Carbohydrate Research
Elsevier Publishing Company Amsterdam
Printed in Belgium

DERIVATIVES OF 5,6-DIDEOXY-5,6-EPIMINO-L-IDITOL

A D BARFORD* AND A C RICHARDSON
Department of Chemistry, Queen Elizabeth College (University of London), London W 8 (Great Britain)
(Received January 22nd, 1970)

ABSTRACT

The 5,6-ditosyl esters of 1,3 2,4-di-*O*-ethylidene- and 1,3 2,4-di-*O*-benzylidene-D-glucitol readily underwent selective displacement of the terminal ester groups by azide anions, and the resulting 6-azido-5-toluene-*p*-sulphonates were converted into the appropriate 5,6-epimines by the action of lithium aluminium hydride The ring-opening reactions of 1,3 2,4-di-*O*-benzylidene-5,6-dideoxy-5,6-epimino-L-iditol and some of its *N*-acyl derivatives have been studied, mainly with chloride and azide anions Predominant, if not exclusive, attack occurs at the terminal position of the epimine ring to give products having the L-*ido* configuration

INTRODUCTION

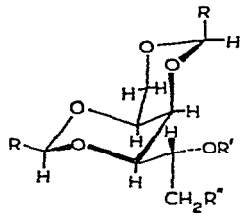
A variety of epimine derivatives of carbohydrates have been prepared in which the epimine ring is either fused to a pyranoside ring[1–11], a furanoside ring[12–14], or to an acyclic portion of the molecule[15 16] One method employed for the preparation of such epimines involves the treatment of *vic-trans*-benzamido-sulphonates with either lithium aluminium hydride or other basic reagents[3–6] However, a drawback of this method is the competing formation of oxazoline derivatives, particularly where free rotation of the benzoyl group about the carbon–nitrogen bond is possible[3]. A more-general method of epimine synthesis utilises *vic-trans*-azido-sulphonates as substrates, which, when reduced under basic conditions, afford the corresponding epimine in high yield The original reagent used for this transformation was hydrazine–Raney nickel[2], but this has the disadvantage that the first-formed epimine may undergo reductive rupture of the ring, and hence the success of this method depends upon the activity of the catalyst[13] This troublesome side reaction is avoided by the use of lithium aluminium hydride Good yields of epimines, which are not affected by the reagent[13,14 16], are usually obtained We have now utilised this latter method for the preparation of some epimino derivatives of alditols

RESULTS AND DISCUSSION

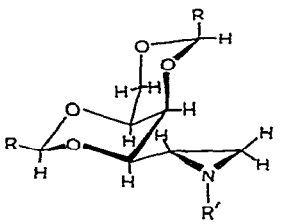
1,3 2,4-Diacetals of D-glucitol, in which the 5,6-hydroxyl groups are free, are prepared readily from the alditol and were used as starting materials for the prepara-

*Present address Chester Beatty Research Institute, Royal Cancer Hospital, Fulham Road, London S W 3, Great Britain

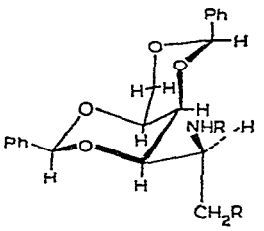
tion of the corresponding 5,6-epimines (**11** and **12**) Initially, we employed the 1,3 2,4 di-*O*-ethylidene derivative **1**, because it was readily transformed into the 5-*O*-acetyl 6-sulphonate **2** by selective monotosylation followed by acetylation[17]. Treatment o **2** with azide anions in *N*,*N*-dimethylformamide gave the 5-*O*-acetyl-6-azide **3**, whic was usually contaminated with small amounts of the 6-azido-5-sulphonate **7** Thi impurity obviously arose from small amounts of the 5,6-disulphonate **6** which con taminated **2** The structure of **7** was demonstrated by an unequivocal synthesis fron the 5-*O*-acetyl-6-azide **3** by *O*-deacetylation to give **4**, followed by tosylation. Th corresponding, syrupy 5-*O*-mesyl derivative **5** was also prepared from **4** and wa readily converted into 5,6-dideoxy-5,6-epimino-1,3 2,4-di-*O*-ethylidene-L-iditol (**11** by the action of lithium aluminium hydride



1 R=Me, R=H R''=OH
2 R=Me, R=Ac, R''=OTs
3 R=Me, R=Ac, R''=N_3
4 R=Me, R'=H, R''=N_3
5 R=Me R'=Ms, R''=N_3
6 R=Me, R'=Ts, R''=OTs
7 R=Me R'=Ts, R''=N_3
8 R=Ph, R'=Ts, R''=OTs
9 R=Ph, R'=Ts, R''=N_3
10 R=Ph, R'=Ts, R''=NHBz



11 R=Me, R=H
12 R=Ph, R=H
13 R=Ph, R=Ac
14 R=Ph, R=Bz
15 R=Ph, R'=Ms



16 R=Ac, R=Cl
17 R=Bz, R=Cl
18 R=H, R'=Cl
19 R=H, R'=N_3
20 R=Ac, R'=N_3
21 R=H, R'=NH_2
22 R=Bz, R'=NHBz
23 R=Ms, R=Cl
24 R=Ms, R=H
25 R=Ms, R'=OMe
26 R=Ms, R=OH
27 R=Bz, R=N_3

An alternative route for the preparation of precursor **4** involved the 5,6-epoxid **28** which was formed by the action of sodium methoxide on the 5-*O*-acetyl-6-sulphon ate[17] **2** The epoxide underwent terminal ring-opening when treated with a mixtur of sodium azide and ammonium chloride in 2-methoxyethanol to give the 6-azide (50% yield) which was identical with the product prepared *via* direct replacement

The synthesis of the epimine by either of these routes was, however, marre by contamination of the 5-*O*-acetyl-6-sulphonate **2** with the 5,6-disulphonate **6** an by the failure of the intermediary 6-azido-5-methanesulphonate **5** to crystallise. Th highly crystalline nature of the 6-azido-5-sulphonate **7**, originally isolated as a impurity in the 6-azido-5-acetate **3**, suggested that this might be a more-convenien precursor of the epimine **11** Accordingly, the 5,6-disulphonate **6** was prepared an readily underwent selective replacement of the primary sulphonate group by azid to give **7** in high yield Subsequent reduction of **7** with lithium aluminium hydrid afforded the 5,6-epimine (43%, *ca* 32% overall yield from **1**) The parallel sequenc of reactions (**8**→**9**→**12**) was also performed with 1,3 2,4-di-*O*-benzylidene-D-glucitol The disulphonate[18] **8** afforded the 6-azido-5-sulphonate **9** (95% yield) which gav the corresponding epimine **12** in 70% yield.

The n m r. spectra of the epimines **11** and **12** were amenable to first-order analysis, and they confirmed the terminal nature of the epimine ring (Table I) The two spectra were very similar, but that from the diethylidene derivative **11** was better resolved, and the decoupling experiments performed on this compound confirmed the assignments (Fig 1) The three single-proton resonances at highest field were assigned to the C-H protons attached to the epimine ring, since previous work[4] [19] has shown that these protons are usually at a higher field (usually above τ 7) than most other ring protons These three resonances consisted of a pair of doublets at τ 8 52 (J 3 2 Hz) and 8 14 (J 6 3 Hz) due to the C-6 protons, and a 1 1 2 2 1 1 sextet at 7 54 due to H-5 Only one limb of the doublet at τ 8 52 could be observed, since it was overlapped with the methyl resonances of the ethylidene groups, but the coupling constant (3.2 Hz) could be found from the H-5 sextet Irradiation of the H-5 sextet collapsed the H-6 doublets into singlets, and a 1 1 1 1 quartet at τ 6 89 (J 7 0 and 1 5 Hz) collapsed into a broad singlet, showing that this was the H-4 resonance Of the remaining resonances, a narrow 1 2 1 triplet at τ 6 41 and a narrow 1 3 3 1 quartet at 6 55 were assigned to H-2 and H-3, and the pair of quartets at 5 87 (J 12 7 and 1 3 Hz) and 6 16 (J 12 7 and 2 0 Hz) were obviously the AB portion of an ABX pattern and were assigned to the two protons at C-1 The H-3 resonance was shown to be that at τ 6 41 by irradia-

TABLE I

P M R DATA FIRST-ORDER CHEMICAL SHIFTS (τ VALUES) AND COUPLING CONSTANTS (Hz) AT 100 MHz

	9[a]	**10**[a]	**11**[a]	**12**[a,b]	**15**[a]	**17**[c]	**27**[d]
H-1*eq*	5 67q[f]	5 68q	5 87q	5 57q	5 64q	—	5 63q
H-1*ax*	5 86q	5 87q	6 16q	5 90q	5 95q	—	5 90q
H-2	6 06q	6 26q	6 55q	6 24q	6 29q	—	~6 1cm
H-3	6 25t	5 88t	6 41t	6 09t	6 15t	—	5 82t
H-4	4 89q	—	6 89q	6 51q	6 42q	5 69q	5 44q
H-5	4 93cm	4 86cm	7 54sex	7 44sex	6 88sex	5 50cm	5 08cm
H-6$^{e}_{trans}$	6 40cm	—	8 14d	8 20d	7 32d	—	6 10cm
H-6$^{e}_{cis}$		—	8 52d	8 45d	7 74d	—	
N-*H*	—	3 35t	9 05s	9 17s	—	1 72d	1 80d
Ar*CH*	4 41s	4 40s	—	4 34s	4 44s	4 39s	4 22s
	4 59s	4 58s	—	4 34s	4 46s	4 42s	4 32s
Ph-*Me*	7 76s	7 73s	—	—	—	—	—
$J_{1ax,1eq}$	12 5	12 5	12 7	12 5	12 5	—	12 5
$J_{1eq,2}$	1 5	1 5	1 3	~1 5	1 5	—	1 4
$J_{1ax\,2}$	1 6	1 8	2 0	~1 5	1 8	—	2 0
$J_{2,3}$	~1 5	~2 0	1 5	~1 5	~2 0	—	~2 0
$J_{3,4}$	1 8	~2 6	1 5	~1 5	2 0	1 8	1.7
$J_{4\,5}$	3 5	~5 0	7 0	~7 0	7 3	8 0	5 8
$J_{5,6trans}$	~3	~5 0	6 3	6 0	7 2	—	—
$J^{e}_{5,6cis}$	~8	~7 0	3 2	3 5	4 4	—	—
$J_{6_{trans}\ 6cis}$	—	—	0	0	0	—	—
$J_{NH\ CH}$	—	~7	—	—	—	~7	~8

[a]In chloroform-*d* [b]At 60 MHz [c]In methyl sulphoxide-d_6 at 75° [d]In pyridine-d_5 [e]*cis* and *trans* applies only to the epimines [f]s = singlet, d = doublet, t = triplet, q = quartet, sex = sextet, cm = complex multiplet

tion at the H-4 resonance, which collapsed this triplet into a narrow doublet, as well as collapsing the H-5 sextet into a quartet Hence, the quartet at τ 6 55 was assigned to H-2 The H-6 resonance, which was partly obscured in the spectrum of the ethylidene derivative, was clearly observed in the spectrum of the benzylidene compound as a doublet (J 3 5 Hz) The notable feature about these spectra is the lack of geminal coupling between the H-6 protons Such an observation is in line with other work[20], in which it has been shown that terminal epimine rings possess very small (0–2 1 Hz) geminal coupling constants, and Paulsen and Stoye[15] have reported a value of 1 Hz for a carbohydrate epimine

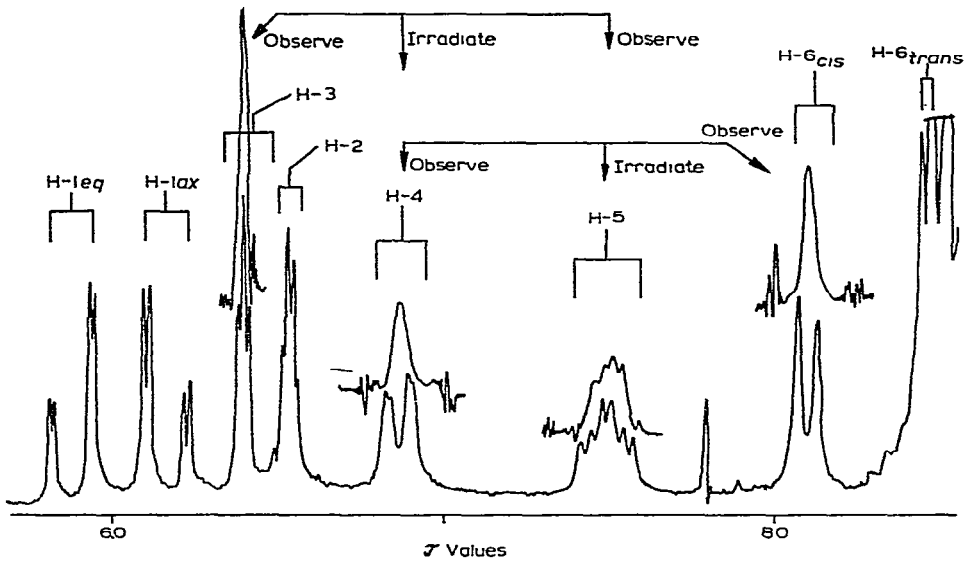


Fig 1. Section of 100 MHz n m r spectrum of 5 6-dideoxy-5 6-epimino-1,3 2,4-di-*O*-ethylidene-L-iditol (**11**) in chloroform-*d* showing the results of decoupling experiments

The assignment of the individual C-1 and C-6 protons was made as follows In a study of various 2-phenylaziridines, Brois and his co-workers[20] have found that $J_{cis} > J_{trans}$ for vicinal coupling across the aziridine ring, so that the doublet at highest field (τ 8 52) is assigned to H-6_{trans}, since it has the smallest splitting, and that at τ 8 14 must be due to H-6_{cis} For the C-1 protons, the equatorial proton H-1*eq* would be deshielded to a greater extent than the axial proton H-1*ax* by the adjacent O-2 which is *cis*-axial to H-1*eq* Hence, the lower-field resonance at τ 5 87 is assigned to H-1*eq* and that at 6 16 to H-1*ax* In agreement with this, one would expect the coupling constant between H-1*eq* and H-2 (*eq–eq*) to be smaller than that between H-1*ax* and H-2 (*ax–eq*), this is, in fact, observed, although the difference between the two coupling constants is small (0 7 Hz)

In the subsequent study of the reactions of epimines of this type, the dibenzylidene derivative **12** was used exclusively It was found that *N*-acylation could be achieved only if acidic conditions or the presence of a nucleophilic anion were avoided

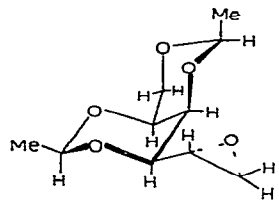
Thus, the epimine **12** was converted into the *N*-acetyl (**13**) and *N*-benzoyl derivatives (**14**) by treatment with the appropriate acid anhydride in ethanol or pyridine However, the use of acid chlorides in pyridine resulted in *N*-acylation and subsequent rupture of the epimine ring by chloride ion to give 5-acylamido-6-chloro derivatives Treatment of **12** with benzoyl chloride or acetyl chloride in pyridine at ~0° or ambient temperatures afforded high yields of the 5-benzamido-6-chloro- and 5-acetamido-6-chloro derivatives, **17** and **16**, respectively, assuming nucleophilic attack by chloride had occurred at the terminal position (see below). The lability of these epimines to ring opening in the presence of pyridinium chloride was shown by the fact that the free epimine **12** underwent ring opening in the presence of pyridinium chloride at room temperature to give the 5-amino-6-chloro derivative **18** in high yield, which was related to the products of acylation with acid chlorides by *N*-benzoylation and *N*-acetylation to give **17** and **16**, respectively. The amino-chloro derivative **18** was readily converted back into the epimine by the action of either sodium methoxide or lithium aluminium hydride It is of note that this method of epimine formation is similar to the original method used by Gabriel[21] for the preparation of "ethylenimines"

The structure of the 5-benzamido-6-chloro derivative **17**, and hence the structures of the amino and acetamido derivatives **18** and **16**, was proved in the following way The compound was converted into an oxazoline derivative (m p 181–183°, $[\alpha]_D$ −112°) by treatment with sodium acetate in boiling 2-methoxyethanol containing 5% of water If the benzamido-chloro derivative had been formed by attack at the secondary carbon atom, the oxazoline formed from this 5-chloro derivative would have the structure **30**, whereas the more plausible 6-chloro derivative would give a different oxazoline **29** An unequivocal synthesis of oxazoline **30** (m p 234–236°, $[\alpha]_D$ +75°) showed that it was not identical with the oxazoline obtained from the benzamido-chloro derivative, which must therefore, by implication, be the 6-chloro derivative The oxazoline **30** was synthesised from the 6-azido-5-sulphonate **9**, the immediate precursor of the epimine **12** The azide was hydrogenated and the product treated with benzoic anhydride to give the 6-benzamido-5-sulphonate **10**, which was then converted into the oxazoline **30** by the action of sodium methoxide in 95% 2-methoxyethanol The non-terminal nature of the benzamido group was also convincingly demonstrated by the p m r spectrum of **17**, in which the resonance due to the amide proton was observed as a doublet at τ 1 72 (methyl sulphoxide-d_6 at 75°) which collapsed to a singlet on irradiation of the complex multiplet due to H-5 at τ 5 50 If the amide group had been at a terminal position, it would have been coupled to two protons and would have appeared as a triplet For example, the n m r spectrum of the 6-benzamido-5-sulphonate **10** showed the amide proton as a triplet at τ 3 35 (chloroform-*d*)

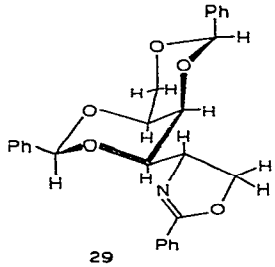
The terminal ring opening of the epimine **12** by chloride ion accords well with the observations that terminal epoxides undergo predominant attack by nucleophilic reagents at the terminal carbon atom[22]

Nucleophilic ring-opening of the epimine **12** and its *N*-acetyl derivative **13** with azide also afforded the terminal azido derivatives **19** and **20**, respectively, the

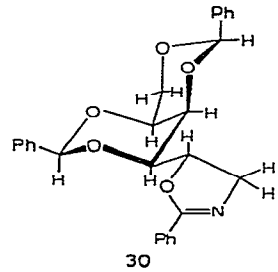
reagent in this case was a mixture of sodium azide and ammonium chloride in 2-methoxyethanol[2] The two products were inter-related by *N*-acetylation of the azido-amine **19** which gave the acetamido-azide **20** in high yield These products were also inter-related with the chloro-amines described above by the displacement of the terminal chloro substituent with azide Thus, the amino-azide **19** was formed in high yield when the chloro-amine **18** was treated with sodium azide in 2-methoxyethanol However, this latter reaction could not be relied upon as proof of the terminal nature of the azido group, since initial ring closure of the chloro-amine **18** to the epimine **12** could have occurred, followed by ring opening with azide When the 5-acetamido-6-chloro-derivative **16** was treated with sodium azide in the same way, an azide was obtained which was identical with that prepared by ring opening of the *N*-acetyl-epimine **13** with azide It is considered unlikely that initial ring closure to the *N*-acetyl-epimine could have occurred in this case, because we have shown above that the related benzamido-chloro derivative is ring closed to the oxazoline derivative rather than the epimine, and these oxazolines are resistent to nucleophilic ring opening under basic, or slightly basic conditions[2,3] The azido amine **19** was reduced to the diamine **21** which was characterised as the di-*N*-benzoyl derivative **22**



28



29



30

Similarly, the epimine **12** underwent both mesylation and ring-opening by chloride ion when treated with mesyl chloride in pyridine, to give the 6-chloro-5-methanesulphonamido derivative **23**, the structure of which was proved by its formation from the 5-amino-6-chloro derivative **18** by mesylation The *N*-mesylepimine **15** was formed with particular ease when **23** was subjected to mildly basic conditions, but it was very sensitive to ring-opening by nucleophilic reagents This greater reactivity of *N*-mesylepimines has been noted before[8], and is undoubtedly due to the greater electron-withdrawing effect of the sulphonate group and the fact that, unlike *N*-acyl derivatives which are readily hydrolysed under mildly basic conditions[3], the *N*-sulphonyl group is resistant to removal and remains on the nitrogen to assist, by its inductive effect, the cleavage of the C–N bond The n m r spectrum of **15** was very similar to that of **12** (Table I)

The 6-chloro-5-methanesulphonamido derivative **23**, which is the precursor of the *N*-mesylepimine, underwent several replacement reactions under basic conditions which obviously proceeded by way of the *N*-mesylepimine **15** Thus, when the chloro derivative was treated with lithium aluminium hydride, the 6-deoxy-5-methanesulphon-

amido derivative **24** was obtained, the structure of which was shown by the presence, in its n m r spectrum, of a three-proton doublet at τ 8 67 due to the terminal methyl group Furthermore, when the chloro derivative was heated with sodium methoxide, a methoxy derivative was formed, almost certainly the 6-methoxy derivative **25** The action of sodium acetate in aqueous 2-methoxyethanol afforded the 6-hydroxy analogue **26** in 94% yield

EXPERIMENTAL

Concentrations were carried out under diminished pressure Melting points were determined on a Kofler microscope hot-stage and are uncorrected Optical rotations were measured to an accuracy of at least $\pm 0\,002°$ with a Bendix-NPL Automatic Polarimeter, using a 0 2-dm tube at $\sim 21°$, and unless otherwise stated, chloroform solutions were used Thin-layer chromatography (t l c) was performed on microscope slides coated with silica gel (Whatman Chromedia SG41) and detection was with ethanolic sulphuric acid Column chromatography was performed on Silica Gel MFC (Hopkin and Williams), 10-ml fractions being collected for examination by t l c. Light petroleum was the fraction of b p 40–60°, and pyridine was dried over sodium hydroxide pellets Infrared spectra were determined on a Unicam SP200 spectrometer, by using Nujol mulls for solids, and were in agreement with the structures proposed

5-O-Acetyl-6-azido-6-deoxy-1,3 2,4-di-O-ethylidene-D-glucitol (**3**) — A mixture of 5-*O*-acetyl-1,3 2,4-di-*O*-ethylidene-6-*O*-tosyl-D-glucitol[17] **2** (40 g) and sodium azide (15 g) was added to boiling *N,N*-dimethylformamide (80 ml), and the mixture was heated under reflux for 10 min, cooled, and treated with ether. After the removal of the precipitated inorganic material, the solution was evaporated to a yellow syrup, which was dissolved in a little ether and purified by chromatography on silica gel with 9 1 ether–light petroleum After the evaporation of the appropriate fractions, the crystalline residue was recrystallised from ether–light petroleum to give **3** (14 5 g, 52%) After a further recrystallisation from the same solvent mixture, the product had m.p. 83–84°, $[\alpha]_D$ −28° (*c* 0 6, water) (Found C, 47 65, H, 6 55, N, 13 85 $C_{12}H_{19}N_3O_6$ calc C, 47 85, H, 6 3, N, 13 9%)

6-Azido-6-deoxy-1,3 2,4-di-O-ethylidene-D-glucitol (**4**) — (*a*) Slightly impure **3** (14 g) was dissolved in methanol (100 ml) and treated with 3M methanolic sodium methoxide (17 ml) After 30 min, a small amount of crystalline product {m p 126–127°, $[\alpha]_D$ −34° (*c* 1 7)} was removed which was shown to be 6-azido-6-deoxy-1,3 2,4-di-*O*-ethylidene-5-*O*-tosyl-D-glucitol (**7**) by comparison with an authentic sample (see below) The filtrate was neutralised with Amberlite IR-120(H^+) resin and concentrated to a syrup which was extracted with ether (150 ml) Concentration of the extract afforded a crystalline solid which was recrystallised from ether–light petroleum to give the 6-azide **4** (8 25 g, 68%), m p 120–122°, $[\alpha]_D$ −9° (*c* 0 9, water) (Found C, 46 5, H, 6 7, N, 16 1 $C_{10}H_{17}N_3O_5$ calc C, 46 35, H, 6 55, N, 16 2%)

A further crop (1 5 g, 13%) was obtained by evaporation of the mother liquors, followed by recrystallisation

(*b*) 5,6-Anhydro-1,3 2,4-di-*O*-ethylidene-D-glucitol[17] **28** (0 3 g) was heated under reflux with sodium azide (0 2 g) and ammonium chloride (0 15 g) in 95% aqueous 2-methoxyethanol (2 ml) for 30 min The mixture was then diluted with water and extracted three times with methylene chloride, and the dried ($MgSO_4$) extracts were concentrated Two recrystallisations of the residue from ether–light petroleum gave the 6-azide **4** (0 18 g, 50%), m p 118–119°, $[\alpha]_D$ −8 1° (*c* 1, water), which was identical (i r) with the product from (*a*)

*6-Azido-6-deoxy-1,3 2,4-di-*O*-ethylidene-5-*O*-tosyl-*D*-glucitol* (**7**) — (*a*) The 5,6-ditoluene-*p*-sulphonate[17] **6** (30 g) was added to a mixture of boiling *N*,*N*-dimethylformamide (100 ml) and sodium azide (15 g) After being heated under reflux for 5 min, the mixture was cooled, and the addition of water afforded the crystalline azide **7** (19 4 g, 85%) which was washed well with water and methanol and dried, m p 126–127 5°, $[\alpha]_D$ −35° (*c* 2 4) (Found C, 49 5; H, 5 9, N, 10 3, S, 7 65 $C_{17}H_{23}N_3O_7S$ calc C, 49 4; H, 5 55; N, 10 15, S, 7 75%)

(*b*) Tosyl chloride (3 g) was added to a solution of the 6-azido-5-hydroxy derivative **4** (0 5 g) in pyridine (10 ml) and the resulting solution was kept overnight at room temperature The reaction mixture was then poured into water, and the oil which was first precipitated crystallised upon seeding and scratching. Recrystallisation from ethanol gave the azido-sulphonate 7 (0 74 g, 93%), m p 127 5–128°, $[\alpha]_D$ −32° (*c* 2), which was identical (i r) with the product from (*a*)

*5,6-Dideoxy-5,6-epimino-1,3 2,4-di-*O*-ethylidene-L-iditol* (**11**) — (*a*) Mesyl chloride (0 5 ml) was added to a solution of the 6-azido-5-hydroxy derivative **4** (0 33 g) in dry pyridine (1 ml), and the solution was kept for 3 h at room temperature and then decomposed by the addition of water The mixture was processed *via* chloroform extraction in the usual way to give the syrupy sulphonate **5**

A solution of this syrup in dry ether (25 ml) was heated under reflux with lithium aluminium hydride (0 4 g) for 20 min The excess of hydride was then decomposed by the addition of a saturated solution of Rochelle salt, the mixture was diluted with chloroform and filtered, and the residue was extracted three times with boiling chloroform The combined extracts and filtrate were concentrated to a crystalline solid, recrystallisation of which from acetone–ether–light petroleum afforded the epimine **11** (0 117 g, 43%), m p. 150–180°, $[\alpha]_D$ −25° (*c* 0 5, water) Further recrystallisation of the epimine failed to improve the m p

(*b*) A solution of the 6-azido-5-toluene-*p*-sulphonate 7 (8 g) in dry ether (200 ml) was heated under reflux with lithium aluminium hydride (4 g) for 15 min The reaction mixture was processed as in (*a*), and the resulting white solid was recrystallised from chloroform–ether–light petroleum to give the product **11** (1 78 g, 43%), m p 150–171°, $[\alpha]_D$ −25° (*c* 2, water), which was identical (i r) with the product from (*a*) (Found C, 55.75, H, 8 2, N, 6 7 $C_{10}H_{17}NO_4$ calc C, 55 8, H, 7 9, N, 6 5%). The wide range in m p could not be improved for this compound and appears to be a characteristic property

*6-Azido-1,3 2,4-di-*O*-benzylidene-6-deoxy-5-*O*-tosyl-*D*-glucitol* (**9**) — The 5,6-

ditoluene-*p*-sulphonate[18] **8** (5 g) was heated under reflux with sodium azide (3 g) in 2-methoxyethanol (23 ml) and water (2 ml) for 1 h The azide **9** (3 84 g, 95%) was precipitated by the addition of water and recrystallised from acetone–ether, m p 142–145°, $[\alpha]_D$ −2 9° (*c* 1 3) (Found C, 60 4, H, 5 25, N, 7 75, S, 5 85 $C_{27}H_{27}N_3O_7S$ calc · C, 60 35, H, 5 05, N, 7 8, S, 5 95%)

1,3.2,4-Di-O-benzylidene-5,6-dideoxy-5,6-epimino-L-iditol (**12**) — (*a*) The azidosulphonate **9** (10 g) was suspended in dry ether (250 ml) and heated under reflux with lithium aluminium hydride (5 g) for 20 min The reaction mixture was then processed in the usual way, and the product was recrystallised from chloroform–light petroleum to give the epimine **12** (1 93 g, 31%), m p 185–195° After two further recrystallisations, it had m p 204–207° and $[\alpha]_D$ +23° (*c* 1 7) (Found C, 70 75, H, 6 25, N, 4 25 $C_{20}H_{21}NO_4$ calc C, 70 8, H, 6 2, N, 4 1%)

A further crop (2 49 g, 39%) was obtained by evaporation of the mother liquors to dryness and recrystallisation of the residue

(*b*) A suspension of the 5-amino-6-chloro derivative **18** (0 1 g) in methanol (5 ml) was heated under reflux with sodium methoxide (0 1 g) for 1 h The addition of water to the mixture afforded the epimine (0 08 g, 89%) which was recrystallised from chloroform–ether, m p 190–195°, $[\alpha]_D$ +21° (*c* 1) After two more recrystallisations, it had m p 197–200° and was identical (i r) with the product from (*a*)

(*c*) The 5-amino-6-chloro derivative **18** (0 05 g) was suspended in dry ether (3 ml) and heated under reflux with lithium aluminium hydride (0 05 g) for 45 min The mixture was processed in the usual way to give the epimine **12** (0 02 g, 44%), m p 180–185° (from chloroform–light petroleum), $[\alpha]_D$ +21° (*c* 1) There was insufficient material to carry out extensive recrystallisations but, despite the poor m p , its i r spectrum was identical with the previous two samples

N-Acyl derivatives were prepared in the usual way by treatment with the appropriate acid anhydride in pyridine, followed by the addition of water The *N*-acetyl derivative **13** had m p 212–215° (from chloroform–ether) and $[\alpha]_D$ −8 6° (*c* 1) (Found C, 69 4, H, 6 35, N, 3 55 $C_{22}H_{23}NO_5$ calc C, 69 3, H, 6 05, N, 3 65%) The *N*-benzoyl derivative **14** had m p 219–222° (from chloroform–ether), $[\alpha]_D$ +36° (*c* 1) (Found C, 72 8, H, 5 55, N, 3 05 $C_{27}H_{25}NO_5$ calc C, 73 15; H, 5 65, N, 3 15%)

5-Amino-1,3 2,4-di-O-benzylidene-6-chloro-5,6-dideoxy-L-iditol (**18**) — The dibenzylidene-epimine **12** (1 g) was suspended in pyridine (5 ml) and treated with pyridinium chloride (1 g) for 3 h at room temperature and then treated with ice–water The precipitated chloro derivative was collected to give **18** (0 77 g, 69%), m p 196–197° (decomp), $[\alpha]_D$ +28° (*c* 1) (Found C, 63 85, H, 5 95, N, 3 7 $C_{20}H_{22}ClNO_4$ calc C, 63 9; H, 5 85, N, 3 75%) Recrystallisation (chloroform–ether) lowered the m p [191–193° (decomp)], and it is inadvisable to subject this compound to prolonged heating in solution because of its ease of ring closure to the epimine, with the consequent liberation of hydrogen chloride

5-Acetamido-1,3 2,4-di-O-benzylidene-6-chloro-5,6-dideoxy-L-iditol (**16**) — (*a*) To a stirred suspension of the epimine **12** (1 g) in pyridine (10 ml) was added acetyl chloride (0 26 ml) in a dropwise fashion The flask was cooled initially, and, after

1 h, the addition of water precipitated the *N*-acetyl derivative (1 06 g, 86%), m p 218–220° It was recrystallised from chloroform–light petroleum to give the analytical sample, m.p 220–221 5°, $[\alpha]_D$ +31° (*c* 0 7, *N,N*-dimethylformamide) (Found C, 62 9, H, 5 9; N, 3 25 $C_{22}H_{24}ClNO_5$ calc C, 63 3; H, 5 5, N, 3 35%)

(*b*) The same compound, prepared by acetylation, in the usual way, of the amine **18** had m p 223–224° (from *N,N*-dimethylformamide–ethanol), $[\alpha]_D$ +30° (*c* 0 7, *N,N*-dimethylformamide) and was identical (i r) with the product from (*a*)

*5-Benzamido-1,3 2,4-di-*O*-benzylidene-6-chloro-5,6-dideoxy-*L*-iditol* (**17**) — (*a*) The epimine **12** (0 5 g) was suspended in pyridine (10 ml) and treated with benzoyl chloride (0 35 ml) The solution was kept for 16 h at below −5° and then treated with water to precipitate the *N*-benzoyl derivative **17** (0 63 g, 89%) After recrystallisation from *N,N*-dimethylformamide–ethanol, it had m p 221–226°, $[\alpha]_D$ +73° (*c* 0 5, *N,N*-dimethylformamide) (Found C, 67 25, H, 5 6; N, 3 15 $C_{27}H_{26}ClNO_5$ calc C, 67 55, H, 5 4, N, 2 9%)

(*b*) The *N*-benzoyl derivative, prepared in the usual way from the amine **18**, had m p 215–220°, $[\alpha]_D$ +63° (*c* 0 3, *N,N*-dimethylformamide), and was identical (i r) with the product from (*a*)

*6-Benzamido-1,3 2,4-di-*O*-benzylidene-6-deoxy-5-*O*-tosyl-*D*-glucitol* (**10**) — The 6-azido-5-toluene-*p*-sulphonate **9** (5 g) was dissolved in a mixture of ethanol (100 ml) and acetone (100 ml) and hydrogenated over Raney nickel T4 catalyst[24] (*ca* 6 g) at *ca* 4 atmos After 4 h, the catalyst was filtered off, and the solution was treated with benzoic anhydride (2 5 g) for 2 5 h at room temperature before evaporation to dryness The crystalline mass was then recrystallised from ethanol–ether–light petroleum to give the *N*-benzoyl derivative **10** (4 3 g, 75%), m p 138–142°, $[\alpha]_D$ −2 1° (*c* 1 3) (Found C, 66 75, H, 5 4, N, 2 4 $C_{34}H_{33}NO_8S$ calc C, 66 35, H, 5 35, N, 2 3%)

Conversion of **10** *into 5-*R*-(2,4 3,5-di-*O*-benzylidene-*L*-xylo-tetrahydroxybutyl)-2-phenyloxazoline* (**30**) — The benzamido-sulphonate **10** (0 1 g) was heated under reflux with sodium methoxide (0 05 g) in 95% 2-methoxyethanol (4 ml) for 5 h. The addition of water gave a solid product which was recrystallised from ethanol to give the oxazoline (0 004 g, 6%), m p 216–219°, $[\alpha]_D$ +75° (*c* 1 6) A further recrystallisation from ethanol gave the analytical sample having m p. 234–236° (Found C, 73 7, H, 5 85, N, 3 2 $C_{27}H_{25}NO_5$ calc C, 73 15, H, 5 65; N, 3 15%).

Conversion of the 5-benzamido-6-chloro derivative **17** *into 4-*R*-(2,4 3,5-di-*O*-benzylidene-*L*-xylo-tetrahydroxybutyl)-2-phenyloxazoline* (**29**) — Compound **17** (0 1 g) was heated under reflux with sodium acetate (0 1 g) in 95% 2-methoxyethanol (6 ml) for 4 h, when t l c indicated the presence of two components The addition of water to the reaction mixture gave a solid which was purified on a column of silica gel by using 1.1 ether–light petroleum as solvent The faster-moving component was recrystallised from ethanol–ether to give a product (0 015 g), m p. 160–163°, which was not further characterised The slower-moving material was recrystallised from ether to give the oxazoline **29** (0 01 g, 11%), m p 177–178°, $[\alpha]_D$ −112° (*c* 0 5) A further recrystallisation from ethyl acetate–ether afforded the analytical sample, m p

182–185° (Found C, 72 95, H, 6 16, N, 2 9 $C_{27}H_{25}NO_5$ calc C, 73 15; H, 5 65, N, 3 15%)

5-Amino-6-azido-1,3 2,4-di-O-benzylidene-5,6-dideoxy-L-iditol (**19**) — (*a*) The epimine **12** (1 g) was heated for 5 min under reflux with sodium azide (1 g) and ammonium chloride (0 2 g) in 95% 2-methoxyethanol (10 ml) The addition of water to the reaction mixture was accompanied by the separation of a solid which was recrystallised from ethanol–water to give the azide **19** (0 85 g, 75%), m p 149–153°, $[\alpha]_D$ +5° (*c* 0 4) (Found C, 62 3, H, 5 75, N, 13 2 $C_{20}H_{22}N_4O_4$ calc C, 62 8; H, 5 75, N, 14 65%)

When the reaction time was increased to 15 min, an impure product was isolated which required purification by column chromatography

(*b*) The 5-amino-6-chloro derivative **18** (0 1 g) was heated for 3 h under reflux with sodium azide (0 1 g) in 95% 2-methoxyethanol (2 6 ml) The reaction mixture was processed as in (*a*) to give the azide **19** (0 95 g, 93%), m p 153–157°, $[\alpha]_D$ +5° (*c* 0 5), which was identical (i r) with the product from (*a*) Further recrystallisations from a variety of solvents did not improve the m p

The *N*-benzoyl derivative **27**, prepared in the usual way by using benzoic anhydride in ethanol, had m p 269–273°, $[\alpha]_D$ +32° (*c* 0 2, *N*,*N*-dimethylformamide) (Found C, 67 3, H, 5 3, N, 11 75 $C_{27}H_{26}N_4O_5$ calc C, 66 7, H, 5 35, N, 11 5%)

5-Acetamido-6-azido-1,3 2,4-di-O-benzylidene-5,6-dideoxy-L-iditol (**20**) — (*a*) The *N*-acetylepimine **13** (0 1 g) was heated for 20 min under reflux with sodium azide (0 1 g) and ammonium chloride (0 05 g) in 95% 2-methoxyethanol (4 ml) The addition of water afforded the azide **20** (0 11 g) which was purified on a column of silica gel by using chloroform as solvent This gave material having m p 230–234° (from methanol–ethyl acetate–ether) and $[\alpha]_D$ +12° (*c* 0 6)

(*b*) The 5-acetamido-6-chloro derivative **16** (0 2 g) was heated for 20 h under reflux with sodium azide (0 2 g) in 2-methoxyethanol (3 ml) T l c (chloroform–methanol, 14 1) indicated that the reaction was essentially complete after *ca* 1 5 h and that two components had been formed The major, fast-moving component was obtained pure after chromatography on silica gel and was found to be the required azide **20** (0 015 g, 7%), m p 230–232° (decomp), $[\alpha]_D$ +11° (*c* 0 5) (Found C, 61 8, H, 5 75, N, 12 7 $C_{22}H_{24}N_4O_5$ calc C, 62 25, H, 5 65, N, 13 2%)

The slower-moving component was not isolated, but it was suspected of being the corresponding 2-methyloxazoline

(*c*) *N*-Acetylation of the amine **19**, in the usual way with acetic anhydride in pyridine, afforded the *N*-acetyl derivative **20** in 80% yield, m p 235–237° (from chloroform–light petroleum), $[\alpha]_D$ +17° (*c* 1) All three products had identical i r spectra

5,6-Diamino-1,3 2,4-di-O-benzylidene-5,6-dideoxy-L-iditol (**21**) — A solution of the 6-azide **19** (0 2 g) in methanol (80 ml) was hydrogenated for 5 h at 4 atmos with Raney nickel T4 catalyst[24] (*ca* 2 g) The catalyst was then removed, and the filtrate was concentrated to dryness to give a syrup which crystallised in the presence of a little ethanol Recrystallisation from ethanol–ether–light petroleum afforded the

diamine **21** (0 047 g, 25%), m p 135–145°, which was best characterised as its di-*N*-benzoyl derivative **22**, prepared by the addition of benzoic anhydride to an ethanolic solution of the diamine. It had m p 305–308°, $[\alpha]_D$ +63° (*c* 0 8, *N*,*N*-dimethylformamide) (Found C, 71 6, H, 5 95, N, 4 9 $C_{34}H_{32}N_2O_6$ calc C, 72 3, H, 5 65, N, 4 95%)

*1,3 2,4-Di-O-benzylidene-6-chloro-5,6-dideoxy-5-methanesulphonamido-*L*-iditol* (**23**) — (*a*) A suspension of 0 3 g of the epimine **12** in pyridine (3 ml) was treated with mesyl chloride (0 1 ml) with cooling and then kept overnight at room temperature The addition of water to the reaction mixture afforded crystals of **23** (0 29 g, 72%), m p 194–204° Recrystallisation from chloroform–ether gave the analytical sample having m p 214–216°, $[\alpha]_D$ +38° (*c* 1 3, acetone) (Found C, 55 65, H, 5 4, N, 3 1 $C_{21}H_{24}ClNO_6S$ calc C, 55 5, H, 5 3, N, 3 1%)

When the reaction was repeated with a reaction time of only 2 5 h, a mixture of the *N*-mesylepimine **15** and the ring-opened chloro derivative **23** was obtained in a ratio of *ca* 1 4, based on the specific rotation of the product (+13°)

(*b*) A suspension of the *N*-mesylepimine **15** (1 06 g) in pyridine (10 ml) was allowed to stand at room temperature for 6 h in the presence of pyridinium chloride (1 g) The addition of water to the mixture afforded **23** (0 8 g, 69%), m p 202–205° After recrystallisation from chloroform–ether, the product had m p 213–215°, $[\alpha]_D$ +33° (*c* 1 1, acetone)

(*c*) A suspension of the 5-amino-6-chloro derivative **18** (0 1 g) in pyridine (3 ml) was treated with mesyl chloride (0 06 ml), and the mixture was kept overnight The slow addition of ice-cold water gave the *N*-mesyl derivative **23** (0 9 g, 74%) After recrystallisation twice from chloroform–ether, the product had m p 212–215°, $[\alpha]_D$ +36° (*c* 1 3, acetone)

The i r spectra of all three samples were identical

1,3 2,4-Di-O-benzylidene-5,6-dideoxy-5,6-mesylepimino L*-iditol* (**15**) — (*a*) The 6-chloro-5-methanesulphonamido derivative **23** (1 g) was suspended in M sodium methoxide (30 ml), and the mixture was stirred for 1 h at room temperature The *N*-mesylepimine **15** (0 92 g, 99%) was precipitated by the addition of water and then recrystallised twice from chloroform–ether to give the analytical sample, m p 230–232°, $[\alpha]_D$ +6° (*c* 1 9) (Found C, 60 1, H, 5 6, N, 3 3 $C_{21}H_{23}NO_6S$ calc C, 60 3, H, 5 5, N, 3 35%)

(*b*) Compound **23** (0 16 g) was heated for 40 min under reflux with sodium acetate (0 16 g) in methanol (2 ml) The *N*-mesylepimine **15** (0 14 g, 95%) was precipitated by the addition of water and recrystallised from chloroform, m p 231–235°, $[\alpha]_D$ +6° (*c* 1 2)

The i r spectra of the two samples were identical

*1,3 2,4-Di-O-benzylidene-5,6-dideoxy-5-methanesulphonamido-*L*-iditol* (**24**) — Compound **23** (0 1 g) was suspended in dry ether (*ca.* 30 ml), lithium aluminium hydride (0 1 g) was added, and the mixture heated under reflux for 1 h and processed in the usual way to give, after recrystallisation from chloroform–ether, **24** (0 06 g, 67%),

m p 220–221°, $[\alpha]_D$ +42° (*c* 0 2) (Found C, 60 0, H, 6 15; N, 3 25 $C_{21}H_{25}NO_6S$ calc C, 60 1; H, 5 95, N, 3 35%)

The n m.r spectrum contained, *inter alia*, a three-proton doublet at τ 8 67 (*J* 6 Hz) which confirmed the presence of the *C*-methyl group.

1,3 2,4-Di-O-benzylidene-5-deoxy-5-methanesulphonamido-6-O-methyl-L-iditol (**25**) — Compound **23** (0.1 g) was suspended in 0 5M sodium methoxide (9 ml) and heated under reflux for 30 min, when a clear solution had been obtained The reaction mixture was then concentrated to dryness and partitioned between chloroform and water. The dried ($MgSO_4$) organic layer was concentrated to yield a solid, recrystallisation of which from ethanol gave **25** (0 04 g, 40%), m p 181 5–182 5°, $[\alpha]_D$ +52° (*c* 0 3) (Found C, 59 0, H, 6 3, N, 3 05 $C_{22}H_{27}NO_7S$ calc C, 58 8, H, 6 0, N, 3 1%)

The n m r spectrum of the product showed a 3-proton singlet at τ 6 66, confirming the presence of a methoxyl group

1,3 2,4-Di-O-benzylidene-5-deoxy-5-methanesulphonamido-L-iditol (**26**) — The 6-chloro-5-sulphonamide **23** (0 1 g) was heated for 2 h under reflux with sodium acetate (0 1 g) in 90% aqueous 2-methoxyethanol (2 ml) The product **26** (0 09 g, 94%), which crystallised from the reaction mixture upon the addition of water, had m p 223–225°. Recrystallisation from ethanol gave the analytical sample, m p 225–228°, $[\alpha]_D$ +39° (*c* 0 3) (Found C, 57 85; H, 6 0, N, 3 1 $C_{21}H_{25}NO_7S$ calc C, 57 9, H, 5 75, N, 3 2%)

The i r. spectrum showed, *inter alia*, peaks at 3560 and 3320 cm^{-1} due to –NH and –OH stretching frequencies

ACKNOWLEDGMENTS

CIBA Ltd is thanked for providing generous financial assistance, and the Physical Chemical Measurements Unit at Harwell is thanked for the 100-MHz p m r. spectra

REFERENCES

1 J E CHRISTENSEN AND L GOODMAN, *J Amer Chem Soc*, 82 (1960) 4738
2 R D GUTHRIE AND D MURPHY, *J Chem Soc*, (1963) 5288
3 D H BUSS, L HOUGH, AND A C RICHARDSON, *J Chem Soc*, (1963) 5295
4 A D BARFORD AND A C RICHARDSON, *Carbohyd Res*, 4 (1967) 408
5 Y ALI, A C RICHARDSON, C F GIBBS, AND L HOUGH, *Carbohyd Res*, 7 (1968) 255
6 C. F. GIBBS, L HOUGH, A C RICHARDSON, AND J TJEBBES, *Carbohyd Res*, 8 (1968) 405
7 B R BAKER AND T NEILSON, *J Org Chem*, 29 (1964) 1047, 1051, 1057
8 B R BAKER AND T L HULLAR, *J Org Chem*, 30 (1965) 4049, 4053
9 D H BUSS, L HOUGH, AND A. C RICHARDSON, *J Chem Soc*, (1965) 2736
10 R D GUTHRIE AND D MURPHY, *J Chem Soc*, (1965) 3828
11 R D GUTHRIE AND D KING, *Carbohyd Res*, 3 (1966) 128
12 J CLEOPHAX, S D GERO, AND R D GUTHRIE, *Tetrahedron Lett*, (1967) 567
13 J CLÉOPHAX, S D GERO, AND J HILDESHEIM, *Chem Commur*, (1968) 94
14 J CLEOPHAX, J HILDESHEIM, A M SEPULCHRE, AND S D GERO, *Compt Rend C*, 266 (1968) 720
15 H PAULSEN AND D STOYE, *Ber*, 102 (1969) 820
16 H SAEKI, T IWASHIGE, AND E OHKI, *Chem Pharm Bull Japan*, 16 (1968) 188
17 L F WIGGINS, *J Chem Soc*, (1946) 388

18 J K WOLFE, R M HANN, AND C S HUDSON, *J Amer Chem Soc*, 64 (1942) 1493
19 D H BUSS, L HOUGH, L D HALL, AND J F. MANVILLE, *Tetrahedron*, 21 (1965) 69
20 S L MANNAT, D D ELLEMAN, AND S J BROIS, *J Amer Chem Soc*, 87 (1965) 2220, S J BROIS AND G P BEARDSLEY, *Tetrahedron Lett*, (1966) 5113, R. CAHILL, R C COOKSON, AND T A CRABB, *Tetrahedron*, 25 (1969) 4681
21 GABRIEL, *Ber*, 21 (1888) 1049
22 R E PARKER AND N S ISSACS, *Chem Rev*, 59 (1959) 737
23 Y ALI AND A. C RICHARDSON, *J Chem Soc (C)*, (1969) 320
24 S NISHIMURA, *Bull Chem Soc Japan*, 32 (1959) 61

Carbohyd Res, 14 (1970) 217–230