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NUCLEOPHILIC REPLACEMENT REACTIONS OF SULPHONATES

PART IV[1]. TRANSFORMATION OF 2-AMINO-2-DEOXY-D-GLUCOSE INTO DERIVATIVES OF 2-AMINO-2-DEOXY-D-GALACTOSE AND 2-AMINO-2,4,6-TRIDEOXY-D-*xylo*-HEXOSE

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ABSTRACT

Methyl 2-acetamido-3-*O*-acetyl-2-deoxy-4,6-di-*O*-methanesulphonyl-α-D-glucopyranoside (**1**) undergoes displacement of both sulphonate groups with sodium benzoate in *N*,*N*-dimethylformamide to give, after saponification, methyl 2-acetamido-2-deoxy-α-D-galactopyranoside (**5**), thereby providing a convenient synthesis of this galactosamine derivative The 6-methanesulphonate group of compound **1** is very easily replaced by a chlorine atom when treated with pyridinium chloride in pyridine, so that the 6-chloro derivative (**2**) is encountered as a by-product in the preparation of compound **1**. The disulphonate also undergoes displacement with the thiocyanate anion to give the corresponding 4,6-dithiocyanato-galactopyranoside **6**, together with the disulphide **7** derived from the dithiocyanate by hydrolysis followed by oxidative ring-closure. The desulphurisation of either of these derivatives gives, after hydrolysis, 2-amino-2,4,6-trideoxy-D-*xylo*-hexose hydrochloride (**11**).

INTRODUCTION

4-*O*-Sulphonyl derivatives of α-D-glucopyranosides and α-D-galactopyranosides undergo S_N2 displacement reactions in *N*,*N*-dimethylformamide with such nucleophilic anions as benzoate, azide, thiocyanate, etc., to give, with inversion of configuration at C-4, the corresponding 4-substituted α-D-galactopyranosides and α-D-glucopyranosides, respectively[2,3]. The use of benzoate provides a convenient method of inverting the configuration of the 4-hydroxyl group, and the use of thiocyanate can be used as a route to the synthesis of 4-thio derivatives, and, by desulphurisation, 4-deoxy derivatives. Since 2-amino-2-deoxy-D-galactopyranose (galactosamine), a constituent of many biological products[4], is difficultly accessible from natural sources, a convenient method of synthesis involving inversion of configuration at C-4 of the readily available 2-amino-2-deoxy-D-glucose was considered feasible by methods analogous to those described previously[2,3].

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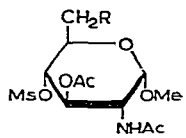
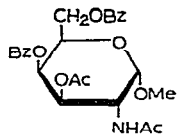
RESULTS AND DISCUSSION

Methyl 2-acetamido-3-*O*-acetyl-2-deoxy-4,6-di-*O*-methanesulphonyl-α-D-glucopyranoside (**1**) was required as starting material for this synthesis. This compound was prepared (60%) from methyl 2-acetamido-3-*O*-acetyl-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside[5] by sequential hydrolysis with mild acid, to remove the benzylidene substituent, and methanesulphonylation. It was essential that the final stage be carried out at low temperature, because, at room temperature, a substantial proportion of a side product was formed. This by-product was isolated by chromatography; the n.m.r. spectrum showed that it was a monomethanesulphonate, and elemental analysis revealed it to be a monochloro derivative to which the 6-chloro structure **2** was assigned. Chlorination has been observed on several occasions during sulphonylation reactions of carbohydrates[6], generally at the primary position, although it is normally observed only when the reaction is carried out at elevated temperatures or for a prolonged time. The same chloro derivative was also obtained by treatment of the dimethanesulphonate **1** with pyridine hydrochloride in hot pyridine. The first-order coupling constants derived from the n.m.r. spectrum of **2** (Table I) were in complete accord with the *gluco* but not the *galacto* configuration, hence showing that it was the 6-chloro derivative and not the 4-chloro compound.



1 R = OMs
2 R = Cl
3 R = OBz



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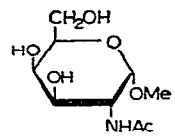

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Treatment of the disulphonate **1** with sodium benzoate in *N*,*N*-dimethylformamide afforded a complex mixture, from which a 41% yield of the known methyl 2-acetamido-2-deoxy-α-D-galactopyranoside (**5**) could be isolated after saponification, thereby providing a convenient synthesis of this galactosamine derivative. The complexity of the original reaction mixture was probably a result of the presence of partially de-esterified products. The two major components of the reaction mixture were isolated by chromatography; one was the expected 4,6-dibenzoate **4** (31% yield), and the other was a related monobenzoate (4%). Their relationship was established by de-esterification to the same compound, namely, methyl 2-acetamido-2-deoxy-α-D-galactopyranoside (**5**). The presence of the monobenzoate was of some interest because it could have arisen by neighbouring-group participation by either the 3-acetoxy or the 6-benzoyloxy group in the displacement of the 4-sulphonate group in the initially formed methyl 2-acetamido-3-*O*-acetyl-6-*O*-benzoyl-2-deoxy-4-*O*-methanesulphonyl-α-D-glucopyranoside (**3**), followed by solvolysis of the intermediary acyloxonium ion. However, we have no evidence as to whether the monobenzoate arises in this way or whether it is formed by partial de-esterification of the 4,6-dibenzoate **4** during the course of the reaction. The same mixture of dibenzoate **4** and monobenzoate was

obtained when the 6-chloro-4-sulphonate **2** was treated similarly with sodium benzoate in *N,N*-dimethylformamide. Two related syntheses of galactosamine derivatives have been described previously, by using 4,6-disulphonates of benzyl glycosides of 2-amino-2-deoxy-D-glucose[7,8], but the sulphonate groups were replaced by acetolysis with potassium acetate in mixtures of acetic acid and acetic anhydride.

TABLE I

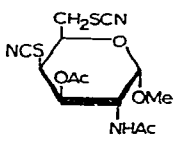
CHEMICAL SHIFTS (τ-VALUES) IN CHLOROFORM-*d* AND FIRST-ORDER COUPLING CONSTANTS

Compound	**2**	**4**	**6**	**7**	**9**[a]
H-1	5.28d[b]	5.13d	5.19d	—	5.15d
H-2	—	5.31q	—	—	—
H-3	4.73q	4.78q	4.69q	4.46q	4.71s
H-4	5.32t	4.27d	5.82q	6.00q	7.97 8.52
H-5	—	—	—	—	—
H-6	—	—	~6.7	~6.62	8.90d
OMe	6.57s	6.59s	6.57s	6.58s	6.8s
OAc	7.93s	8.13s	7.86s	7.95s	7.93s
NAc	8.07s	8.18s	8.06s	8.06s	8.03s
OMs	6.96s	—	—	—	—
$J_{1,2}$	3.5	3.0	3.5	—	3.5
$J_{2,3}$	11.0	11.0	10.5	10.0	11.0
$J_{3,4}$	9.0	3.0	3.5	5.0	3,4*a*, 11.0 3,4*e*, 5.0
$J_{4,5}$	9.0	<1	2.0	2.5	—
$J_{5,6}$	—	—	—	—	6.0

[a]In pyridine-d_5.
[b]d = doublet, s = singlet, q = quartet, t = triplet.

The dimethanesulphonate **1** also underwent replacement with the thiocyanate anion in dry *N,N*-dimethylformamide to give, *inter alia*, two products which could be readily separated by fractional crystallisation. The former was the expected galacto-pyranoside 4,6-dithiocyanate **6** (13%), and the latter was the corresponding disulphide (4%) formed by hydrolysis of compound **6** followed by oxidation. This result is analogous to those obtained with methyl 2,3-di-*O*-acetyl-4,6-di-*O*-methanesulphonyl-α-D-glucopyranoside[3] from which both the dithiocyanate and the disulphide were isolated; the respective yields depended upon the amount of water present in the reaction mixture, since water favours hydrolysis of the dithiocyanate and hence formation of the disulphide. In agreement with this, when the reaction was carried out in the presence of 5% of water, only the disulphide **7** (18%) could be isolated. The structures of the two products **6** and **7** were assigned from their n.m.r. spectra. For the dithiocyanate **6**, the resonance due to H-3 was seen to low field (τ 4.82) of all other ring protons, because of the deshielding by the acetoxy group. It occurred as a quartet with splittings of 10.5 and 3.5 Hz which indicated an *eq*, *ax*, *ax*, arrangement of H-4, H-3, and H-2, respectively, in agreement with the *galacto* configuration.

The signal for H-1 occurred as a doublet at τ 5.31 (J 3.5 Hz) and that for H-4 as a quartet at τ 5.92 (J 3.5 and 2.0 Hz). The small value of $J_{4,5}$ is a characteristic feature of galactopyranosides[9]. In the spectrum of the disulphide **7**, the resonance due to H-3 was again clearly discernible as a quartet at τ 4.39, with coupling constants of 10.0 and 5.0 Hz, and H-4 was observed at τ 6.10 as a quartet with splittings of 5.0 and 2.5 Hz. Treatment of either the dithiocyanate **6** or the 3-*O*-acetyl-disulphide **7** with sodium ethoxide afforded the de-acetylated disulphide **8**.



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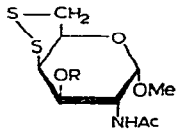
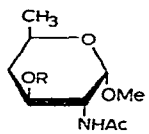
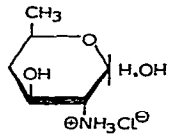


7 R = Ac
8 R = H



9 R=Ac
10 R=H



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Desulphurisation of either the dithiocyanate **6** or the 3-*O*-acetyl-disulphide **7** with Raney nickel gave methyl 2-acetamido-3-*O*-acetyl-2,4,6-trideoxy-α-D-*xylo*-hexopyranoside (**9**), the structure of which was confirmed by its n.m.r. spectrum. The signal for H-3 was observed at lowest field (τ 4.71) as a well-defined sextet with $J_{2,3}$ 11.0, $J_{3,4e}$ 5.0, and $J_{3,4a}$ 11.0 Hz, and H-1 as a doublet at τ 5.15 with $J_{1,2}$ 3.5 Hz. The protons at C-4 produced a complex multiplet at about τ 8.5, and the assignment of other ring protons was not possible with any certainty. Deacetylation of the product afforded methyl 2-acetamido-2,4,6-trideoxy-α-D-*xylo*-hexopyranoside (**10**) which, upon acid hydrolysis, gave the crystalline 2-amino-2,4,6-trideoxy-D-*xylo*-hexose (4,6-dideoxy-glucosamine) hydrochloride (**11**). Although a number of aminotrideoxy-hexoses have been isolated from natural sources[10], some of which have been synthesised[11], this represents the first preparation of such a compound having the basic group at C-2.

EXPERIMENTAL

For general notes on experimental procedures, see Ref. 2.

Methyl 2-acetamido-3-O-acetyl-2-deoxy-4,6-di-O-methanesulphonyl-α-D-gluco-pyranoside (**1**). — A mixture of methyl 2-acetamido-3-*O*-acetyl-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside[5] (48.5 g), 50% acetic acid (500 ml), and acetone (150 ml) was heated for 25 min at 90° (reaction complete by t.l.c.) and then concentrated to a syrup which was extracted with light petroleum (to remove benzaldehyde) and then dried thoroughly *in vacuo*. A solution of the syrup in pyridine (600 ml) was cooled in an ice-bath and treated with methanesulphonyl chloride (31 ml; 3 mol. proportions) in three portions (temperature $\neq 0°$). After being kept for three days at 0°, the reaction mixture was decomposed by the addition of water and then concentrated to give a black syrup. A solution of this product in chloroform (600 ml) was washed successively with N hydrochloric acid, aqueous sodium hydrogen carbonate, and water. The organic

layer was then decolorised with charcoal, dried, and evaporated. Recrystallisation of the residue from ethanol–light petroleum gave disulphonate **1** as colourless crystals (32 g; 60%), m.p. 151–152°, $[\alpha]_D$ +70° (*c* 0.92) (Found: C, 36.2; H, 5.25; N, 3.15; S, 14.8. $C_{13}H_{23}NO_{11}S_2$ calc.: C, 36.05; H, 5.3; N, 3.25; S, 14.8%).

In an early preparation, carried out at room temperature with a large excess of the acid chloride, the yield of the diester **1** was only 22%, and t.l.c. showed a major impurity to be present. After isolation by chloroform extraction, the mixture was fractionated on a column of silica gel with chloroform–acetone (8:1). The impurity (12% yield) was identified as the 6-chloro derivative **2**, identical with the product obtained below.

*Methyl 2-acetamido-3-O-acetyl-6-chloro-2,6-dideoxy-4-O-methanesulphonyl-α-*D*-glucopyranoside* (**2**). — A solution of disulphonate **1** (5 g) in pyridine (240 ml) was heated for 48 h at 70° with pyridine hydrochloride (10 g), whereupon t.l.c. showed the reaction to be complete. The mixture was diluted with water, and the product was isolated by chloroform extraction in the usual way to give 2.63 g (58%) of compound **2** (from ethanol–light petroleum), m.p. 165–167°, $[\alpha]_D$ +80° (*c* 1.24) (Found: C, 38.6; H, 5.45; N, 3.75; S, 8.65; Cl, 9.5. $C_{12}H_{20}ClNO_8S$ calc.: C, 38.6; H, 5.35; N, 3.75; S, 8.6; Cl, 9.5%).

Treatment of disulphonate **1** *with sodium benzoate in* N,N*-dimethylformamide.* — The dimethanesulphonate **1** (3.2 g) and sodium benzoate (3 g) were heated in *N,N*-dimethylformamide (40 ml) for 24 h at 130°. The resulting mixture was then diluted with chloroform (200 ml), filtered, and concentrated. A solution of the black, syrupy residue in chloroform was washed successively with N sulphuric acid, aqueous sodium hydrogen carbonate, and water, and then decolorised with charcoal and dried (Na_2SO_4). Evaporation gave a syrup (2.8 g) which was shown by t.l.c. to be a complex mixture. The product was subjected to chromatography on silica gel with chloroform–acetone (8:1) as eluant. The first component eluted was crystallised from ethanol–light petroleum to give 0.88 g of the 4,6-dibenzoate **4**, m.p. 191–193°, $[\alpha]_D$ +100° (*c* 1.1) (Found: C, 61.6; H, 5.6; N, 2.9. $C_{25}H_{27}NO_9$ calc.: C, 61.9; H, 5.55; N, 2.85%).

The major, slower-moving component crystallised from ethanol–light petroleum to give 97 mg (3.5%) of a monobenzoate, m.p. 212–214°, $[\alpha]_D$ +86° (*c* 0.61) (Found: C, 56.65; H, 5.95; N, 3.7. $C_{18}H_{23}NO_8$ calc.: C, 56.7; H, 6.05; N, 3.65%).

A comparable result was obtained when the 6-chloro derivative **2** was treated in the same way.

*Methyl 2-acetamido-2-deoxy-α-*D*-galactopyranoside* (**5**). — (*a*) The 4,6-dimethanesulphonate **1** (1 g) and sodium benzoate (0.9 g) were heated for 18 h at 130° in *N,N*-dimethylformamide (25 ml) and then under reflux for a further hour. The black reaction mixture was cooled, diluted with chloroform (50 ml), filtered, and concentrated. A solution of the resulting black syrup in chloroform was decolorised with charcoal and dried (Na_2SO_4). After filtration, concentration gave a syrup which was dissolved in ethanol (25 ml) and treated with M ethanolic sodium ethoxide (1 ml). After 4 h, water was added, and the solution was deionised with Amberlite IR-120(H^+) resin and then extracted with ether to remove benzoic acid. Evaporation of the aqueous

layer gave a solid, recrystallisation of which from ethanol–light petroleum gave 36 mg (41%) of the galactopyranoside **5**, m.p. 218–221°, $[\alpha]_D$ +168° (*c* 1.03); lit.[12], m.p. 217–218°, $[\alpha]_D$ +170°.

(*b*) Methyl 2-acetamido-3-*O*-acetyl-4,6-di-*O*-benzoyl-2-deoxy-α-D-galactopyranoside (**4**) (0.72 g) was dissolved in ethanol (20 ml), and M ethanolic sodium ethoxide solution was added. After being kept overnight, the reaction mixture was processed as above to give the same product (**5**) (80% in two crops), m.p. 219–220°.

(*c*) The monobenzoate (0.1 g) obtained in the above replacement reaction was dissolved in ethanol (10 ml) and saponified as above to give compound **5** (47 mg; 80%), m.p. 217–220°, identical with the two previous samples.

Treatment of disulphonate **1** *with potassium thiocyanate in* N,N-*dimethylformamide.* — (*a*) A mixture of 5.65 g of disulphonate **1** and 11.3 g of potassium thiocyanate was thoroughly dried *in vacuo* and then heated for 24 h at 145° in dry *N*,*N*-dimethylformamide (45 ml), whereupon the reaction was judged to be complete by t.l.c. The mixture was then concentrated to dryness, and the product was isolated in the usual way by chloroform extraction. The resulting solid was recrystallised twice from ethanol–light petroleum to give methyl 2-acetamido-3-*O*-acetyl-2,4,6-trideoxy-4,6-dithiocyanato-α-D-galactopyranoside (**6**) as long, colourless needles (0.61 g; 13%), m.p. 161–163°, $[\alpha]_D$ +80° (*c* 0.75) (Found: C, 43.4; H, 4.8; N, 11.85; S, 17.7. $C_{13}H_{17}N_3O_5S_2$ calc.: C, 43.45; H, 4.7; N, 11.7; S, 17.8%).

Concentration of the mother liquors from the first recrystallisation gave a syrup which crystallised from ethanol to give methyl 2-acetamido-3-*O*-acetyl-2,4,6-trideoxy-4,6-epidithio-α-D-galactopyranoside (**7**) as pale-yellow crystals (4%) identical with the product obtained below.

(*b*) A mixture of 3 g of disulphonate **1** and 6 g of potassium thiocyanate was heated for 22 h at 145° in a mixture of *N*,*N*-dimethylformamide (25 ml) and water (2 ml); after 20 h, more water (2 ml) was added. The product was isolated in the usual way by chloroform extraction. Recrystallisation of the resulting product from ethanol–light petroleum gave the disulphide **7** as pale-yellow crystals (0.36 g; 18%), m.p. 211–212°, $[\alpha]_D$ +129° (*c* 0.82), λ_{max} 222 (ε 419) and 336 nm (ε 85) (Found: C, 42.8; H, 5.25; N, 4.55; S, 20.65. $C_{11}H_{17}NO_5S_2$ calc.: C, 43.0; H, 5.55; N, 4.55; S, 20.85%).

*Methyl 2-acetamido-2-deoxy-4,6-epidithio-α-*D*-galactopyranoside* (**8**). — (*a*) The 3-acetate **7** (0.1 g) was dissolved in ethanol (20 ml) and treated with M ethanolic sodium ethoxide (2 ml). After 3 h at room temperature, when t.l.c. indicated the reaction to be complete, the mixture was diluted with water, de-ionised with Amberlite IR-120(H^+) resin, and then concentrated to a yellow solid. Recrystallisation from ethanol–light petroleum gave 44 mg (60%) of disulphide **8** as yellow needles, m.p. 252–255°, $[\alpha]_D$ +188° (*c* 0.32 in ethanol), λ_{max} 220 (ε 1103) and 336 nm (ε 74) (Found: C, 40.6; H, 5.75; N, 5.5; S, 24.3. $C_9H_{15}NO_4S_2$ calc.: C, 40.75; H, 5.65; N, 5.3; S, 24.15%).

(*b*) The dithiocyanate **6** (0.12 g) was dissolved in 20 ml of M methanolic sodium methoxide and heated for 20 min under reflux. After dilution with water, the solution was de-ionised with Amberlite IR-120(H^+) resin, decolorised with charcoal, and

evaporated to dryness. The resulting yellow solid was recrystallised from ethanol to give the disulphide **8** (38 mg; 42%), identical with the product from (*a*).

*Methyl 2-acetamido-3-*O*-acetyl-2,3,6-trideoxy-α-*D*-xylo-hexopyranoside* (**9**). — (*a*) The 3-*O*-acetyl-disulphide **7** (0.67 g) was dissolved in ethanol (70 ml) and heated under gentle reflux with Raney nickel (*ca.* 10 g) for 3 h. After filtration, the nickel was washed well with ethanol, and the combined filtrates were concentrated to dryness. Recrystallisation of the residue from ethanol–light petroleum gave compound **9** as colourless crystals (0.27 g, 51%), m.p. 171–173°, $[\alpha]_D$ +85° (*c* 0.86) (Found: C, 53.8; H, 7.9; N, 5.5. $C_{11}H_{19}NO_5$ calc.: C, 53.9; H, 7.75; N, 5.70%).

(*b*) Methyl 2-acetamido-3-*O*-acetyl-2,4,6-trideoxy-4,6-dithiocyanato-α-D-galactopyranoside (**6**) (0.52 g) was desulphurised as described in (*a*). The resulting product was, however, found to be a more-complex mixture, and only 59 mg of compound **9** could be obtained.

*Methyl 2-acetamido-2,4,6-trideoxy-α-*D*-xylo-hexopyranoside* (**10**). — The 3-acetate **9** (0.26 g) was dissolved in ethanol (20 ml), and M ethanolic sodium ethoxide (1 ml) was added. After 2 h, a small amount of water was added, and concentration of the solution gave a solid mass, the bulk of which dissolved in boiling ethyl acetate. After removal of the insoluble inorganic material, the ethyl acetate extract was concentrated to a smaller bulk, whereupon compound **10** was obtained as three crops of crystals (0.36 g; 80%), m.p. 168–170° (decomp.), $[\alpha]_D$ +99° (*c* 0.89) (Found: C, 53.2; H, 8.65; N, 6.8. $C_9H_{17}NO_4$ calc.: C, 53.2; H, 8.35; N, 6.9%).

*2-Amino-2,4,6-trideoxy-*D*-xylo-hexopyranose hydrochloride* (**11**). — Compound **10** (0.26 g) was dissolved in 2N hydrochloric acid (5 ml) and heated on a boiling-water bath for 2 h, and then concentrated to a syrup which readily crystallised. The hydrochloride **11** was isolated by trituration with a 1:1 mixture of ethanol–acetone, to give 102 mg of colourless crystals. A further crop (77 mg) was obtained by decolorisation of the mother liquors, followed by concentration and trituration; total yield, 76%. Recrystallisation from methanol–acetone–light petroleum afforded an analytical sample of hydrochloride **11**, m.p. 166–168° (decomp.), $[\alpha]_D$ +98 (2 min)→ +54° (2 h, const.) (*c* 1.54 in water) (Found: C, 39.25; H, 7.85, Cl; 19.45; N, 7.65. $C_6H_{14}ClNO_3$ calc.: C, 39.25; H, 7.65; Cl, 19.35; N, 7.65%).

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