1283. *Nitrogen-containing Carbohydrate Derivatives. Part IX.* Synthesis of 2,3-Diamino-2,3-dideoxyhexose Derivatives*

By R. D. Guthrie and D. Murphy

The sulphonyloxy-group in methyl 2-azido-4,6-*O*-benzylidene-2-deoxy-α-D-altroside and in methyl 4,6-*O*-benzylidene-2-deoxy-D-*ribo*-hexopyranoside 3-sulphonyl esters have been displaced by azide ion; inversion occurred at the reaction site. An attempted similar displacement on methyl 3-azido-4,6-*O*-benzylidene-3-deoxy-α-D-altroside 2-sulphonyl esters was unsuccessful. These results are discussed.

The fission of secondary carbohydrate sulphonate esters by nitrogen-containing nucleophiles is an established and convenient method for the synthesis of amino-sugar derivatives. The use of hydrazine [1,2] and ammonia [3] has been widely reported, but the powerfully nucleophilic azide ion is a much more convenient reagent. When this work was started azide ion had been used only in the displacement of primary glycoside 6-toluene-*p*-sulphonate groups,[4] but it has recently been shown that sodium azide in boiling *NN*-dimethylformamide will also displace secondary methanesulphonyloxy-groups with inversion.[5,6]

The preparation of derivatives of 2,3-diamino-2,3-dideoxy-D-glucose and D-altrose *via* the fission by azide ion of epimino-glycoside derivatives has been reported.[7] The preparation of *cis*-2,3-diamino-glycoside derivatives by direct displacement of secondary sulphonyloxy-groups has now been explored.

Reaction of methyl 2-azido-4,6-*O*-benzylidene-2-deoxy-α-D-altroside 3-toluene-*p*-sulphonate [8] (Ia) with sodium azide gave a methyl 2,3-diazido-4,6-*O*-benzylidene-2,3-dideoxy-α-D-glycoside (II) in 49% yield. Use of the corresponding methanesulphonate (Ib) did not substantially alter the yield. The product (II) which was assumed to have the D-*manno*-configuration was reduced to a syrupy diamino-compound (III), characterised as the crystalline diacetamido-derivative. This latter compound was different from methyl 2,3-diacetamido-4,6-*O*-benzylidene-2,3-dideoxy-α-D-altroside, prepared *via* an epimino-ring opening reaction.[9] The D-*altro*-product would have resulted had the azido-group on C-2 in (Ia) participated in the displacement of the sulphonyloxy-group from C-3. That the product had the D-*manno*-configuration proved that no such assistance occurred.

This result is in conflict with the work of Streitwieser and Pulver.[10] They studied the acetolysis of *trans*-2-azidocyclohexyl toluene-*p*-sulphonate and obtained *trans*-2-azidocyclohexyl acetate, albeit in only 37% yield. From this result (no other products were recorded) it was concluded that the azido-group had participated, but without giving any anchimeric assistance. It is possible that the proposed [10] azidonium intermediate is favoured only in acidic media. Further study is obviously necessary to determine the presence or absence of participation by an azide group under various conditions.

To investigate the displacement of sulphonyloxy-groups without any possible participation we have displaced the methanesulphonyloxy-group from methyl 4,6-*O*-benzylidene-2-deoxy-α-D-*ribo*-hexopyranoside 3-methanesulphonate with azide ion to give methyl

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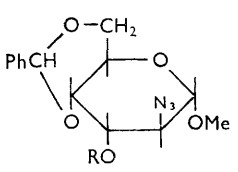
[5] E. J. Reist, B. R. Baker, and L. Goodman, *Chem. and Ind.*, 1962, 1794.
[6] J. Hill, L. Hough, and A. C. Richardson, *Proc. Chem. Soc.*, 1963, 346.
[7] R. D. Guthrie and D. Murphy, *J.*, 1965, 3828.
[8] R. D. Guthrie and D. Murphy, *J.*, 1963, 5288.
[9] D. A. Prins, *J. Amer. Chem. Soc.*, 1948, **70**, 3955.
[10] A. Streitwieser and S. Pulver, *J. Amer. Chem. Soc.*, 1964, **86**, 1587.

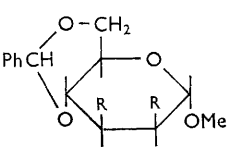
3-azido-4,6-*O*-benzylidene-2,3-dideoxy-α-D-*arabino*-hexopyranoside, characterised by reduction and acetylation to give the corresponding 3-acetamido-derivative, which was identical with an authentic sample.[11] Thus, the displacement readily took place without any neighbouring group, and Walden inversion occurred.

Partial hydrolysis of the 2,3-diazidomannoside (II) gave the syrupy methyl 2,3-diazido-2,3-dideoxy-α-D-mannoside, characterised as the 4,6-diacetate and 4,6-dimethanesulphonate. The syrupy 2,3-diaminomannoside (III) consumed 0·96 mole of sodium periodate in unbuffered solution in 200 min. The white crystalline product of this oxidation differed from that obtained by reacting the corresponding oxidised diol with ammonia. Attempted acid hydrolysis of the syrupy methyl 2,3-diazido-2,3-dideoxy-α-D-mannoside using hydrochloric acid (1—6N) gave only unchanged starting material, or dark syrups, indicating extensive decomposition. Treatment of methyl 2,3-diazido-2,3-dideoxy-α-D-mannoside 4,6-diacetate with methanolic hydrazine hydrate–Raney nickel gave syrupy methyl 2,3-diamino-2,3-dideoxy-α-D-mannoside, characterised as the crystalline tetra-acetate.

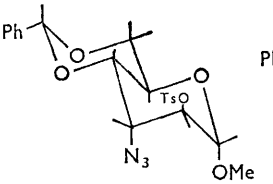
Methyl 2,3-diazido-2,3-dideoxy-α-D-mannoside 4,6-dimethanesulphonate with sodium azide gave a triazidomethanesulphonylglycoside in 44% yield assumed to be methyl 2,3,6-triazido-2,3,6-trideoxy-α-D-mannoside 4-methanesulphonate. No trace of a tetra-azido-compound or any other characterisable product could be found, although it has been shown [6] that 4-methanesulphonate groups are readily displaced under the same conditions. The triazidomannoside has the highest percentage nitrogen content so far reported for nitrogen-containing carbohydrates (36·3%); considerable thermal decomposition is therefore to be expected.



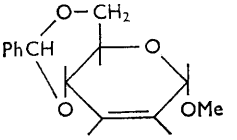
(I: a, R = Ts;
b, R = Ms)



(II: R = N_3)
(III: R = NH_2)



(IV)



(V)

Attempts were then made to extend the displacement of the sulphonate group in the 2-azidoaltroside (Ia) to the isomeric 3-azidoaltroside (IV). The attempted displacement by azide ion was tried over a range of temperatures, but only unchanged starting material (0—89%) could be isolated from the product mixtures. Decomposition increased sharply above 135—140°. The failure of this reaction may have been due to the stereochemistry of the starting material. Axial groups on C-1 and C-3 in the 3-azidoaltroside (IV) would hinder the approach of a nucleophile to the rear side of C-2. A similar effect has been discussed elsewhere.[12] The azide ion also failed to displace the methanesulphonyloxy-group in methyl 3-azido-4,6-*O*-benzylidene-3-deoxy-α-D-glucoside 2-methanesulphonate; only unchanged starting material (80%) was obtained.

The nitrobenzene-*p*-sulphonate group has been recommended [13] as a good leaving group in displacement reactions, since the nitro-substituent should facilitate electron recession in the departing group. Reaction of methyl 3-azido-4,6-*O*-benzylidene-3-deoxy-α-D-altroside 2-nitrobenzene-*p*-sulphonate with sodium azide gave methyl 3-azido-4,6-*O*-benzylidene-3-deoxy-α-D-altroside (20%) as the only characterisable product. Thus, the reactivity of the nitrobenzene-*p*-sulphonate group has permitted the uncommon S–O cleavage; such behaviour has been noted previously [14] in the ammonolysis of 1,2:5,6-di-*O*-isopropylidene-D-glucose 3-nitrobenzene-*p*-sulphonate.

[11] D. H. Buss, L. Hough, and A. C. Richardson, *J.*, 1965, 2736.
[12] D. Horton, M. L. Wolfrom, and A. Thompson, *J. Org. Chem.*, 1961, **26**, 5069.
[13] R. S. Tipson, *Adv. Carbohydrate Chem.*, 1953, **8**, 211.
[14] B. Coxon and L. Hough, *J.*, 1961, 1643.

Reaction of methyl 2-azido-4,6-*O*-benzylidene-2-deoxy-α-D-altroside 3-nitrobenzene-*p*-sulphonate with sodium azide gave the 2,3-diazidomannoside (II) (27%).

Following the suggestion by Horton and his co-workers [15] that hydrazine is a much more effective nucleophile than azide ion in the displacement of hindered sulphonate esters, the use of this reagent in displacing the sulphonyloxy-group of the 3-azidoaltroside 2-toluene-*p*-sulphonate (IV) was explored. Rather surprisingly, the product was methyl 4,6-*O*-benzylidene-2,3-didehydro-2,3-dideoxy-α-D-*erythro*-hexopyranoside (V). Further studies on this reaction will be reported in a subsequent Paper.

Experimental

All solutions were concentrated at reduced pressure. Optical rotations are for chloroform solutions unless otherwise stated. Where possible compounds were identified by mixed m. p. and by infrared spectroscopy; new compounds had infrared spectra consistent with the assigned structures.

Preparation of Sulphonate Esters.—(*a*) *Methyl* 4,6-O-*benzylidene*-2-*deoxy*-α-D-ribo-*hexopyranoside* 3-*methanesulphonate*. Methyl 4,6-*O*-benzylidene-2-deoxy-α-D-*ribo*-hexopyranoside (2 g.) in pyridine (20 ml.) at 0° was treated with methanesulphonyl chloride (1·5 ml.), and the solution kept overnight at 0°. After hydrolysis of the excess of methanesulphonyl chloride, the solution was poured into ice–water (200 ml.). Filtration gave a white crystalline product, which on recrystallisation from ethanol gave the *product* (81%), m. p. 118—119° (decomp.), $[\alpha]_D^{20}$ +134° (*c* 1·28) (Found: C, 52·5; H, 5·8. $C_{15}H_{20}O_7S$ requires C, 52·3; H, 5·9%).

(*b*) *Methyl* 3-*azido*-4,6-O-*benzylidene*-3-*deoxy*-α-D-*altroside* 2-*nitrobenzene*-p-*sulphonate*. Methyl 3-azido-4,6-*O*-benzylidene-3-deoxy-α-D-altroside [8] (2 g.) and nitrobenzene-*p*-sulphonyl chloride (2 g.) in pyridine (25 ml.) were kept at room temperature for 7 days. After hydrolysis of excess of nitrobenzene-*p*-sulphonyl chloride the mixture was poured into ice–water (250 ml.) and extracted with chloroform. The extract was washed successively with cold dilute hydrochloric acid, sodium hydrogen carbonate solution, and water. Drying and evaporation of the extract gave a brown solid, which on two recrystallisations from propan-2-ol gave the *product* (83%), m. p. 124—126°, $[\alpha]_D^{21}$ +13·6° (*c* 1·32) (Found: C, 48·5; H, 3·9. $C_{20}H_{20}N_4O_9S$ requires C, 48·8; H, 4·1%).

(*c*) *Methyl* 2-*azido*-4,6-O-*benzylidene*-2-*deoxy*-α-D-*altroside* 3-*nitrobenzene*-p-*sulphonate*. Methyl 2-azido-4,6-*O*-benzylidene-2-deoxy-α-D-altroside [8] was treated with nitrobenzene-*p*-sulphonyl chloride as described above for the 3-azidoaltroside. The brown solid product, after two recrystallisations from propan-2-ol, gave the *product* (76%), m. p. 175° (decomp.), $[\alpha]_D^{26}$ +102° (*c* 0·92) (Found: C, 48·6; H, 3·9. $C_{20}H_{20}N_4O_9S$ requires C, 48·8; H, 4·1%).

Displacements with Sodium Azide.—(*a*) *Methyl* 2-*azido*-4,6-O-*benzylidene*-2-*deoxy*-α-D-*altroside* 3-*toluene*-p-*sulphonate* (Ia). The 2-azidoaltroside [8] (Ia) (1·5 g.) and sodium azide (1·5 g.) in *NN*-dimethylformamide (20 ml.) and dioxan (5 ml.) were boiled under reflux for 40 hr. The black solution was poured into ice–water (400 ml.) and the precipitate collected after 4 hr. at 0°. This was extracted with boiling dry acetone (3 × 50 ml.) and the extract decolourised with charcoal. Filtration, evaporation, and recrystallisation of the residue from ethanol gave white needles of *methyl* 2,3-*diazido*-4,6-O-*benzylidene*-2,3-*dideoxy*-α-D-*mannoside* (II) (49%), m. p. 151—152° (decomp.), $[\alpha]_D^{18}$ +107° (*c* 0·67) (Found: C, 50·6; H, 6·6; N, 25·2. $C_{14}H_{16}N_6O_4$ requires C, 50·6; H, 6·5; N, 25·3%).

Repetition of the above, but using the 2-azidoaltroside 3-methanesulphonate [8] (Ib) (5 g.) gave the diazidomannoside (II) (43%).

(*b*) *Methyl* 3-*azido*-4,6-O-*benzylidene*-3-*deoxy*-α-D-*altroside* 2-*toluene*-p-*sulphonate* (IV). The 3-azidoaltroside 2-toluene-*p*-sulphonate [8] (1·5 g.) and sodium azide (1·5 g.) in *NN*-dimethylformamide (50 ml.) and dioxan (20 ml.) were boiled under reflux at 120—125° for 48 hr. Pouring into water gave a white precipitate, which on crystallisation from methanol gave unchanged starting material (89%), m. p. 116—117°.

Repetition of the above, but using decreasing amounts of dioxan, gave in each case only unchanged starting material, m. p. 116—117° in decreasing yield.

NN-Dimethylformamide : dioxan	5 : 1	10 : 1	100 : 1
Unchanged starting material (%)	62	21	1

[15] M. L. Wolfrom, J. Bernsmann, and D. Horton, *J. Org. Chem.*, 1962, **27**, 4505.

(*c*) *Methyl* 3-*azido*-4,6-O-*benzylidene*-3-*deoxy*-α-D-*altroside* 2-*nitrobenzene*-p-*sulphonate*. The 3-azidoaltroside derivative was treated with sodium azide in *NN*-dimethylformamide as described for the toluene-*p*-sulphonate derivative. The syrupy product was chromatographed on alumina. Elution with chloroform gave methyl 3-azido-4,6-*O*-benzylidene-3-deoxy-α-D-altroside (20%), m. p. 134—135°. A syrupy compound eluted by benzene–chloroform (1 : 1) could not be characterised.

(*d*) *Methyl* 2-*azido*-4,6-O-*benzylidene*-2-*deoxy*-α-D-*altroside* 3-*nitrobenzene*-p-*sulphonate*. The 2-azidoaltroside derivative was treated with sodium azide as described above. Recrystallisation of the white crystalline product from ethanol gave methyl 2,3-diazido-4,6-*O*-benzylidene-2,3-dideoxy-α-D-mannoside (II) (27%), m. p. 151—152°.

(*e*) *Methyl* 4,6-O-*benzylidene*-2-*deoxy*-α-D-ribo-*hexopyranoside* 3-*methanesulphonate*. The 2-deoxy-*ribo*-hexopyranoside derivative (8 g.) and sodium azide (5 g.) in *NN*-dimethylformamide (500 ml.) and dioxan (25 ml.) were boiled under reflux for 10 hr. The solution was poured into ice–water (3000 ml.). Chloroform extraction gave a syrup, crystallised by addition of light petroleum. The solid on recrystallisation from propan-2-ol gave *methyl* 3-*azido*-4,6-O-*benzylidene*-2,3-*dideoxy*-α-D-*arabino*-*hexopyranoside* (55%), m. p. 82—84°, $[\alpha]_D^{20}$ +105° (*c* 0·98) (Found: C, 57·9; H, 6·0; N, 14·3. $C_{14}H_{17}N_3O_4$ requires C, 57·7; H, 5·8; N, 14·4%).

Reduction of the 3-azido-*arabino*-hexopyranoside using boiling methanolic hydrazine hydrate–Raney nickel gave a syrupy 3-amino-compound, treated overnight at room temperature with acetic anhydride–pyridine. The mixture was poured into ice–water, and the solution extracted with chloroform. Drying and evaporation of the extract gave a white solid, which on recrystallisation from propan-2-ol gave methyl 3-acetamido-4,6-*O*-benzylidene-2,3-dideoxy-α-D-*arabino*-hexopyranoside (60%), m. p. 240—244° (sublimation), $[\alpha]_D^{25}$ +52° (*c* 0·4) {lit.,[11] sublimation, 240—245°, $[\alpha]_D^{29}$ +53° (*c* 0·3)}.

Reduction of Methyl 2,3-*Diazido*-4,6-O-*benzylidene*-2,3-*dideoxy*-α-D-*mannoside* (II).—The diazidomannoside (2 g.) in methanol (100 ml.) was hydrogenated for 1 hr. at 1 atm. and at room temperature in the presence of Adams catalyst. Filtration and evaporation gave a thick syrup (1·95 g.), $[\alpha]_D^{18}$ +29·1° (*c* 0·89), consisting mainly of the expected 2,3-diamino-compound. Acetylation of the syrupy diaminomannoside, using pyridine–acetic anhydride, gave a white solid product which on two recrystallisations from ethanol gave *methyl* 2,3-*diacetamido*-4,6-O-*benzylidene*-2,3-*dideoxy*-α-D-*mannoside* (65%), m. p. 303° (decomp.), 310—311° (preheated to 300°), $[\alpha]_D^{20}$ −36·2° (*c* 0·99, $HCONMe_2$) (Found: C, 59·5; H, 6·7. $C_{18}H_{24}N_2O_6$ requires C, 59·3; H, 6·6%).

Periodate Oxidation of Methyl 2,3-*Diamino*-4,6-O-*benzylidene*-2,3-*dideoxy*-α-D-*mannoside* (III).—(*a*) The syrupy diaminomannoside ($2·90 \times 10^{-3}$M) was oxidised by an unbuffered solution of sodium periodate approximately $15·15 \times 10^{-3}$ molar with respect to periodate. Analysis of the solution gave the following results:

Time (min.)	0	15	30	60	200
Periodate uptake (moles)	0	0·69	0·78	0·90	0·96

(*b*) The diaminomannoside (0·5 g.) in water (200 ml.) was treated with sodium periodate (0·8 g.) and the solution kept overnight in the dark at room temperature. Filtration gave a white crystalline solid (0·15 g.). This material was found to be different from periodate-oxidised methyl 4,6-*O*-benzylidene-α-D-glucoside, and from the product obtained by treating this dialdehyde with ammonia.

Partial Hydrolysis of Methyl 2,3-*Diazido*-4,6-O-*benzylidene*-2,3-*dideoxy*-α-D-*mannoside*.—The diazidomannoside (2·5 g.) in 60% aqueous acetic acid (50 ml.) was boiled under reflux for 30 min. Acetic acid and benzaldehyde were removed by co-distillation with water, and the solution evaporated to give a thick syrup (2·41 g.), $[\alpha]_D^{20}$ +108° (*c* 1·03 MeOH). The infrared spectrum was consistent with that expected for methyl 2,3-diazido-2,3-dideoxy-α-D-mannoside. Attempts to crystallise the syrup from the common solvents were all unsuccessful.

The syrupy methyl 2,3-diazido-2,3-dideoxy-α-D-mannoside (0·5 g.) was acetylated using acetic anhydride–pyridine. Two recrystallisations of the white solid product from aqueous ethanol gave *methyl* 2,3-*diazido*-2,3-*dideoxy*-α-D-*mannoside* 4,6-*diacetate* (75%), m. p. 82—83°, $[\alpha]_D^{20}$ +114° (*c* 0·93) (Found: C, 40·2; H, 4·9. $C_{11}H_{16}N_6O_6$ requires C, 40·3; H, 5·0%).

Treatment of the syrupy methyl 2,3-diazido-2,3-dideoxy-α-D-mannoside with methanesulphonyl chloride–pyridine as described above gave a white solid which on two recrystallisations from propan-2-ol, formed *methyl* 2,3-*diazido*-2,3-*dideoxy*-α-D-*mannoside* 4,6-*dimethanesulphonate*

(67%), m. p. 106—108°, $[\alpha]_D^{22}$ +72·1° (*c* 0·68) (Found: C, 72·2; H, 4·1; N, 20·8. $C_9H_{16}N_6O_8S_2$ requires C, 27·0; H, 4·0; N, 21·0%).

Reduction of the syrupy methyl 2,3-diazidomannoside using hydrazine hydrate–10% palladium–charcoal in methanol gave a yellow syrup. Acetylation of the syrup using pyridine–acetic anhydride gave a product which on two recrystallisations from toluene–propan-2-ol gave *methyl* 2,3-*diacetamido*-2,3-*dideoxy*-α-D-*mannoside* 4,6-*diacetate* (13%), m. p. 200—202°, $[\alpha]_D^{25}$ +89·2° (*c* 0·94) (Found: C, 50·1; H, 6·9; N, 7·9. $C_{15}H_{24}N_2O_8$ requires C, 50·1; H, 7·0; N, 7·8%).

The syrupy 2,3-diazidomannoside (4 g.) in 2N-aqueous hydrochloric acid was boiled under reflux for 8 hr. Evaporation gave a dark syrup which did not reduce Fehling's solution. Acetylation of the syrup gave, after one recrystallisation from methanol, the 2,3-diazidomannoside 4,6-diacetate (51%), m. p. 81—82°.

Repetition of the above acid hydrolysis, but using successively N-, 4N-, and 6N-aqueous hydrochloric acid gave only unchanged starting material in varying yield (isolated as the 4,6-diacetate), or dark syrups which could not be characterised.

Methyl 2,3,6-*Triazido*-2,3,6-*trideoxy*-α-D-*mannoside* 4-*Methanesulphonate*.—The 2,3-diazidomannoside 4,6-dimethanesulphonate (1·5 g.) and sodium azide (1·5 g.) in *NN*-dimethylformamide (25 ml.) were boiled for 3 hr. under reflux. The cooled solution was poured into dry acetone (300 ml.) and the resulting suspension stirred overnight with active charcoal (5 g.) at room temperature. Filtration and evaporation gave a syrup which was treated with water (10 ml.) and extracted with ether (3 × 25 ml.). Evaporation of the extract gave a white solid, which on two recrystallisations from propan-2-ol gave *methyl* 2,3,6-*triazido*-2,3,6-*trideoxy*-α-D-*mannoside* 4-*methanesulphonate* (44%), m. p. 84—86°, $[\alpha]_D^{22}$ +50·1° (*c* 0·61) (Found: C, 27·8; H, 3·9; N, 36·7. $C_8H_{13}N_9O_5S$ requires C, 27·7; H, 3·8; N, 36·3%).

Examination of the crude reaction mixture by thin-layer chromatography revealed a very complex mixture; similar examination of the mother-liquors from the purified triazidomannoside revealed only a trace of unchanged 4,6-dimethanesulphonate.

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