol with di-*O*-isopropylidene-D-glucose.

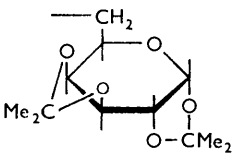
Introduction of a primary amine group has been achieved by starting from the methoxycarbonylmethyl ethers of 1,2:5,6-di-*O*-isopropylidene-D-glucofuranose and 1,2:3,4-di-*O*-isopropylidene-D-galactopyranose. These are prepared by treating the sodium salt of the sugar derivative with methyl halogenoacetate as described by Shyluk and Timell.[2] 1,2:5,6-Di-*O*-isopropylidene-3-*O*-methoxycarbonylmethyl-D-glucofuranose (IV) is readily converted into the corresponding amide (V) by aqueous ammonia, and this is reduced by lithium aluminium hydride, in high yield, to 3-*O*-2′-aminoethyl-1,2:5,6-di-*O*-isopropylidene-D-glucofuranose (VI). The same series of reactions has been successfully applied to 1,2:3,4-di-*O*-isopropylidene-D-galactopyranose, but in this case the initial methyl ester is a syrup and is difficult to purify: it led to the isolation of di-*O*-isopropylidene-D-galactose and of glycine amide hydrochloride as well as of the amide of the galactose derivative.

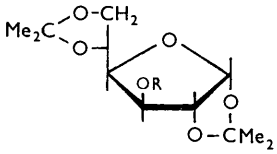


(I)

R_3N and R_2NH where R =

(II) (III)





	R		R
(IV)	$CH_2 \cdot CO_2Me$	(VII)	$CH_2 \cdot CH_2 \cdot CN$
(V)	$CH_2 \cdot CO \cdot NH_2$	(VIII)	$CH_2 \cdot CH_2 \cdot CH_2 \cdot NH_2$
(VI)	$CH_2 \cdot CH_2 \cdot NH_2$		

The use of acrylonitrile has also been examined. 1,2:5,6-Di-*O*-isopropylidene-D-glucofuranose reacted with acrylonitrile in the presence of sodium methoxide to give in low yield 3-*O*-2′-cyanoethyldi-*O*-isopropylidene-D-glucofuranose (VII) as a liquid which was difficult to purify. Attempted reduction of the cyanoethyl ether with lithium aluminium hydride caused cleavage of the cyanoethyl group, and di-*O*-isopropylidene-D-glucose was isolated in high yield. However, reduction by hydrogen over Raney nickel gave the amine (VIII) smoothly. Di-*O*-isopropylidene-D-galactopyranose behaved similarly except that the 2′-cyanoethyl ether was obtained in a higher yield and was readily purified by distillation.

Experimental

Reactions of 6-*Deoxy*-6-*iodo*-1,2:3,4-*di*-O-*isopropylidene*-D-*galactose*.—(a) *With methanolic ammonia.* The iodo-derivative (4·742 g.) in methyl alcohol (200 ml.) previously saturated

[2] Shyluk and Timell, *Canad. J. Chem.*, 1956, **34**, 575.

at 0° with ammonia was heated at 130° for 18 hr. Concentration of the solution gave a brown syrup (6·806 g.) which partly crystallised from ethyl acetate, to give ammonium iodide. The ethyl acetate solution was concentrated to a syrup (5·027 g.) which was dissolved in chloroform, then washed with aqueous sodium thiosulphate followed by water, dried (Na_2SO_4), treated with charcoal, and concentrated to a pale brown syrup (3·147 g.). It was mainly 6-*deoxy*-1,2:3,4-*di*-O-*isopropylidene*-6-*methylamino*-D-*galactopyranose* and had b. p. 140°/0·01 mm. (bath-temp.), n_D^{23} 1·4710, $[\alpha]_D^{25}$ −63·8° (*c* 0·97 in chloroform) (Found: C, 57·0; H, 8·4; N, 5·0%). It was redistilled, the bulk having b. p. 125°/0·02 mm. (bath-temp.) (Found: C, 57·2; H, 8·4; N, 5·2; NMe, 3·1. $C_{13}H_{23}NO_5$ requires C, 57·2; H, 8·5; N, 5·1; NMe, 11·2%).

The syrup (0·425 g.) gave with picrolonic acid (0·433 g.) in ethyl alcohol (10 ml.) the *amine picrolonate* (0·513 g., 61%), m. p. 233° (decomp.) (from ethyl alcohol) (Found: C, 51·3; H, 5·9; N, 12·3. $C_{23}H_{31}N_5O_{10}$ requires C, 51·4; H, 5·8; N, 13·0%). In contrast the syrup (0·282 g.) gave with phenyl isocyanate the N′-*phenylurea derivative* (0·138 g., 34%), m. p. 153° (from aqueous alcohol) (Found: C, 60·4; H, 7·1; N, 7·2. $C_{19}H_{26}N_2O_6$ requires C, 60·3; H, 7·0; N, 7·4%).

(b) *With aqueous ammonia.* The iodo-derivative (2·000 g.) was heated with aqueous ammonia (50 ml.; *d* 0·9) for 5 hr. at 110°. The mixture was extracted with chloroform, and the extract dried (Na_2SO_4) and concentrated to a syrup (1·504 g.) which crystallised from light petroleum (b. p. 40—60°). 6,6′,6″-*Nitrilotri*-(6-*deoxy*-1,2:3,4-*di*-O-*isopropylidene*-D-*galactopyranose*) (II) (0·596 g.), m. p. 207—210° (decomp.), had, after two recrystallisations from aqueous alcohol, m. p. 239—240° (decomp.), $[\alpha]_D^{21}$ −56·0° (*c* 0·5 in chloroform) [Found: C, 58·0; H, 7·7; N, 1·6%, *M* (Rast), *ca.* 800. $C_{36}H_{57}NO_{15}$ requires C, 58·2; H, 7·7; N, 1·9%; *M*, 743]. Further material was isolated from the petroleum mother-liquors.

(c) *With ammonia in dioxan.* The iodo-derivative (5·320 g.) in dioxan (200 ml.), previously saturated at 0° with ammonia, was heated at 130° for 5½ hr. The mixture was concentrated under reduced pressure and the residue dissolved in chloroform, washed with water, dried (Na_2SO_4), treated with charcoal, and concentrated to a brown syrup (2·656 g.). This partly crystallised from aqueous alcohol to give crystals which after one recrystallisation from aqueous alcohol had m. p. 211° and an infrared spectrum identical with that of the product obtained as in (b).

The aqueous-alcohol solution was concentrated and a sample of the syrup (0·965 g.) in a little ether was chromatographed on alumina (40 × 1·3 cm.). Elution with a mixture of light petroleum (b. p. 40—60°; 300 ml.) and ether (600 ml.), followed by chloroform (300 ml.), gave an amorphous mass (0·371 g.) which crystallised from di-isopropyl ether to give material of m. p. 129—131°. The chloroform eluate gave further crystals (0·201 g.), m. p. 126·5—128·5°. The two fractions were combined and recrystallised twice from di-isopropyl ether to give 6,6′-iminodi-(6-deoxydi-*O*-isopropylidene-D-galactopyranose (III), m. p. 130—131°, $[\alpha]_D^{21}$ −81·2° (*c* 0·8 in chloroform) {Freudenberg and Doser [3] give m. p. 125—126°, $[\alpha]_{378}^{18}$ −84·4° (in acetone)} [Found: C, 57·8; H, 8·0; N, 2·4%; *M* (Rast), *ca.* 445. Calc. for $C_{24}H_{39}NO_{10}$: C, 57·6; H, 7·9; N, 2·8%; *M*, 501].

3-O-2′-*Hydroxyethyl*-1,2:5,6-*di*-O-*isopropylidene*-D-*glucofuranose*.—To the sodium salt of 1,2:5,6-di-*O*-isopropylidene-D-glucofuranose (25·0 g.) in light petroleum (b. p. 60—80°; 150 ml.) was added 2-chloroethanol (8 ml.). After the vigorous exothermic reaction had subsided, the mixture was refluxed for 2 hr., and then chloroform was added. The solid material was filtered off, and the filtrate concentrated (charcoal) to a syrup which crystallised from light petroleum (b. p. 60—80°) to give di-*O*-isopropylidene-D-glucose (15·7 g.). Concentration of the mother-liquors gave a golden syrup (6·1 g.) which distilled at 125°/0·005 mm. (bath-temp.). The 3-O-2′-*hydroxyethyl ether* had $[\alpha]_D^{21}$ −2·2° (*c* 1·4 in chloroform), n_D^{21} 1·4710 (Found: C, 55·7; H, 7·9. $C_{14}H_{24}O_7$ requires C, 55·3; H, 8·0%).

3-O-*Carbamoylmethyl*-1,2:5,6-*di*-O-*isopropylidene*-D-*glucofuranose*.—1,2:5,6-Di-*O*-isopropylidene-3-*O*-methoxycarbonylmethyl-D-glucose [2] (2·2 g.) was suspended in aqueous ammonia (100 ml.), dissolving in 4 hr. The solution was concentrated under reduced pressure to a syrup. This crystallised, and after digestion with light petroleum (b. p. 40—60°) the *amide* (1·8 g.; m. p. 100—102°) after several recrystallisations from di-isopropyl ether, had m. p. 104·5—105·5°, $[\alpha]_D^{21}$ −67·8° (*c* 2·0 in chloroform) (Found: C, 53·2; H, 7·4; N, 4·5. $C_{14}H_{23}NO_7$ requires C, 53·1; H, 7·3; N, 4·4%).

3-O-2′-*Aminoethyl*-1,2:5,6-*di*-O-*isopropylidene*-D-*glucofuranose*.—To a solution of the above

[3] Freudenberg and Doser, *Ber.*, 1925, **58**, 294.

amide (1·807 g.) in dry ether (50 ml.) was slowly added with stirring an ether suspension of lithium aluminium hydride (2·95 g.). The stirring was continued for 18 hr., then the excess of hydride was decomposed by ethyl acetate, and the mixture concentrated. The residue was extracted with chloroform, and the extract concentrated to a brown syrup (1·474 g.). Distillation gave 3-O-2′-*aminoethyl*-1,2:5,6-*di*-O-*isopropylidene*-D-*glucofuranose* (0·587 g.), b. p. 140°/0·005 mm. (bath-temp.), n_D^{21} 1·4660, $[\alpha]_D^{22}$ −36·0° (*c* 1·0 in ethanol) (Found: C, 55·8; H, 8·4; N, 4·1. $C_{14}H_{25}NO_6$ requires C, 55·5; H, 8·3; N, 4·6%).

1,2:3,4-*Di*-O-*isopropylidene*-6-O-*methoxycarbonylmethyl*-D-*galactose*.—To the sodium salt of 1,2:3,4-di-*O*-isopropylidene-D-galactopyranose (20·3 g.) in light petroleum (b. p. 60—80°) was added methyl chloroacetate (14 ml., 1·22 equiv.), and the mixture heated at 70° for 2 hr. before being diluted with chloroform. The mixture was then washed with water, treated with charcoal, dried (Na_2SO_4), and concentrated to a brown syrup. This was distilled to give the *ester-ether* (13·6 g.), b. p. 110—112°/0·01 mm., n_D^{24} 1·4673, $[\alpha]_D^{24}$ −57·8° (*c* 1·5 in chloroform) (Found: C, 54·2; H, 7·4. $C_{15}H_{24}O_8$ requires C, 54·3; H, 7·3%).

6-O-*Carbamoylmethyl*-1,2:3,4-*di*-O-*isopropylidene*-D-*galactopyranose*.—The galactose ester (7·139 g.) was dissolved in aqueous ammonia (100 ml.; *d* 0·9) and after 3 hr. at room temperature there separated needles, m. p. 125—127°. The *amide* (2·396 g.), after one recrystallisation from ethanol–di-isopropyl ether, had m. p. 126·5—128°, $[\alpha]_D^{21}$ −97·0° (*c* 0·95 in chloroform) (Found: C, 53·1; H, 7·3; N, 4·6. $C_{14}H_{23}NO_7$ requires C, 53·1; H, 7·3; N, 4·4%).

The ammoniacal liquors were concentrated and the residue digested with ethanol–di-isopropyl ether. The residue partly crystallised from aqueous acetone to give glycine amide hydrochloride, m. p. 215—217°. Bergell and van Wülfing [4] give m. p. 186—189° (Found: C, 21·7; H, 6·6; N, 25·1; Cl, 31·1. Calc. for $C_2H_7ClN_2O$: C, 21·7; H, 6·4; N, 25·3; Cl, 32·1%).

Concentration of the ethanol–di-isopropyl ether mother-liquors gave a syrup (3·671 g.), b. p. 150—170°/0·005 mm. (bath-temp.), n_D^{21} 1·4690, $[\alpha]_D^{25}$ −61·5° (*c* 1·6 in chloroform). It was impure di-*O*-isopropylidene-D-galactose (Found: C, 55·3; H, 8·0; N, 0·8; OMe, 0·3. Calc. for $C_{12}H_{20}O_6$: C, 55·5; H, 7·8%).

6-O-2′-*Aminoethyl*-1,2:3,4-*di*-O-*isopropylidene*-D-*galactopyranose*.—The galactose amide (2·419 g.) was reduced with lithium aluminium hydride (4·12 g.), to give the *aminoethyl ether* (0·903 g.), b. p. 145°/0·01 mm. (bath-temp.), n_D^{17} 1·4683 (Found: C, 55·8; H, 8·6; N, 4·1. $C_{14}H_{25}NO_6$ requires C, 55·5; H, 8·3; N, 4·6%).

3-O-2′-*Cyanoethyl*-1,2:5,6-*di*-O-*isopropylidene*-D-*glucofuranose*.—To di-*O*-isopropylidene-D-glucose (7·716 g.) in dry dioxan (10 ml.) was added with stirring sodium methoxide (*ca.* 0·2 g.) followed by acrylonitrile (3 ml.). The stirring was continued for 19 hr. at 60° and then the mixture was diluted with chloroform. The solution was washed with dilute sulphuric acid, aqueous sodium hydrogen carbonate, and finally water, dried (Na_2SO_4), and concentrated to a clear syrup (6·760 g.). This was fractionally distilled to give two fractions. The first (3·269 g.), b. p. 120—124°/0·01 mm., crystallised from light petroleum (b. p. 60—80°) to give di-*O*-isopropylidene-D-glucose, m. p. and mixed m. p. 103—108·5°. The second fraction (1·632 g.), b. p. 128—140°/0·01 mm., had n_D^{20} 1·4630, $[\alpha]_D^{20}$ −24·3° (*c* 2·8 in chloroform), and was 3-O-2′-*cyanoethyl*-1,2:5,6-*di*-O-*isopropylidene*-D-*glucofuranose* (Found: C, 57·6; H, 7·6; N, 4·3. $C_{15}H_{23}NO_6$ requires C, 57·6; H, 7·4; N, 4·5%).

3-O-3′-*Aminopropyl*-1,2:5,6-*di*-O-*isopropylidene*-D-*glucosefuranose*.—Reduction of the cyanoethyl ester in ether solution with lithium aluminium hydride gave di-*O*-isopropylidene-D-glucose in 73% yield. A solution of the impure cyanoethyl ether (8·0 g.) in dry methanol was hydrogenated for 2 hr. over Raney nickel (0·5 g.) at 130°/130 atm. The cooled mixture was filtered, and the filtrate concentrated to a syrup which was distilled, to give the *aminopropyl ether* (3·2 g.), b. p. 130—140°/0·005 mm., n_D^{23} 1·4649, $[\alpha]_D^{22}$ −33·4° (*c* 1·2 in chloroform) (Found: C, 56·6; H, 8·8; N, 3·1. $C_{15}H_{27}NO_6$ requires C, 56·8; H, 8·6; N, 4·4%).

6-O-2′-*Cyanoethyl*-1,2:3,4-*di*-O-*isopropylidene*-D-*galactopyranose*.—Di-*O*-isopropylidene-D-galactose (12·652 g.) was treated with acrylonitrile (6 ml.) to give the *cyanoethyl ether* (10·661 g.), b. p. 138°/0·005 mm., n_D^{20} 1·4670, $[\alpha]_D^{21}$ −62·9° (*c* 1·7 in chloroform) (Found: C, 57·6; H, 7·6; N, 4·6. $C_{15}H_{23}NO_6$ requires C, 57·6; H, 7·4; N, 4·5%).

6-O-3′-*Aminopropyl*-1,2:3,4-*di*-O-*isopropylidene*-D-*galactopyranose*.—Reduction of the galactose cyanoethyl ether in ether solution with lithium aluminium hydride gave di-*O*-isopropylidene-D-galactose in 99% yield. A solution of the ether (34·36 g.) in dry methanol was hydrogenated over Raney nickel (1·0 g.) at 130°/130 atm. of hydrogen for 2 hr. The *aminopropyl*

[4] Bergell and van Wülfing, *Z. physiol. Chem.*, 1910, **64**, 353.

ether produced was fractionally distilled to give fraction (*a*) (11·83 g.), b. p. 130°/0·005 mm., n_D^{22} 1·4690, $[\alpha]_D^{23}$ −60·5° (*c* 1·0 chloroform) (Found: C, 56·4; H, 8·5; N, 3·9. $C_{15}H_{27}NO_6$ requires C, 56·8; H, 8·6; N, 4·4%), and fraction (*b*) (13·47 g.), b. p. 135°/0·01 mm., n_D^{22} 1·4680, $[\alpha]_D^{23}$ −67·5° (*c* 1·0 in chloroform) (Found: C, 56·7; H, 8·7; N, 4·3%).

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