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# 1,6-DIAMINO-2,5-ANHYDRO-1,6-DIDEOXY-L-IDITOL AND SOME DERIVATIVES THEREOF

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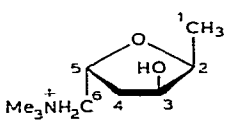
ABSTRACT

1,6-Diamino-2,5-anhydro-1,6-dideoxy-L-iditol (**31**) and its derivatives were synthesized starting from 2,4-*O*-benzylidene-1,6-di-*O*-tosyl-D-glucitol. The 1,6-bis-(acetamido)-L-*talo* epoxide was readily hydrolyzed to the corresponding L-iditol derivative under anchimeric assistance of the 1-acetamido group. On treatment with formaldehyde–formic acid, diamine **31** gave a tricyclic, 1,4:3,6-bis(*N*,*O*-methylene) derivative which was stable under acidic conditions but, according to $^{13}$C-n.m.r. spectroscopy, was readily hydrolyzed to an equilibrium mixture in neutral, aqueous solution. The corresponding 1,6-bis(dimethylamino) derivative could be obtained by reducing this equilibrium mixture with borohydride. The different, quaternary salts obtained on methylation of the corresponding 1,6-bis(dimethylamino) derivatives with methyl iodide (aiming at the structure of *epi-allo*-muscarine) showed no muscarine-like, biological activity.

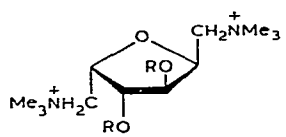
## INTRODUCTION

The biological activity of muscarine and its isomers has prompted extensive studies concerning structure–activity relationships[1–4]. The synthesis of these chiral compounds, starting from 2-amino-2-deoxy-D-glucose or its gluconic acid, was described in the late fifties[5–7]. Wang *et al.*[8] have published a new, facile synthesis of D-*epi-allo*-muscarine, starting from D-glucose.

From structure–activity studies, it became clear[2] that the relative, steric arrangement of the basic center and the oxygen atom of the oxolane ring is essential for activity. Furthermore, since, as in all muscarines isolated from natural sources, C-2 has the *S* configuration[9], the synthesis of "double-headed" analogs (compounds




Muscimol
(*epi-allo*-muscarine)

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of type **1**), containing two terminal, trimethylamino groups in trans arrangement (2*S*, 5*S*), was decided on, aiming, at the structure of muscimol (*epi-allo*-muscarine)*

The ready formation, under acidic conditions[10–13], of 2,5-anhydrohexitols from hexitol derivatives possessing a free hydroxyl group at C-2(5) and a strongly polarized C-5(2) atom provides a new and convenient synthetic approach to such chiral compounds, starting from hexitols

## RESULTS AND DISCUSSION

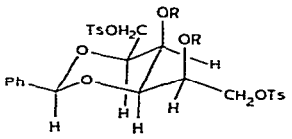
For synthesizing 2,5-anhydro-L-iditol derivatives, compounds of the type of **1**, D-glucitol may be used as the starting material, and the 2,5-anhydro ring has then to be introduced with simultaneous inversion at C-5 For this reason, the readily available 2 4-*O*-benzylidene-1,6-di-*O*-tosyl-D-glucitol[14] (**2**) was converted into its diacetate[15] (**3**) which, on treatment with sodium azide in aqueous *N*,*N*-dimethylformamide, gave, besides the 6-azide (**4**), the 1,6-diazide **7** The structure of the monoazide **4** was proved by its deacetylation with sodium methoxide, yielding compound **5** In the case of a 1-azido-6-tosylate, the corresponding 5,6-epoxide should be formed under similar conditions[15]

The diazide **7** gave, after deacetylation to **8** and subsequent mesylation of **8**, the 3,5-dimesylate **9**, which, on treatment with conc hydrochloric acid in ethanol at elevated temperature, underwent deprotection and ring closure, affording 2,5-anhydro-1,6-diazido-1,6-dideoxy-3-*O*-mesyl-L-iditol (**10**) For large-scale preparations, the synthesis of this key intermediate was simplified, as the benzylidene compound **2** could be converted into diazide **8** without protection of the hydroxyl groups On the other hand, the dimesyl-diazide **9** could be prepared *via* mesylation of the tosyl-azide **5** in very low yield only, as the resulting dimesylate **6** gave, on treatment with sodium azide, a mixture of further-substituted derivatives The anhydride **10**, a syrup, had to be freed from the accompanying benzaldehyde by column chromatography, as all attempts to remove the aldehyde by chemical methods were unsuccessful

Mesylation of **10** gave the crystalline dimesylate **11**, which was reduced to the diamine **13** with hydrogen sulfide in pyridine[16] When the reaction was repeated on a larger scale, a new L-altritol derivative (**18**) could be separated from the mother liquor, this was formed from **13** *via* 1,4(or 3,6)-anhydro-ring formation (by elimination of methanesulfonic acid), and is a member of the 2-oxa-5-azabicyclo[2 2 1]heptane system[17].

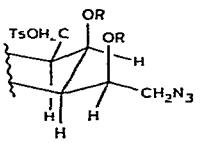
On acetylation, compound **13** gave a crystalline, diacetamido derivative **14**, and, on methylation with formaldehyde–formic acid[18], the corresponding 1,6-bis(dimethylamino) derivative **15** From the latter, the bis(*N*-oxide) **16** could be obtained with hydrogen peroxide, but this underwent no Cope elimination[19] on heating in

*epi-allo*-Muscarine is a 2*S*,5*R* isomer[9], but, in compounds of type **1**, an oxygen atom is attached to C-4, and, therefore, the absolute configuration of C-5 is changed to *S*



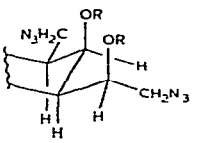
2 R = H
3 R = Ac

Ts = $SO_2C_6H_4Me$ *p*

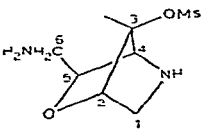


4 R = Ac
5 R = H
6 R = Ms

Ms = $MeSO_2$



7 R = Ac
8 R = H
9 R = Ms



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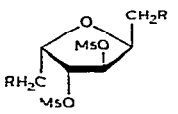
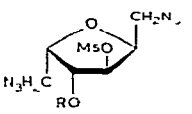
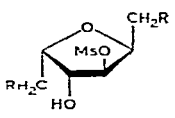


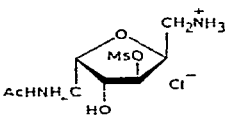
13 R = $NH_2$ HCl
14 R = NHAc
15 R = $NMe_2$ HCl
16 R = $NOMe_2$
17 R = $NMe_3^+ I^-$



10 R = H
11 R = Ms
12 R = Ac



19 R = $NH_2$ HCl
20 R = $NMe_2$ HCl
21 R = $NMe_3^+ I^-$



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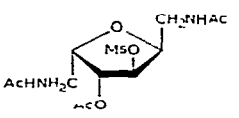

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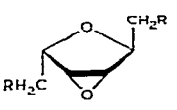
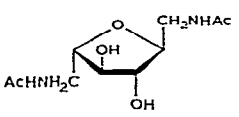


22 R = $NMe_2$
23 R = $NMe_3^+ I^-$



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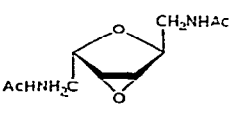

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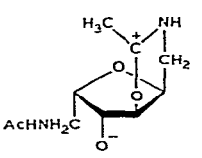

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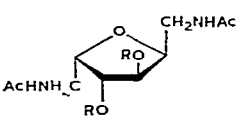
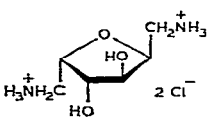


29 R = H
30 R = Ac



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dimethyl sulfoxide Treatment of **15** with methyl iodide afforded the corresponding bis-quaternary salt **17**, which showed no muscarine-like activity

Because the presence of a free hydroxyl group seems to be necessary for biological activity, subsequent experiments were conducted with the monomesyl derivative **10**, reduction of which gave the diamine **19** in moderate yield The yield could be substantially increased when the 4-*O*-acetyl derivative **12** was reduced, but, in this case, an O→N acetyl migration took place, and the 6-acetamido compound **24** could be separated For convenience, the crude reaction-mixture was directly converted into the triacetate **25**, which was obtained in excellent yield Acid hydrolysis of **24** or **25** afforded the diamine **19** On methylation with formaldehyde–formic acid, **19** gave the 1,6-bis(dimethylamino) derivative **20**, which was quaternized with methyl iodide, to afford **21**

When **20** was treated with sodium methoxide, the corresponding L-*talo* epoxide **22** was obtained and, on methylation with methyl iodide, this gave **23**

For obtaining derivatives having the OH-3 and OH-4 groups free, the triacetate **25** was treated with sodium methoxide However on hydrolysis with weak acid, the resulting 1,6-bis(acetamido)-L-*talo* epoxide **26** gave, not the expected[1] L-*manno* isomer **27**, but, exclusively the L-iditol derivative **29** the structure of which was unambiguously proved by $^1$H-n m r spectroscopy

In the $^1$H-n m r spectra of furanosides, a $J_{cis} > J_{trans}$ relationship exists for the coupling constants of vicinal ring-protons[23] This general rule is valid in the case of five-membered rings (included 2,5-anhydro derivatives), as for example, in the spectrum of the mixed ester **12**, where all signals appear well resolved, the coupling constants for the *cis*-related H-2,3 and H-4,5 were $J_{2\,3} \sim 4\,3$ and $J_{4\,5} \sim 4\,5$ Hz, respectively, whereas the *trans*-related H-3,4 had a coupling of only 1 6 Hz, verified by a decoupling experiment In the symmetrical 3,4-dimesylate **11**, the equivalent H-3 and H-4 gave a doublet having $J_{2\,3} = J_{4\,5} = 4$ Hz A similar doublet of 4 Hz appeared at 5 26 p p m for H-3,4 in the spectrum of the symmetrical peracetate **30** (obtained on acetylation of **29**), proving the *cis*-relationship of H-2,3 and H-4 5, respectively (corresponding to the L-iditol configuration) Hydrolysis of **29** or **30** with hydrochloric acid afforded the diamine **31** in quantitative yield.

The strict stereoselectivity** of the cleavage of the oxirane ring, as well as the unusually fast reaction, which was complete in ~15 min at 90°, even in the absence of acid, suggested neighboring-group participation The 1-acetamido group can readily form an "oxazine' ring by attack of its carbonyl group on C-3 of the oxirane ring, and the intermediate **28** so formed is hydrolyzed by attack of water on the carbonium cation

When the diamine **31** was methylated with formaldehyde–formic acid[17], the

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*The attack of water would be expected to take place mainly at the less hindered, C-4 bridge-atom of the oxirane ring[21]

**In the mother liquor of **29**, no other isomer was present, according to g l c investigation of the crude residue obtained after evaporation and subsequent acetylation

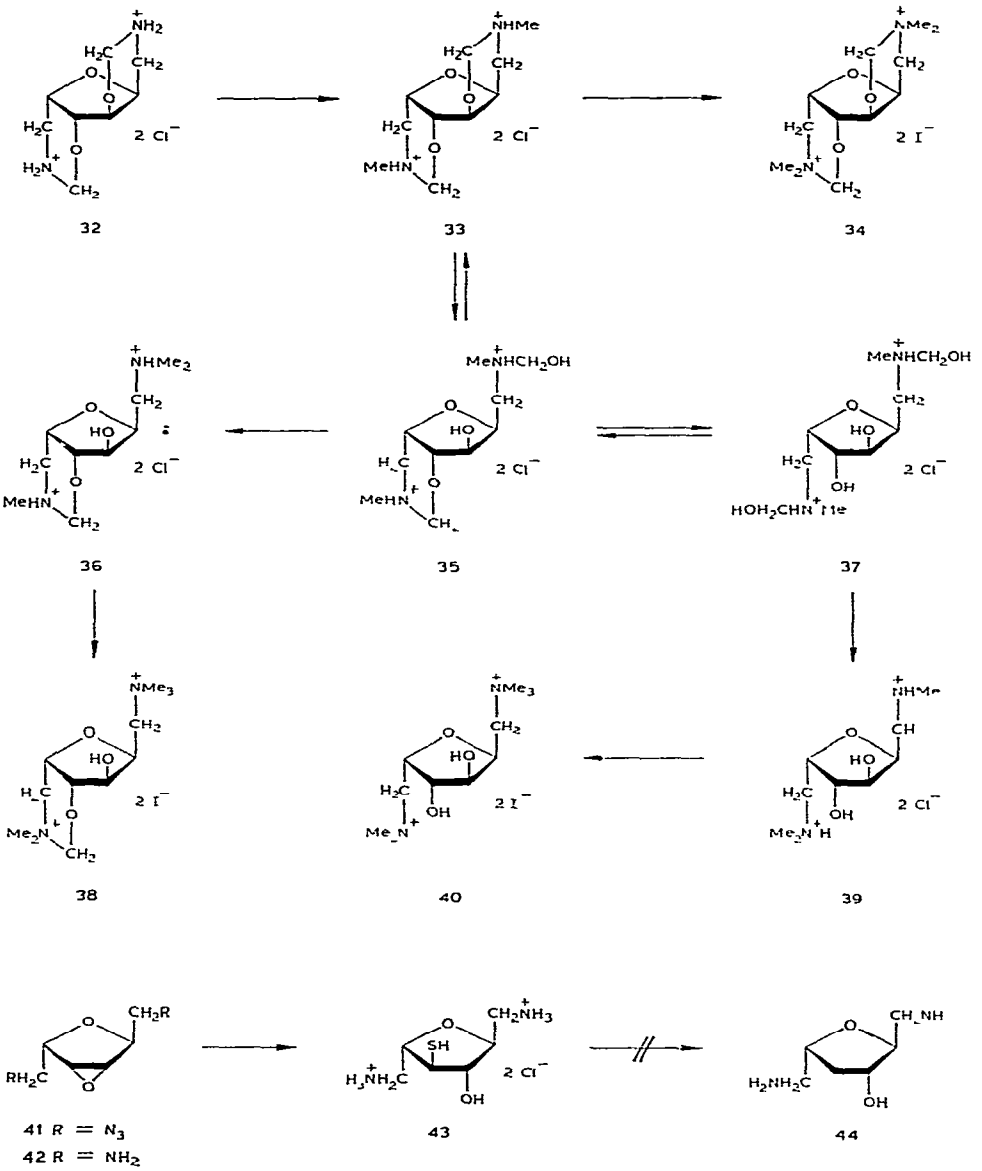
32
33
34
36
35
37
38
40
39
41 R = N3
42 R = NH2
43
44
45 R1 = N3, R2 = H
46 R1 = N3, R2 = Ac
47 R1 = NH2 HCl R2 = H
48 R1 = NHAc R2 = Ac
49 R1 = N3, R2 = H
50 R1 = N3, R2 = Ac
51 R1 = NH2 HCl R2 = H
52 R1 = NHAc R2 = Ac

TABLE I

$^1$H-N M R DATA[a] FOR 2,4-*O*-BENZYLIDENE DERIVATIVES **4–9**

| *Compound* | *H-1* | *H-2* | *H-3* | *H-4* | *H-5* | *H-6* | *CHPh* | *Other protons* |
|---|---|---|---|---|---|---|---|---|
| **4**[b] | 4 15 | 4 10 | 5 10 | 4 15 | 5 02 | 3 51 | 5 57 | 2 05 and 2 00 acetyl |
| **5**[c] | 4 1 | 3 8 | 3 80 | 4 2 | 4 2 | 3 43 | 5 62 | 5 43 and 4 86 OH |
| **6**[b] | 4 3 | 4 3 | 4 96 | 4 35 | 4 88 | 3 97<br>3 63 | 5 62 | 3 37 mesyl |
| **7**[b] | 3 48<br>3 17 | 4 15 | 5 05 | 4 15 | 5 15 | 3 53 | 5 66 | 2 03 and 2 06 acetyl |
| **8**[c] | | | 3 5–4 2 | | | 3 40 | 5 67 | 5 42 and 4 88 OH |
| **9**[b] | 3 86<br>3 50 | 4 35 | 4 92 | 4 4 | 4 90 | 4 04<br>3 67 | 5 70 | 3 21 and 3 16 mesyl |

[a]On the $\delta$ scale [b]Chloroform-*d* solution [c]$Me_2SO$-$d_6$ solution

resulting, methylated compound showed several *N*-methyl signals in the $^1$H-n m r spectrum of its aqueous solution, but, by m s , the product proved to be homogeneous The mass spectrum gave a molecular peak at *m/z* 214 (61 %), suggesting the presence of the 1,3 4,6-bis(*N,O*-methylene) derivative **33** Quaternization of **33**, using methyl iodide, gave **34**, showing two distinct, methyl signals in its $^1$H-n m r spectrum, at 3 10 and 3 21 p p m , representing two methyl groups each, this is in full agreement with the proposed dioxazine structure **34**, containing two *exo*- and two *endo*-situated *N*-methyl groups These facts suggested that, in the presence of formaldehyde, diamine **31** is first converted into the bis(dioxazine) **32**, which is subsequently methylated to **33** A similar reaction was described in 1971 by Magerlein[20], who investigated the *N*-methylation of lincomycin in the presence of formaldehyde

Under acidic conditions (aqueous formic acid), this tricyclic compound **33** is fairly stable, as, even after repeated treatment with formaldehyde–formic acid, the dimethylamino derivative **36** (which must be formed *via* the hydrolyzed intermediate **35**) is present only as a minor component This could be proved by converting the crude, methylated mixture into its quaternary salt, which, on crystallization, gave, besides the pure, tricyclic derivative **34**, the mono-(trimethylamino) derivative **38** in ~25% yield The carbon atoms attached to the 1-situated N atom have well resolved, $^{13}C$–$^{14}N$ couplings of ~3 5 Hz, due to the almost tetrahedral arrangement In the case of the ring-incorporated, 6-situated N atom, this arrangement is less symmetrical, and, consequently, the couplings are less resolved, of ~2 6 Hz, because of the faster relaxation[24] of $^{14}N$

It is interesting that, in compound **33**, the *N,O*-acetal rings are readily hydrolyzed under neutral conditions, causing the further splitting of the *N*-methyl signals in the

TABLE II

$^1$H-N M R DATA[a] FOR 2,5-ANHYDRO DERIVATIVES **10–21, 23–26, 29–31, 33, 34, 39–41, 43, 46, 50,** AND **48 + 52**

| *Compound* | *H-1 6* | *H-2* | *H-3* | *H-4* | *H-5* | *N$^+$-Me* | *Mesyl* | *Other protons* |
|---|---|---|---|---|---|---|---|---|
| **10**[c] | ~3 5 | 4 35 | 5 00 | 4 1–4 65 | | — | 3 13 | — |
| **11**[c] | 3 50 | 4 47 | 5 28 | 5 28 | 4 47 | — | 3 15 | — |
| **12**[c] | 3 50 | ~4 4 | 5 36 | 5 03 | ~4 4 | — | 3 15 | 2 10 acetyl |
| | 3 42 | | | | | | | |
| **13**[b] | ~3 35 | 4 67 | 5 60 | 5 60 | 4 67 | — | 3 36 | — |
| **14**[b] | ~3 35 | 4 33 | 5 32 | 5 32 | 4 33 | — | 3 36 | 1 82 acetyl, 8 0 N*H*Ac |
| **15**[d] | 3 50 | 4 93 | 5 60 | 5 60 | 4 93 | 3 00 | 3 40 | — |
| **16**[d] | 3 48 | 5 10 | 5 56 | 5 56 | 5 10 | 3 20 | 3 34 | — |
| | 3 77 | | | | | 3 25 | | |
| **17**[d] | 3 80 | 5 16 | 5 52 | 5 72 | 5 16 | 3 33 | 3 48 | — |
| | 3 87 | | | | | | | |
| **19**[d] | ~3 35 | ~4 8 | 5 23 | ~4 55 | ~4 8 | — | 3 33 | — |
| **20**[d] | 3 47 | ~4 9 | 5 22 | 4 80 | ~4 7 | 3 00 | 3 34 | — |
| **21**[d] | ~3 75 | ~4 9 | 5 28 | 4 70 | ~4 8 | 3 25 | 3 36 | — |
| **23**[d] | 3 58 | ~4 9 | 4 00 | 4 17 | ~4 9 | 3 28 | — | — |
| | 3 77 | | | | | 3 24 | | |
| **24**[d] | ~3 5 | ~4 75[e] | 3 30 | 4 65 | ~4 35[e] | — | 3 43 | 2 1 acetyl |
| **25**[b] | ~3 3 | 4 26 | 5 33 | 5 13 | 4 26 | — | 3 36 | 1 85 and 2 1 acetyl |
| **26**[d] | 3 38 | 4 15 | ~3 9 | ~3 9 | 4 15 | — | — | 2 05 acetyl |
| **29**[b] | 3 10 | 3 95 | 3 89 | 3 89 | 3 95 | — | — | 1 84 acetyl, 7 95 NH, |
| | 3 29 | | | | | | | 5 12 OH |
| **30**[d] | 3 35 | 4 38 | 5 26 | 5 26 | 4 38 | — | — | 1 95 and 2 13 acetyl |
| | 3 37 | | | | | | | |
| **31**[d] | 3 34 | ~4 4 | 4 38 | 4 38 | ~4 4 | — | — | — |
| **33**[d] | 3 58 | 4 98 | 4 70 | 4 70 | 4 98 | 2 80 | — | ~4 45 $NCH_2O$ |
| | 3 91 | | | | | | | |
| **34**[d] | 3 77 | 4 95 | ~4 7 | ~4 7 | 4 95 | 3 10 | — | ~4 75 $NCH_2O$ |
| | 4 04 | | | | | 3 21 | | |
| **39**[d] | 3 38 | 4 59 | 4 27 | 4 27 | 4 59 | 3 00 | — | — |
| **40**[d] | 3 62 | 4 70 | 4 31 | 4 31 | 4 70 | 3 20 | — | — |
| | 3 69 | | | | | | | |
| **41**[c] | ~3 5 | ~4 2 | 3 67[e] | 3 78[e] | ~4 2 | — | — | — |
| **43**[d] | ~3 3 | ~4 2 | ~4 55 | ~4 2 | ~4 2 | — | — | — |
| **46**[c] | ~3 45 | ~4 18 | 5 1 | 4 1 | 4 1 | — | — | — |
| **50**[c] | ~3 4 | 4 1 | 4 1 | 5 25 | 4 30 | — | — | — |
| **48+52**[c] | ~3 4 | ~4 0 | ~5 0 | ~4 0 | ~4 0 | — | — | ~2 0 acetyl |

[a]On the $\delta$ scale [b]$Me_2SO$-$d_6$ solution [c]Chloroform-*d* solution [d]$D_2O$ solution [e]Arbitrary assignments

$^1$H-n m r spectrum, as already mentioned In aqueous solution, a fast equilibrium is reached, in which, besides the diacetal **33** and the *N*-(hydroxymethyl)-monoacetal **35**, the fully hydrolyzed 1,6-bis-*N*-(hydroxymethyl) compound **37** is also present This was proved by $^{13}$C-n m r spectroscopy, as, in the spectrum of **33** in dry $Me_2SO$, a total of five signals, namely, one *N*-methyl signal (39 3 p p m ), two signals corresponding to the oxolane carbon atoms C-2 ≡ C-5 and C-3 ≡ C-4 (73 1 and 78 8

TABLE III

$^{13}C$-NMR DATA[a] FOR *N*-METHYL DERIVATIVES **33–35**, AND **37–40**

| *Compound* | *C-1* | *C-2* | *C-3* | *C-4* | *C-5* | *C-6* | $N^+CH_3$ | $N^-CH_2O$ | *Other protons* |
|---|---|---|---|---|---|---|---|---|---|
| **33**[b] | 52 5 | 73 1 | 78 8 | 78 8 | 73 1 | 52 5 | 39 3 | 80 8 | — |
| **34**[c] | 61 7 | 73 2 | 79 4 | 79 4 | 73 2 | 61 7 | 52 7<br>50 9 | 88 3 | — |
| **35**[c+b] | 49 9 | 72 9 | 77 4 | 83 2 | 78 4 | 50 0 | 35 0<br>39 4 | 81 7 | 81 6[d] $N^-CH_2OH$ |
| **37**[c-b] | 49 9 | 73 6 | 78 1 | 78 1 | 73 6 | 49 9 | 35 0 | — | 81 9[d] $N^-CH_2OH$ |
| **38**[c] | 68 1 | 79 7 | 73 6 | 82 4 | 76 5 | 62 0 | 56 8[e]<br>52 9[f]<br>51 7[f] | 89 1 | $N^+CH_3$[e] $^1J_{C-N} \sim 3\,5$ Hz<br>$NCH_3$[f] $^1J_{C-N} \sim 2\,6$ Hz |
| **39**[c] | 69 4 | 79 3 | 77 1 | 77 1 | 79 3 | 69 4 | 56 8 | — | $NCH_3$ $^1J_{C-N} \sim 3\,9$ Hz<br>$NCH_2O$ $^1J_{C-N} \sim 3\,8$ Hz |
| **40**[c] | 59 8 | 79 3 | 77 5 | 77 5 | 79 3 | 59 8 | 46 4 | — | — |

[a]On the $\delta$ scale [b]$Me_2SO$-$d_6$ solution [c]$D_2O$ solution [d]Arbitrary assignment [e]C-1-N [f]C-6-N

p p m ), the signal of the terminal methylene groups (C-1 ≡ C-6, 5 25 p p m ), and those of the *N,O*-methylene groups (80 8 p p m ), could be detected, due to the $C_2$ symmetry of the molecule

On adding water to the solution, the number of signals for the oxolane carbon atoms increased from two to eight proving that besides the two symmetrical structures **33** and **37** the asymmetrical **35** must also be present (see Table III) The equilibrium between the closed-ring form and the hydrolyzed structures is reached in ~30 min at room temperature as indicated by the "mutarotation' of compound **33** in water the optical rotation changing from +39° (5 min) to +22° at 30 min

For obtaining the desired *N,N'*-tetramethyl derivative **39** the dioxazine **33** was hydrogenated according to the literature[20], over Pd–C as the catalyst, but no substantial reaction could be observed As the hydroxymethyl groups of the intermediate **35** (and **37**) should be readily reducible by borohydride, the aqueous solution of **33** was treated with an excess of this reagent, giving **39** in excellent yield Methylation of **39** with methyl iodide afforded the crystalline, quaternary salt **40**

For investigating the influence, on the biological activity, of the two OH groups, removal of one of them was desired Treatment of the 3-mesyl-diazide **10** with sodium methoxide afforded the L-talitol epoxide **41** which, on catalytic reduction with hydrogen in the presence of Pd–C, gave the diamine **42** as an unstable syrup When reduction of diazide **41** was conducted with hydrogen sulfide in pyridine, not only were the azido groups reduced, but simultaneous addition of hydrogen sulfide to the oxirane ring occurred, and the crystalline 4-thio-L-mannitol derivative **43** was obtained. The thiol group of **43** could not be eliminated by treatment with Raney nickel as, instead of the 4-deoxy derivative **44**, only decomposition products were formed When the epoxide **41** was boiled in aqueous solution as for the acetamido derivative

**26**, no hydrolytic cleavage of the oxirane ring took place, even after boiling the solution for 8 h in the presence of acetic acid The different behavior of these two epoxides clearly indicates participation of the acetamido groups in the hydrolysis of epoxide **26**

The oxirane ring of **41** may be opened by strong nucleophiles *e g*, sodium azide slowly converted it into a 43 7 mixture of the corresponding triazido-L-*manno* (**45**) and -L-*ido* (**49**) derivatives, which means that, in this case, the electronic and steric effects seem to oppose each other in the cleavage of **41** by azide ion, but that the electronic effect of the azidomethyl group is less pronounced than that of the methoxyl group[21] In t l c , epoxide **41** had the same $R_1$ value as the triazido isomers **45** and **49**, but, after acetylation, the resulting mixture (**46** + **50**) could be separated from unchanged starting-material by column chromatography All attempts to separate the two triazido isomers failed, and separation after deacetylation (**45** + **49**) reduction (**47** + **51**), and subsequent acetylation (**48** + **52**) was also unsuccessful

On biological testing, the quaternary salts **17**, **21** **23**, **34**, and **40** proved to be relatively nontoxic ($LD_{50}$ > 200 mg/kg), but none of them possessed muscarine-like activity

## EXPERIMENTAL

*General methods* — After organic solutions had been dried with sodium sulfate, all evaporations were conducted in a rotary evaporator under diminished pressure Light petroleum had b p 60–80° Optical rotations were determined in chloroform (*c* 1), if not stated otherwise T l c was effected on Kieselgel G with ethyl acetate–carbon tetrachloride, 1 1 (*A*), 1 3 (*B*) 1 5 (*C*), and 1 9 (*D*), with conc ammonium hydroxide–ethanol 1 3 (*E*) and 1 9 (*F*), and with water (*G*) For detection, 1 1 0 1M potassium permanganate–M sulfuric acid was used at 105° Column chromatography was performed on Kieselgel 40 (63–200 μm) $^{13}$C-N m r spectra (25 2 MHz) and $^{1}$H-n m r spectra (90 MHz) were recorded at room temperature with a Varian XL-100 FT and a Varian EM-390 spectrometer respectively, for solutions in chloroform-*d*, with tetramethylsilane as the internal standard, or for solutions in $D_2O$ or dimethyl sulfoxide-$d_6$, with 2 2-dimethyl-2-silapentane-1-sulfonic acid, sodium salt, as the internal standard G l c was conducted with a Hewlett–Packard 5720 A gas chromatograph, using 10% of UWC 982 on Gas Chrom Q (80–100 mesh), temperature 250°, and nitrogen as the carrier gas at the rate of 45 mL min$^{-1}$ Mass spectra were recorded with a Varian-MAT SM-1 spectrometer at 70 eV (electron energy) and 2 600 MeV (multiplier voltage)

*3,5-Di-*O*-acetyl-6-azido-2,4-*O*-benzylidene-6-deoxy-1-*O*-p-tolylsulfonyl-*D*-glucitol* (**4**) *and 3,5-di-*O*-acetyl-1,6-diazido-2,4-*O*-benzylidene-1,6-dideoxy-*D*-glucitol* (**7**) — A solution of the diacetyl-ditosylate[15] **3** (66 g) and sodium azide (13 g) in *N*,*N*-dimethylformamide (330 mL) and water (50 mL) was heated on a steam bath for 2 h The residue obtained after evaporation of the mixture was partitioned between chloroform and water, and the organic solution was washed with water, dried, and

evaporated The residue gave on crystallization from ethanol pure monoazide **4** (25 2 g 46 5%). m p 105–107° $[\alpha]_D^{20}$ +2°. $R_F$ 0 50 (*B*)

*Anal* Calc for $C_{24}H_{27}N_3O_9S$ C. 54 02 H, 5 10 N, 7 88, S, 6 01 Found C 54 30 H. 5 03 N 7 83. S 5 88

The mother liquor was evaporated and treated for 8 h with sodium azide (10 g) as just described. to give, after similar processing and recrystallization from carbon tetrachloride–light petroleum, pure diazide **7** (14 5 g, 35 9%), m p 86–88°, $[\alpha]_D^{20}$ −6° $R_F$ 0 70 (*B*)

*Anal* Calc for $C_{17}H_{20}N_6O_6$ C 50 49 H, 4 99, N, 20 78 Found C, 50 62, H. 5 10. N. 20 42

*6-Azido-2,4-O-benzylidene-6-deoxy-1-O-p-tolylsulfonyl-D-glucitol* (**5**) — To a solution of compound **4** (10 7 g) in dry chloroform (20 mL) and methanol (10 mL) was added M methanolic sodium methoxide solution (0 1 mL) After 15 min at room temperature, crystallization of **5** started The crystals were filtered off after 20 h, and recrystallized from acetone (300 mL) to yield pure **5** (5 4 g, 60%), m p 163° (dec ). $[\alpha]_D^{20}$ +22° (acetone) $R_F$ 0 65 (*A*)

*Anal* Calc for $C_{20}H_{23}N_3O_7S$ C. 53 44 H 5 16 N, 9 35 S 7 13 Found C. 53 36 H 5 17 N. 9 55. S 6 90

*6-Azido-2 4-O-benzylidene-6-deoxy-3 4-di-O-(methylsulfonyl)-1-O-p-tolylsulfonyl-D-glucitol* (**6**) — A solution of **5** (2 6 g) in pyridine (15 mL) was treated with mesyl chloride (2 mL) to give, after the usual processing, and evaporation of the chloroform solution, a syrup that crystallized on treatment with ethanol The m p (136–139°) of the crude **6** decreased to m p 128–130° on recrystallization from ethyl acetate–light petroleum (2 6 g, 74 2%), $[\alpha]_D^{20}$ −3° $R_F$ 0 80 (*A*)

*Anal* Calc for $C_{22}H_{27}N_3O_{11}S_3$ C. 43 63; H. 4 49 N 6 94 S, 15 88 Found C, 43 66 H 4 43 N, 6 99 S. 15 52

*1,6-Diazido-2,4-O-benzylidene-1 6-dideoxy-D-glucitol* (**8**) — *Method a* The diacetate **7** (20 2 g) was deacetylated as described for **5** and the crystals were filtered off and washed with methanol and water to give pure **8** (14 1 g 88%), m p 187–189°, $[\alpha]_D^{20}$ +31° (*N,N*-dimethylformamide) $R_F$ 0 45 (*B*) On recrystallization from *N,N*-dimethylformamide–water. the m p decreased to 159–161°

*Method b* A solution of the ditosylate[14] **2** (289 g) and sodium azide (125 g) in *N,N*-dimethylformamide (2 L) and water (250 mL) was boiled for 30 min The solution was cooled, and poured into water (4 L), and the resulting precipitate was filtered off. and successively washed with water and methanol, to give **8** (153 g, 95 5%), identical with that obtained by method *a*

*Anal* Calc for $C_{13}H_{16}N_6O_4$ C 48 75 H, 5 04 N, 26 24. Found C, 48 64, H, 5 10 N, 26 11

*1,6-Diazido-2 4-O-benzylidene-1 6-dideoxy-3,4-di-O-(methylsulfonyl)-D-glucitol* (**9**) — A stirred, water-cooled slurry of diazide **8** (160 g) in pyridine (800 mL) was treated with mesyl chloride (150 mL) giving a clear solution The mixture was kept overnight at room temperature, and. after the usual processing, and treatment of the evaporated residue with methanol, gave crude **9** (224 g, 94%, m p 129–130°) pure enough for

the next step Recrystallization from ethyl acetate–ether–light petroleum gave pure **9** (183 g, 80 5%), m p 130–132° $[\alpha]_D^{20}$ 0° $R_F$ 0 60 (*B*)

*Anal* Calc for $C_{15}H_{20}N_6O_8S_2$ C, 37 81, H, 4 23 N, 17 64 S, 13 46 Found C, 37 95 H, 4 20. N, 17 62 S, 13 22

*2,5-Anhydro-1,6-diazido-1,6-dideoxy-3-O-(methylsulfonyl)-L-iditol* (**10**) — A stirred slurry of dimesylate **9** (130 g) in ethanol (1 3 L) and conc hydrochloric acid (400 mL) was boiled on a steam bath for 1 h The clear solution was cooled, and made neutral by addition of solid sodium hydrogencarbonate The suspension was filtered, the filtrate evaporated, the residue partitioned between ether and water and the organic solution washed with water, dried, and evaporated The residue was chromatographed on a column of silica gel (700 g) prepared with carbon tetrachloride The column was washed first with solvent *D* (~1 5 L) to remove benzaldehyde, and then with *B* Evaporation of the fractions having $R_F$ 0 70 (*A*) gave pure **10** as a slightly yellow syrup (67 g, 83 7%), $[\alpha]_D^{20}$ +24°

*Anal* Calc for $C_7H_{12}N_6O_5S$ N, 28 76, S, 10 97 Found N, 28 15 S, 11 24

*2,5-Anhydro-1,6-diazido-1 6-dideoxy-3,4-di-O-(methylsulfonyl)-L-iditol* (**11**) — A solution of syrupy **10** (60 g) in pyridine (120 mL) was treated with mesyl chloride (26 mL) The mixture was kept overnight at room temperature and then poured into water The precipitated solid was filtered off (69 g. 90 5%) to give, after recrystallization from methanol (10 vol ), pure **11** (60 g, 78 5%), m p 111–113° $[\alpha]_D^{20}$ 0°, $R_F$ 0 70 (*A*) The compound is slightly sensitive to light and can be stored without decomposition only in the dark

*Anal* Calc for $C_8H_{14}N_6O_7S_2$ C, 25 94 H, 3 81 N, 22 70 S, 17 31 Found C, 25 89, H, 3 95, N, 22 63 S, 17 22

*4-O-Acetyl-2,5-anhydro-1,6-diazido-1 6-dideoxy-3-O-(methylsulfonyl)-L-iditol* (**12**) — A solution of **10** (30 g) in pyridine (30 mL) and acetic anhydride (15 mL) was kept overnight at room temperature, to give, after the usual processing crude **12** (31 4 g) which was recrystallized from ethanol (30 8 g, 91%), m p 72–74°, $[\alpha]_D^{20}$ −5° $R_F$ 0 40 (*B*)

*Anal* Calc for $C_9H_{14}N_6O_6S$ C, 32 33, H 4 22 S, 9 59 Found C 32 55 H, 4 34, S, 9 15

*1,6-Diamino-2,5-anhydro-1,6-dideoxy-3,4-di-O-(methylsulfonyl)-L-iditol dihydrochloride* (**13**) *and 1,6-diamino-1 4 2,5-dianhydro-1,6-dideoxy-3-O-(methylsulfonyl)-L-altritol* (**18**) — Through a solution of diazide **11** (18 5 g) in pyridine (185 mL) and water (90 mL) was passed a stream of hydrogen sulfide An exothermic reaction took place, and the temperature of the reaction mixture rose to 50° In t l c (*F*), besides the spot of the starting material ($R_F$ 0 95), two new components, $R_F$ 0 80 (monoamino-monoazide) and $R_F$ 0 55 (**13**), were detected After 3 h, when the reduction was complete (single spot of **13**, in t l c ), acetic acid (10 mL) was added, and the solution was evaporated The residue was filtered with the aid of water, to remove the precipitated sulfur The filtrate was evaporated, and ethanol was added to, and evaporated from, the residue, which was then dissolved in ethanol (40 mL), and conc hydrochloric acid (10 mL) was added The precipitated salt was filtered

off and washed with ethanol to give pure **13** (14 3 g, 73 2%). m p 210–213° (dec ). $[\alpha]_D^{20}$ −24° (water) $R_F$ 0 55 (*F*)

*Anal* Calc for $C_8H_{18}N_2O_7S_2$ 2 HCl C, 24 55 H, 5 15. Cl, 18 12 N, 7 15 S. 16 38 Found C 24 42 H 5 21, Cl 18 20. N, 7 08, S 16 15

The ethanolic mother liquor was evaporated. and the solid residue (3 g) was twice recrystallized from water–ethanol to give pure dianhydride **18** as its mesylate hydrochloride (0 8 g 4 5%) m p 240°. $[\alpha]_D^{20}$ −46° (water). $R_F$ 0 50 (*F*), $^1$H-n m r data $\delta$ 5 53 (m. H-3). 4 99 (d H-2), 4 6 (m, H-4) 4 5 (m. H-5), 3 8 (s, H-1.1′), 3 15 and 3 24 (m H-6 6′) 3 39 (mesyl-Me), and 2 78 (mesylate-Me)

*Anal* Calc for $C_7H_{14}N_2O_4S$ HCl $CH_3SO_3H$ C, 27 07 H, 5 39 Cl, 9 94. N 7 89 S, 18 07 Found C, 27 02 H, 5 50 Cl, 9 88 N, 7 70 S, 17 85

*1,6-Bis(acetamido)-2 5-anhydro-1,6-dideoxy-3 4-di-O-(methylsulfonyl)-*L*-iditol* (**14**) — A solution of **13** (1 7 g) and sodium acetate (1 g) in pyridine (10 mL) and acetic anhydride (5 mL) was kept for two days at room temperature The mixture was then evaporated. the residue mixed with acetone and the suspension filtered The filtrate was evaporated the residue was dissolved in water, and the solution freed of salts by treatment with ion-exchange resins The filtrate was evaporated, and the solid residue was filtered with the aid of acetone to give pure **14** (1 g, 57 2%) m p 144–146°, $[\alpha]_D^{20}$ −26 5° (water), $R_F$ 0 70 (*G*)

*Anal* Calc for $C_{12}H_{22}N_2O_9S_2$ C. 35 81, H, 5 51, N. 6 96. S, 15 93 Found C 36 05. H, 5 45 N, 6 81, S, 15 76

*2,5-Anhydro-1,6-dideoxy-1 6-bis(dimethylamino)-3,4-di-O-(methylsulfonyl)-*L*-iditol dihydrochloride* (**15**) — A solution of **13** (2 g) in aqueous formaldehyde (36%, 10 mL) and formic acid (90%, 15 mL) was heated on a steam bath for 10 h The solution was evaporated, and the residue was filtered with the aid of M hydrochloric acid (10 mL) to give, after evaporation of the filtrate and treatment of the residue with ethanol. pure **15** (1 7 g, 75%), m p 225° (dec ), $[\alpha]_D^{20}$ −27° (water), $R_F$ 0 80 (*F*)

*Anal* Calc for $C_{12}H_{26}N_2O_7S_2$ 2 HCl C, 32 21 H, 6 30 Cl, 15 85 N, 6 26 S, 14 33 Found C 32 05, H, 6 48 Cl, 15 57, N 6 11, S, 14 18

*2,5-Anhydro-1,6-dideoxy-1,6-bis(dimethylamino)-3,4-di-O-(methylsulfonyl)-*L*-iditol bis(N-oxide)* (**16**) — To a stirred slurry of **15** (1 5 g) in methanol (15 mL) was added 4 4M methanolic sodium methoxide (1 5 mL), and the precipitated sodium chloride was filtered off Hydrogen peroxide (30%, 1 5 mL) was then added to the filtrate and the solution was kept in a desiccator over conc sulfuric acid for three days The crystals that separated were filtered off, and washed with ethanol, to give pure **16** (1 1 g 81%) m p 152° (dec ), $[\alpha]_D^{20}$ — 25° (water), $R_F$ 0 40 (*E*)

*Anal* Calc for $C_{12}H_{26}N_2O_9S_2$ C, 35 45, H 6 44 N 6 89 S, 15 77 Found C, 35 30. H. 6 52, N 6 76 S, 15 52

*2 5-Anhydro-1,6-dideoxy-3,4-di-O-(methylsulfonyl)-1 6-bis(trimethylamino)-*L*-iditol diiodide* (**17**) — To a stirred slurry of **15** (3 2 g) in methanol (32 mL) was added 4 6M methanolic sodium methoxide (3 2 mL), the slurry was evaporated, and the residue filtered with the aid of acetone (20 mL) Methyl iodide (7 mL) was added to

the filtrate, and the crystalline, quaternary salt **17** was filtered off, after 30 min and washed with acetone (4 6 g, 87%), m p 300°, $[\alpha]_D^{20}$ −11° (water)

*Anal* Calc for $C_{14}H_{32}I_2N_2O_7S_2$ C, 25 53, H, 4 89 I 38 55, N, 4 25 S, 9 74 Found C, 25 38 H, 5 10, I, 38 65, N, 4 09, S, 9 58

*1,6-Diamino-2,5-anhydro-1,6-dideoxy-3-O-(methylsulfonyl)-L-iditol dihydrochloride* (**19**) — A solution of diazide **10** (3 g) in pyridine (30 mL) and water (15 mL) was reduced with hydrogen sulfide as described for compound **13**, to give **19** (2 1 g, 69%), m p 207°, $[\alpha]_D^{20}$ −14° (water), $R_F$ 0 55 (*E*)

When the experiment was conducted on a larger scale, the yield of **19** decreased to 35%

*Anal* Calc for $C_7H_{16}N_2O_5S$ 2 HCl C, 26 84, H, 5 79, Cl, 22 64, N, 8 94, S 10 23 Found C 26 71 H 5 89, Cl, 22 30 N, 8 72 S, 10 00

*2,5-Anhydro-1,6-dideoxy-1,6-bis(dimethylamino)-3-O-(methylsulfonyl)-L-iditol dihydrochloride* (**20**) — A solution of **19** (4 5 g) in aqueous formaldehyde (36%, 30 mL) and formic acid (90%, 45 mL) was heated on a steam bath for 24 h The solution was evaporated and the residue was mixed with M hydrochloric acid (20 mL), the suspension filtered, and the filtrate evaporated Then ethanol was added to, and evaporated from, the residue, which became a solid foam The crude **20** (4 4 g, 83%) so obtained could not be crystallized, but was pure enough for further experiments $[\alpha]_D^{20}$ −10° (water) $R_F$ 0 60 (*E*)

*Anal* Calc for $C_{11}H_{24}N_2O_5S$ 2 HCl Cl, 19 20, N, 7 58 S 8 68 Found Cl, 18 90, N, 7 43 S, 8 75

*2,5-Anhydro-1,6-dideoxy-3-O-(methylsulfonyl)-1,6-bis(trimethylamino)-L-iditol diiodide* (**21**) — A solution of amorphous **20** (3 9 g) in methanol (10 mL) was made alkaline (in the presence of phenolphthalein) with 4 4M methanolic sodium methoxide (5 3 mL) Acetone (10 mL) was added to the resulting slurry, and the sodium chloride was filtered off Methyl iodide (3 mL) was added to the filtrate, and, after 1 h at room temperature, the mixture was concentrated to 10 mL The precipitated crystals (4 2 g 69%) gave, after recrystallization from water–ethanol pure **21** (2 15 g 35 3%), m p 227° (dec ), $[\alpha]_D^{20}$ −5 3° (water)

*Anal* Calc for $C_{13}H_{30}I_2N_2O_5S$ C, 26 90, H, 5 21 I, 43 74 N, 4 82 S 5 52 Found C, 26 76, H, 5 38 I, 42 95, N 4 70, S, 5 58

*2 5 3,4-Dianhydro-1,6-dideoxy-1,6-bis(trimethylamino)-L-talitol diiodide* (**23**) — To a solution of amorphous **20** (1 85 g) in methanol (10 mL) was added 4 4M methanolic sodium methoxide (3 5 mL, 3 1 equiv ), and the mixture was boiled for 4 h The starting material ($R_F$ 0 60, *I*) was completely converted into the epoxide **22** ($R_F$ 0 70) The mixture was cooled, and made neutral with carbon dioxide, and the salts were filtered off The filtrate was evaporated, and the residue was taken up in acetone the suspension filtered, and methyl iodide (4 mL) added The mixture was boiled for 30 min, cooled, and evaporated, and the solid residue was filtered with the aid of methanol, to give pure **23** (1 45 g, 59 5%), m p 260°, $[\alpha]_D^{20}$ −6° (water)

*Anal* Calc for $C_{12}H_{26}I_2N_2O_2$ C, 29 76, H, 5 41, I, 52 42, N, 5 78 Found C, 29 65, H, 5 48, I, 51 95, N, 5 66

*6-Acetamido-1-amino-2,5-anhydro-1,6-dideoxy-3-O-(methylsulfonyl)-L-iditol hydrochloride* (**24**) — A solution of diazide **12** (16 7 g) in pyridine (160 mL) and water (50 mL) was reduced with hydrogen sulfide as described for **13** The hydrochloride did not crystallize from the ethanolic solution on addition of hydrochloric acid and therefore the solution was evaporated to a semisolid residue, which was twice recrystallized from ethanol. to yield pure **24** (3 7 g. 23 2%), m p 170–171°, $[\alpha]_D^{20}$ −21° (water). $R_F$ 0 60 (*F*)

*Anal* Calc for $C_9H_{18}N_2O_6S$ HCl C 33 90, H 6 00, Cl 11 12 N, 8 78 S. 10 05 Found C 33 78. H 6 12 Cl, 11 38 N, 8 62, S 9 86

*1,6-Bis(acetamido)-4-O-acetyl-2 5-anhydro-1,6-dideoxy-3-O-(methylsulfonyl)-L-iditol* (**25**) — *Method a* A solution of diazide **12** (25 g) in pyridine (250 mL) and water (80 mL) was reduced by passing a stream of hydrogen sulfide through it The temperature of the reaction mixture rose to 60°. and the reduction was complete in 2 h Acetic acid (10 mL) was then added the mixture was evaporated and the residue was dissolved in water, filtered from sulfur and evaporated Then ethanol was twice added to, and evaporated from, the residue, the residue was dissolved in pyridine (70 mL), and acetic acid (50 mL) was added without cooling After the exothermic reaction had ended crystallization of the acetylation product started After 3 h at room temperature. the crystals were filtered off, and washed with water to give pure **25** (22 2 g. 80 8%) m p 178–180°, $[\alpha]_D^{20}$ −24° (water), $R_F$ 0 60 (*G*)

*Method b* A slurry of **24** (3 g) and sodium acetate (0 8 g) in pyridine (10 mL) and acetic anhydride (5 mL) was stirred for 48 h at room temperature evaporated and the residue filtered with the aid of water. to give **25** (3 g 76 5%) identical with that just described

*Anal* Calc for $C_{13}H_{22}N_2O_8S$ C, 42 61 H, 6 05 N 7 64, S 8 75 Found C 42 92 H 5 90, N. 7 49 S. 8 69

*1,6-Bis(acetamido)-2,5 3 4-dianhydro-1 6-dideoxy-L-talitol* (**26**). — A slurry of compound **25** (18 3 g) in methanol (60 mL) and 4 4M methanolic sodium methoxide (12 5 mL) was stirred for 20 h at room temperature. and then made neutral with carbon dioxide The precipitated salt was filtered off and the filtrate was evaporated The solid residue was boiled with ethanol (300 mL) and the hot suspension was filtered, and the filtrate evaporated On filtration with the aid of acetone, the residue gave **26** (10 9 g. 96%) m p 163–165°, $[\alpha]_D^{20}$ +36 6° (water). $R_F$ 0 60 (*G*)

*Anal* Calc for $C_{10}H_{16}N_2O_4$ C, 52 61, H, 7 06 N, 12 27 Found C 52 67 H. 7 07 N, 12 15

*1,6-Bis(acetamido)-2,5-anhydro-1,6-dideoxy-L-iditol* (**29**) — Epoxide **26** (11 4 g) was boiled in water (70 mL) for 20 min, to give, after evaporation and filtration with the aid of ethanol, pure **29** (11 2 g 91%) m p 174–176°, $[\alpha]_D^{20}$ −43 3° (water), $R_F$ 0 75 (*G*)

*Anal* Calc for $C_{10}H_{18}N_2O_5$ C 48 76 H, 7 36, N 11 37 Found C, 48 71 H 7 44, N, 11 25

*1,6-Bis(acetamido)-3,4-di-O-acetyl-2,5-anhydro-1,6-dideoxy-L-iditol* (**30**) — A

solution of **29** (3 25 g) in pyridine (10 mL) and acetic anhydride (7 mL) was heated on a steam bath for 1 5 h, and then evaporated The residue was filtered with the aid of acetone, to give after recrystallization from ethanol, pure **30** (2 9 g, 66 6%), m p 158–159° $[\alpha]_D^{20}$ −24° (water), $R_F$ 0 55 (*G*)

*Anal* Calc for $C_{14}H_{22}N_2O_7$ C, 50 90 H, 6 71, N, 8 48 Found C 50 86 H, 6 80, N 8 36

*1,6-Diamino-2 5-anhydro-1,6-dideoxy-L-iditol dihydrochloride* (**31**) — The diacetate **29** (7 8 g) was boiled in M hydrochloric acid (100 mL) for 1 5 h The solution was evaporated, and the residue filtered with the aid of ethanol, to give pure **31** (6 8 g 92 6%), m p 231–233° $[\alpha]_D^{20}$ +3° (water) $R_F$ 0 30 (*E*)

*Anal* Calc for $C_6H_{14}N_2O_3$ 2 HCl C 30 64, H 6 85 Cl 30 16 N 11 91 Found C, 30 59, H, 6 92, Cl 30 21 N 11 45

The same compound was obtained, in a yield of 90% when tetraacetate **30** was used as the starting material

*2,5-Anhydro-1,6-dideoxy-1,6-bis(methylamino)-1 3 4,6-di-*N,O*-methylene-L-iditol dihydrochloride* (**33**) — A solution of **31** (4 7 g) in aqueous formaldehyde (36% 8 mL) and formic acid (90%, 12 5 mL) was kept for 8 h at 90° cooled, and evaporated and the residue was taken up in M hydrochloric acid (10 mL) the suspension filtered, and the filtrate evaporated Ethanol was added to, and evaporated from the residue which gradually solidified The residue was filtered with the aid of ethanol, to yield pure **33** (5 1 g, 88%), m p 213° (dec ) $[\alpha]_D^{20}$ +44° (dimethyl sulfoxide), +39 (5 min)→+22° (water 24 h)

*Anal* Calc for $C_{10}H_{18}N_2O_3$ 2 HCl C, 41 80, H, 7 01 Cl 24 69 N 9 75 Found C, 41 89, H, 7 12 Cl, 24 55 N, 9 68

*2,5-Anhydro-1,6-dideoxy-1,6-bis(dimethylamino)-1,3 4,6-di-*N,O*-methylene-L-iditol diiodide* (**34**) — A solution of **33** (2 9 g) in methanol (30 mL) was made alkaline (in the presence of phenolphthalein) with 5 5M methanolic sodium methoxide (4 mL) Acetone (30 mL) was then added to the mixture, and the precipitated sodium chloride was filtered off Methyl iodide (4 5 mL) was added to the solution, which was then kept for 20 h at +5° The precipitated crystals were filtered off, and washed with ethanol, to give pure **34** (4 4 g, 88%) m.p 240° (dec ) $[\alpha]_D^{20}$ +40° (water)

*Anal* Calc for $C_{12}H_{24}I_2N_2O_3$ C, 28 93, H, 4 83 I, 50 96 N 5 62 Found C, 29 12, H, 4 95, I, 50 38 N, 5 51

When the treatment of **31** with formaldehyde–formic acid was repeated three times, and the solid material obtained was converted into the quaternary salt by methyl iodide as just described, only 2 4 g (48%) of **34** crystallized from the ethanolic solution Evaporation of the mother liquor gave a ~2 3 mixture of **34** and **38** (2 4 g), as determined by $^{13}$C-n m r spectroscopy

*2,5-Anhydro-1,6-dideoxy-1,6-bis(dimethylamino)-L-iditol dihydrochloride* (**39**) — A solution of **31** (5 6 g) was methylated as described for **33**, but the residue from evaporation of the hydrochloric acid solution was dissolved in water (10 mL) and the solution made alkaline with 2M sodium hydroxide (30 mL) Then, sodium borohydride (1 5 g) was gradually added to the stirred solution and stirring was continued for 2 h

at room temperature The solution was acidified with 2M hydrochloric acid (using Methyl Red as indicator), and evaporated, and then methanol (3 × 100 mL) was added to, and evaporated from the residue (to remove the boric acid) The residue was dissolved in methanol (20 mL), the solution was made alkaline with 5M methanolic sodium methoxide, the precipitated inorganic salts were filtered off, the filtrate was evaporated, and the residue was taken up in ethanol, and the suspension filtered

The filtrate was acidified with 5M methanolic hydrochloric acid, and evaporated, the solid residue was dissolved in boiling methanol (100 mL), and the solution concentrated to 30 mL, and diluted with ethanol (30 mL), to give crystalline **39** (5 65 g, 81 3%), m p 150° (dec ), $[\alpha]_D^{20}$ −9 4° (water), $R_F$ 0 70 (*E*)

*Anal* Calc for $C_{10}H_{22}N_2O_3$ 2 HCl C, 41 25, H, 8 27, Cl, 24 35, N, 9 62 Found C, 41 19 H, 8 35, Cl, 24 17, N, 9 58

*2,5-Anhydro-1,6-dideoxy-1,6-bis(trimethylamino)-*L*-iditol diiodide* (**40**) — A solution of **39** (2 9 g) in methanol was treated with methyl iodide as described for compound **34**, to give, after recrystallization from methanol–water, pure **40** (3 4 g, 68%), m p >260°, $[\alpha]_D^{20}$ −1° (water)

*Anal* Calc for $C_{12}H_{28}I_2N_2O_3$ C, 28 69 H, 5 62, I, 50 54 N 5 57 Found C, 28 52 H, 5 58, I, 49 83, N, 5 60

*2,5 3 4-Dianhydro-1,6-diazido-1,6-dideoxy-*L*-talitol* (**41**) — To a solution of the syrupy diazide **10** (14 5 g) or its crystalline acetate **12** (16 7 g) in chloroform (150 mL) and methanol (30 mL) was added 4M methanolic sodium methoxide (13 mL) at room temperature The mixture was stirred for 30 min and was then made neutral with solid carbon dioxide, and evaporated The residue was partitioned between chloroform and water, and the chloroform solution was washed with water, dried, evaporated, and the residue purified by column chromatography (*B*), yielding **41** as a colorless syrup (18 5 g, 94 5%), $[\alpha]_D^{20}$ +26°; $R_F$ 0 70 (*B*)

*Anal* Calc for $C_6H_8N_6O_2$ N, 42 84 Found N, 42 37

*1,6-Diamino-2,5 3,4-dianhydro-1 6-dideoxy-*L*-iditol* (**42**) — A solution of diazide **41** (2 g) in ethanol (150 mL) was hydrogenated in the presence of 10% Pd–C catalyst (1 g), the reaction being complete after 1 5 h The suspension was filtered, and the filtrate evaporated, to give **42** as a pale-yellow syrup (1 3 g, 87%), which decomposed slowly on standing at room temperature In t l c , **42** gave a single spot ($R_F$ 0 55, *E*), both on developing with permanganate, or 4-(*p*-nitrobenzyl)pyridine (the latter reagent being specific for epoxides[22])

*Anal* Calc for $C_6H_{12}N_2O_2$ N, 19 43 Found N, 19 16

*1 6-Diamino-2,5-anhydro-1 6-dideoxy-4-thio-*L*-mannitol dihydrochloride* (**43**) — The epoxy-azide **41** (20 g) was reduced with hydrogen sulfide as described for compound **13**, to give **43** (19 7 g, 77%) m p >260°, $[\alpha]_D^{20}$ +11° (water), $R_F$ 0 55 (*E*)

*Anal* Calc for $C_6H_{14}N_2O_2S$ 2 HCl C, 28 88, H, 6 42, Cl, 28 23 N, 11 15, S, 12 76 Found C, 28 76, H, 6 30, Cl, 27 90, N, 10 97, S, 12 95

*2,5-Anhydro-1,4,6-triazido-1,4,6-trideoxy-*L*-mannitol and -*L*-iditol* (**45** + **49**) — A solution of epoxide **41** (6 3 g) and sodium azide (4 1 g) in methanol (60 mL) and water (15 mL) was boiled on a steam bath, and the developing alkalinity was continu-

ally neutralized with acetic acid, using phenolphthalein as indicator After 8 h, when the reaction mixture remained neutral, it was evaporated, and the residue was acetylated with pyridine (25 mL)–acetic anhydride (10 mL) After the usual processing, the resulting syrup was separated by column chromatography, using solvent *C* for elution Evaporation of the fractions having $R_F$ 0 75 gave (according to g l c ) a 43 7 mixture of the isomeric triazides **46** and **50** (5 8 g, 64 5%), $[\alpha]_D^{20}$ −164°, with retention times of 3 72 and 4 14 min, respectively and evaporation of the fractions having $R_F$ 0 60 gave unreacted epoxide **41** (1 3 g, 20 6%)

The mixture of acetates (**46** + **50**) gave, on deacetylation with sodium methoxide, a mixture of **45** and **49**, $[\alpha]_D^{20}$ −180°, $R_F$ 0 60 (*C*)

*1,4,6-Triamino-2,5-anhydro-1,4,6-trideoxy-L-mannitol and -L-iditol trihydrochloride* (**47** + **51**) — A solution of the mixture of triazides **45** + **49** (5 g) in methanol (50 mL) was hydrogenated over 10% Pd–C (3 g) for 6 h The suspension was filtered the filtrate evaporated the residue acidified with 5M hydrochloric acid, the solution mixed with charcoal and filtered, and the filtrate evaporated Ethanol was then added to, and evaporated from, the residue, which gave a mixture of **47** and **51** as a solid foam (4 9 g, 90%), $[\alpha]_D^{20}$ −42° (water) $R_F$ 0 45 (*E*)

*Anal* Calc for $C_6H_{15}N_3O_2$ 3 HCl Cl, 39 30, N 15 52 Found Cl, 38 85 N, 15 36

Acetylation of this mixture of **47** and **51** was conducted with pyridine (30 mL) acetic anhydride (20 mL), and sodium acetate (1 g) The mixture was kept for 20 h at room temperature and then evaporated The residue was dissolved in water, freed of salts by means of ion-exchange resins, and evaporated Ethanol was added to and evaporated from the residue which gave a mixture of the tetraacetates **48** and **52** (4 g, 67 0%) as a solid foam, $[\alpha]_D^{20}$ −40° (water) $R_F$ 0 70 (ethanol)

*Anal* Calc for $C_{14}H_{23}N_3O_6$ N, 12 75 Found N, 12 58

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