Carbohydrate Research, 85 (1980) 259–269.
Elsevier Scientific Publishing Company, Amsterdam – Printed in The Netherlands

SYNTHESIS AND BIOLOGICAL ACTIVITY OF 1,4:3,6-DIANHYDRO-2,5-DIAZIDO-2,5-DIDEOXYHEXITOLS

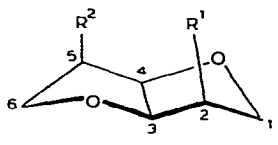
JÁNOS KUSZMANN AND GÁBOR MEDGYES
Institute for Drug Research, H-1325 Budapest 4, P.O. Box 82 (Hungary)
(Received March 20th, 1980; accepted for publication, April 11th, 1980)

ABSTRACT

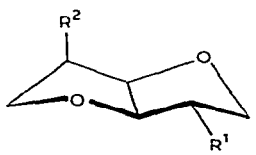
Reaction of 1,4:3,6-dianhydro-2,5-di-*O*-mesyl- and -tosyl-D-mannitol with sodium azide afforded the 2,5-diazido-L-iditol derivative. The analogous D-glucitol isomer was obtained in a similar reaction starting from the corresponding D-glucitol derivatives, and showed significant, hypnotic activity. For establishing the structure–activity relationship, 1,4:3,6-dianhydro-2,5-diazido-2,5-dideoxy-L-mannitol (**19**), as well as its antipode **27**, was synthesized, starting from D-mannitol. Compound **19** was as effective as Doriden® (3-ethyl-3-phenylglutarimide), a well known, hypnotic drug. The antipode **27** and the bioisosteric 1(4),3(6)-dithio derivative were, however, inactive.

INTRODUCTION

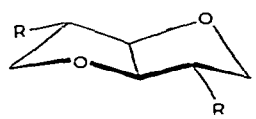
In a previous article[1], it was shown that the rule[2–6] according to which only *endo*-situated groups in 1,4:3,6-dianhydro-2,5-di-*O*-mesyl- and -tosyl-hexitols can be exchanged, *via* an SN2 type of mechanism, by "large" nucleophiles, is not valid for D-mannitol derivatives **1** and **2**, using iodide as the nucleophile. In this case, the *exo*-iodide of the 2-iodo-5-*O*-mesyl-D-glucitol intermediate **5** undergoes a fast iodo–



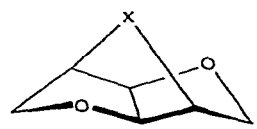
1 $R^1 = R^2 =$ OMs
2 $R^1 = R^2 =$ OTs
3 $R^1 = I, R^2 =$ OMs
4 $R^1 = R^2 = NH_2$



5 $R^1 = I, R^2 =$ OMs
6 $R^1 = R^2 =$ OMs
7 $R^1 = R^2 = NH_2$
8 $R^1 = R^2 = NMe_2$
9 $R^1 = R^2 =$ OTs
10 $R^1 = R^2 = N_3$



11 R = OMs
12 R = N_3



13

0008-6215/80/0000–0000/$ 02.25,

iodo exchange-reaction, yielding the mannitol isomer **3**. A similar substitution of an *exo*-situated group has so far, only been described for such "small" nucleophiles as ammonia[7,8] or dimethylamine[5], by which the D-glucitol dimesylate **6** was converted into the corresponding 2,5-diamino (**7**) and 2,5-bis(dimethylamino) (**8**) derivatives, respectively. When both leaving-groups, on C-2 and C-5 were *exo*-situated, as in the L-iditol derivative **11**, instead of the expected D-mannitol isomer **4**, the corresponding trianhydromannitol derivatives, of type **13** (X=O or NH), were obtained[5,8] as the sole products. For establishing the steric and electronic scope and limitations of these substitution reactions, experiments were conducted with the azide anion, which is a very strong, but relatively small, nucleophile.

DISCUSSION

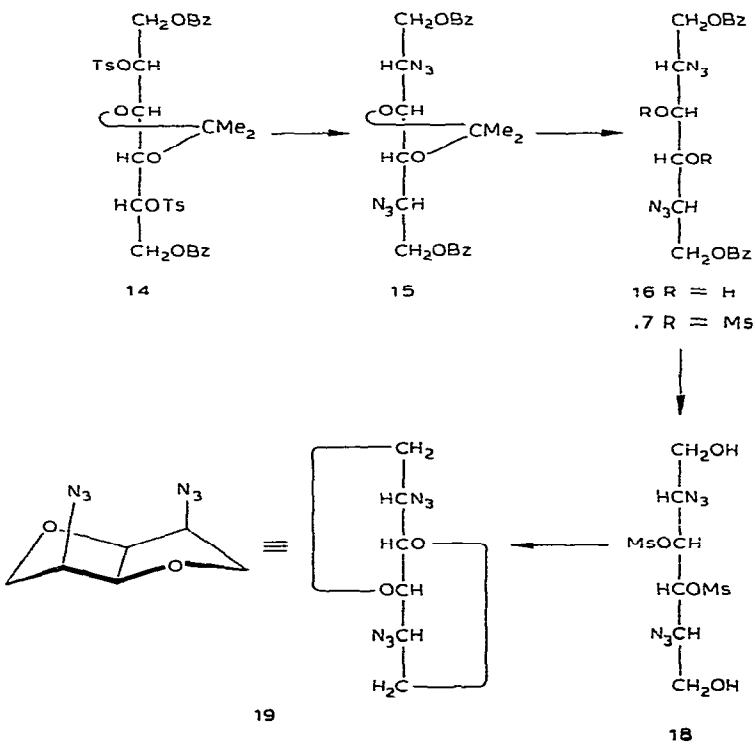
On treatment with sodium azide in *N*,*N*-dimethylformamide for 2 h at 120°, the 2,5-di-*O*-mesyl- (**1**) or -tosyl-D-mannitol derivative **2** gave the diazido-L-iditol derivative **12** in a yield of 86%. When the 2,5-di-*O*-mesyl- (**6**) or -tosyl-D-glucitol derivative **9** was similarly treated, the reaction temperature had to be increased to the boiling point of the solution, and a reaction time of 4.5 h was needed in order to complete the replacement of both ester groups.

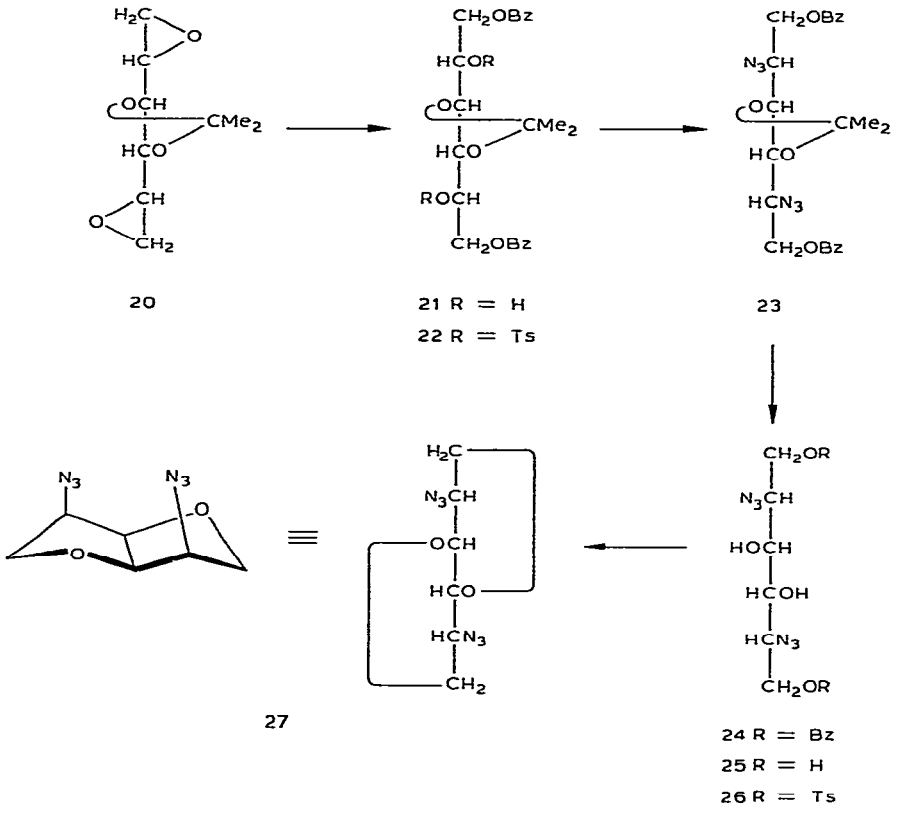
In biological testing, the 1,4:3,6-dianhydro-2,5-diazido-2,5-dideoxy-D-glucitol (**10**) so obtained showed significant hypnotic activity, whereas the corresponding L-iditol isomer **12** was inactive. For studying the structure–activity relationship, synthesis of the 2,5-diazido-D-mannitol derivative **27** was decided on.

Attempts to replace the 2,5-situated mesyloxy groups in the L-iditol derivative **11** by azide were unsuccessful, as the starting material remained unchanged in *N*,*N*-dimethylformamide at 120°, and only slow decomposition took place at the boiling temperature. Experiments using other conditions (*e.g.*, hexamethylphosphoric triamide as the solvent or 18-crown-6 as the catalyst) were also unsuccessful, and therefore a "reversed" synthesis was carried out, introducing first the azido groups at C-2 and C-5 in a properly substituted, acyclic hexitol, and closing the anhydro rings later.

This strategy was first tested for the preparation of the corresponding L-mannitol isomer **19**, a synthesis that was simpler than that of its antipode. As the starting material, D-mannitol was used; this was converted into the known[9] 1,6-di-*O*-benzoyl-3,4-*O*-isopropylidene-2,5-di-*O*-tosyl-D-mannitol (**14**), the tosyloxy groups of which could be readily replaced, with inversion of configuration, by azide, yielding the 2,5-diazido-L-iditol derivative **15**. The isopropylidene group of **15** was then split off at 90° in 5:1 acetic acid–M hydrochloric acid, and the resulting 3,4-dihydroxy compound **16** was mesylated, to afford **17**. Treatment of this mixed ester with an excess of sodium methoxide gave the 1,6-dihydroxy derivative **18** as an intermediate that underwent spontaneous ring-closure, affording 1,4:3,6-dianhydro-2,5-diazido-2,5-dideoxy-L-mannitol (**19**) as a pale-yellow syrup. In biological testing, this compound showed a hypnotic effect of the same order as that of Doriden®.

This favorable result prompted the synthesis of the D-mannitol antipode **27**. For a synthesis analogous to that described for the L-mannitol isomer **19**, the very expensive L-mannitol would have been needed. To avoid this problem, a different synthetic approach, starting from D-mannitol, was evolved. To retain the D configuration, the 2- and 5-azido groups had to be introduced by double inversion, and the anhydro rings had to be formed without inversion, demanding free hydroxyl groups at C-3 and C-4, and leaving groups at C-1 and C-6. As the starting material, compound **14** was again used; it was converted into the known[10] L-iditol diepoxide **20**. The oxirane rings were cleaved by using benzoic acid–sodium benzoate in *N*,*N*-dimethylformamide, to yield the 1,6-dibenzoate **21** which was converted into the 2,5-ditosylate **22**. As the replacement of the tosyloxy groups by azide is not sterically hindered, the reaction required only 1 h at 120° in *N*,*N*-dimethylformamide to be complete. The 3,4-*O*-isopropylidene group of the resulting 2,5-diazido-D-mannitol derivative **23** was split off, to yield the crystalline 3,4-dihydroxy compound **24** in a yield of 85%. The terminal benzoyl groups were removed by Zemplén deacylation, and the 1,3,4,6-tetraol **25** obtained was partially tosylated, at the terminal hydroxyl groups. The resulting, crude ditosylate **26** was converted (without purification), by treatment with an excess of sodium methoxide, into 1,4:3,6-dianhydro-2,5-diazido-2,5-dideoxy-D-mannitol (**27**), which was obtained as a homogenous syrup. The optical rotations of the supposed antipodes were in good agreement (−343° for **19**, and +338° for **27**), but their fused, five-membered ring-structures had to be proved, as antipodes having





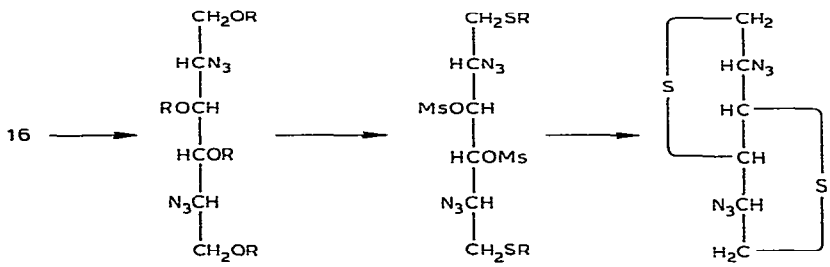
1,3:4,6-situated, four-membered rings could be formed from both precursors (the 3,4-dimesylate **18**, as well as the 1,6-ditosylate **26**). The presence of two fused, five-membered rings in compounds **19** and **27** was established unambiguously by ^{1}H-n.m.r. investigation (see later).

The D-mannitol isomer **27** was completely inactive in biological testing, and consequently, the hypnotic activity of the 2,5-diazido-dianhydro-hexitols is strictly stereospecific.

It was of further interest to explore the steric requirements of this biological activity; that is, whether the presence of the anhydro rings, which keep the two azido groups in a fairly rigid, steric arrangement, is needed. For this reason, the 2,5-diazido-1,6-dibenzoate **16** was debenzoylated to the corresponding tetraol **28**, containing the two azido groups in an "L-*threo*" arrangement similar to that of the biologically active **19**. This compound was, however, completely inactive. To exclude the influence of the free hydroxyl groups, which might change both the transport and the biological pathway of the molecule, the tetraol **28** was permethylated, but the resulting water-insoluble, lipophilic, tetra-*O*-methyl derivative **29** also showed no activity. From these facts, not only the relative, steric arrangement of the azido groups but also the presence of the anhydro rings seem to be essential requirements for the biological activity.

The relatively low activity of the D-glucitol isomer **10** and the inactivity of the L-iditol derivative **12** suggest that the "diaxial" (di-*endo*) arrangement of the two azido groups in the L-mannitol isomer **19** is a crucial condition for the biological activity. Nevertheless, the skeleton of the molecule must play an important role too, as the D antipode **27**, containing the two azido groups in the identical "diaxial" arrangement, is inactive.

As it is known from the literature that bioisosteres may possess similar activity[11], the synthesis of the dithio analog of **19**, containing sulfur instead of oxygen atoms in the anhydro rings, was decided on, For this purpose, the tetraol **28** was converted into the 1,3,4,6-tetramesylate **30**, the terminal mesyloxy groups of which were selectively replaced by thiobenzoate to give the mixed ester **31**. Treatment of **31** with an excess of sodium methoxide gave the dithiol **32** as an intermediate that underwent spontaneous ring-closure, yielding 1,4:3,6-dianhydro-2,5-diazido-2,5-dideoxy-1(4), 3(6)-dithio-L-mannitol (**33**). This bioisostere of **19** proved, however, to be inactive, probably owing to the sensitivity of the thioether groups towards biological oxidation.



28 R = H
29 R = Me
30 R = Ms

31 R = Bz
32 R = H

33

The ^{1}H-n.m.r. data for the dianhydro-diazido compounds (see Table I) not only proved their structures, but, by intercomparing the data for the different isomers, some conclusions regarding their conformations could be drawn. The L-iditol derivative **12** gave the simplest spectrum, in which H-3,4 appeared as a sharp singlet at 4.55 p.p.m., in accordance with the symmetry of the molecule and the lack of coupling[12,13] with H-2,5. The six other protons appeared as an overlapped multiplet. For the other symmetrical isomers, the D- and L-mannitol derivatives **19** and **27** (which gave identical spectra), the double envelope ($_6EE_1$) conformation* of the fused-ring system would contain two "diaxially" arranged azido groups, and, consequently, the conformational equilibrium is rather shifted towards the twisted ($_5EE_2$) conformation, in which these two groups are "diequatorially" oriented[1]. In accordance with this conformational change, besides the expected coupling between H-3 and H-2 (H-4 and H-5), a long-range coupling between H-3 and H-6,6′ (H-4

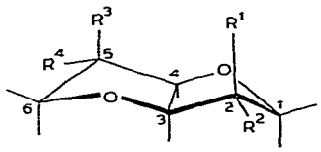
*For a detailed discussion of the conformers theoretically possible, see ref. 1.

TABLE I

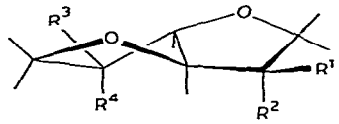
^{1}H-N.M.R.[a] AND I.R.[b] DATA FOR COMPOUNDS **10**, **12**, **19**, **27**, AND **33**

Compound	*H-3*	*H-4*	*Other protons*	ν_{azide} *(cm^{-1})*
10	4.45 d[c]	4.80 t[a]	3.55–4.10 m (6 H)	2110
12	4.55 s		3.70–4.10 m (6 H)	2100
19	4.70 m[e]		3.65–4.25 m (6 H)	2110
27	4.70 m[e]		3.65–4.25 m (6 H)	2120
33	4.25 m[e]		4.88 dd[f] (2 H)	
			2.80–3.45 m (4 H)	2110

[a]On the δ scale, for chloroform-*d* solution; coupling constants are given in Hz. [b]cm^{-1}. [c]$J_{3,4}$ 3. [d]$J_{3,4} \approx J_{4,5} = 3$. [e]Narrow multiplet, with splitting of $\sim 2 + 2$ Hz. [f]$J_{1,2} \equiv J_{5,6} = 3$; $J_{1',2} \equiv J_{5,6'} = 5$; H-2,5.



$_6EE_1$



$_5EE_2$

D-Glucitol derivative 10 $R^1 = R^4 = H, R^2 = R^3 = N_3$

L-Iditol derivative 12 $R^1 = R^3 = H, R^2 = R^4 = N_3$

D-Mannitol derivative 27 $R^1 = R^3 = N_3, R^2 = R^4 = H$

and H-1,1') also appears. As a consequence, the original singlet of H-3,4 is broadened to a narrow multiplet.

The asymmetrical D-glucitol derivative **10** gives a spectrum consistent with the (most stable) $_6EE_1$ conformation. Accordingly, the signals of the chemically different H-3 and H-4 appear separated, at 4.45 and 4.8 p.p.m., respectively. The former signal is a doublet ($J_{3,4}$ 3, $J_{2,3}$ 0 Hz), and consequently, no coupling exists between H-3 and H-2, suggesting the same steric arrangements for these protons as in the L-iditol isomer **12**. On the other hand, the triplet of H-4 suggests a somewhat larger coupling between H-4 and H-5 ($J_{4,5}$ 3 Hz) than that for the mannitol isomers **19** and **27** ($J_{4,5}$ 2 Hz). This is also in agreement with the $_6EE_1$ conformation suggested for **10**, in which only one of the azido groups (that on C-5) is axially oriented, and consequently, no steric strain would be released *via* a $_6EE_1 \rightarrow {}_5EE_2$ shift that simultaneously turns the other azido group (on C-2) into the axial orientation.

EXPERIMENTAL

General methods. — Melting points are uncorrected. All evaporations were conducted in a rotary evaporator under diminished pressure, after the organic solution had been dried with sodium sulfate. The light petroleum used 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: 5:1 (*A*), 1:1 (*B*), 1:2 (*C*), 1:3 (*D*), 1:5 (*E*), and 1:9 (*F*). 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). ^{1}H-N.m.r. spectra (60 MHz) were recorded at room temperature with a JEOL 60-HL spectrometer, and (100 MHz) with a Varian XL-100 F.t.-spectrometer, respectively, for solutions in chloroform-*d*, with tetramethylsilane as the internal standard. I.r. spectra were recorded, for KBr pellets, with a Perkin–Elmer 577 spectrometer.

1,4:3,6-Dianhydro-2,5-diazido-2,5-dideoxy-D-*glucitol* (**10**). — To a stirred solution of the 2,5-dimesylate **6** (45 g) or ditosylate **9** (67.7 g) in dry *N*,*N*-dimethylformamide (1.5 L) was added sodium azide (30 g), and the slurry was boiled for 4.5 h. The mixture was cooled, filtered, and the filtrate evaporated, and the residue was mixed with chloroform (300 mL). The undissolved salts were filtered off, and the filtrate was washed with water, dried, and evaporated. The crude diazide was purified by column chromatography, using solvent *E* for elution. On evaporation, the fractions having R_F 0.40 gave pure **10** as a pale-yellow liquid (23 g, 79%), $[\alpha]_D^{20}$ +170°.

Anal. Calc. for $C_6H_8N_6O_2$: C, 36.73; H, 4.11; N, 42.84. Found: C, 36.89; H, 4.21; N, 42.63.

1,4:3,6-Dianhydro-2,5-diazido-2,5-dideoxy-L-*iditol* (**12**). — To a solution of the dimesylate **1** (45 g) or ditosylate **2** (67.7 g) in dry *N*,*N*-dimethylformamide (1.5 L) was added sodium azide (30 g), and the slurry was stirred for 2 h at 120°. The mixture was processed as described for compound **10**, to give the diazide **12** as a pale-yellow liquid (25 g, 86%), $[\alpha]_D^{20}$ +111°; R_F 0.40 (*E*).

Anal. Calc. for $C_6H_8N_6O_2$: C, 36.73; H, 4.11; N, 42.84. Found: C, 36.86; H, 4.19; N, 42.48.

2,5-Diazido-1,6-di-O-*benzoyl-2,5-dideoxy-3,4*-O-*isopropylidene*-L-*iditol* (**15**). — To a solution of the ditosylate **14** (74 g) in *N*,*N*-dimethylformamide (800 mL) was added sodium azide (16 g), and the slurry was stirred for 1 h at 125°. The resulting, clear solution was evaporated, the residue was dissolved in chloroform (1 L), and the solution washed with water, dried, and evaporated, to give crude **15** (45.3 g, 94.5%) which was pure enough for the next step; $[\alpha]_D^{20}$ +13°; R_F 0.80 (*E*).

Anal. Calc. for $C_{23}H_{24}N_6O_6$: C, 57.49; H, 5.04; N, 17.49. Found: C, 57.62; H, 5.09; N, 17.41.

2,5-Diazido-1,6-di-O-*benzoyl-2,5-dideoxy*-L-*iditol* (**16**). — To a solution of compound **15** (200 g) in acetic acid (1 L) was added M hydrochloric acid (200 mL), and the mixture was heated on a steam bath for 30 min, and cooled. Crushed ice (800 g) was added, and the crystals deposited were filtered off, and successively washed with 50% aqueous acetic acid and water, to yield pure **16** (121 g, 70%), m.p. 128–130°, $[\alpha]_D^{20}$ −10.7°; R_F 0.35 (*D*).

Anal. Calc. for $C_{20}H_{20}N_6O_6$: C, 54.54; H, 4.58; N, 19.08. Found: C, 54.59; H, 4.60; N, 19.05.

1,4:3,6-Dianhydro-2,5-diazido-2,5-dideoxy-L-*mannitol* (**19**). — To a stirred

solution of the dibenzoate **16** (66 g) in dry pyridine (150 mL) was added mesyl chloride (30 mL) during 30 min at +10°. The mixture was kept for 4 h at room temperature, and then processed in the usual way. The dried chloroform solution containing compound **17** as the main component (R_F 0.6, *D*) was concentrated to 500 mL, and treated with 4.65M methanolic sodium methoxide (100 mL). The temperature of the reaction mixture was raised to 40–45° and kept at this temperature for 1 h. The solution was then cooled, washed with water, dried, and evaporated. The residue contained, besides **19** (R_F 0.60), methyl benzoate (R_F 0.95) and an impurity (R_F 0.1); the last two were removed by column chromatography using solvent *D* for elution, to yield pure **19** (16.9 g, 57.5%) as a pale-yellow liquid, $[\alpha]_D^{20}$ −343° (*c* 0.5).

Anal. Calc. for $C_6H_8N_6O_2$: C, 36.73; H, 4.11; N, 42.84. Found: C, 36.52; H, 4.00; N, 42.56.

1,6-Di-O-benzoyl-3,4-O-isopropylidene-L-iditol (**21**). — To a stirred solution of 1,2:5,6-dianhydro-3,4-*O*-isopropylidene-L-iditol (20.74 g) in *N*,*N*-dimethylformamide (2 L) at 120° were added benzoic acid (100 g) and sodium benzoate (60 g). The mixture was stirred for 4 h, cooled, filtered, and the filtrate evaporated. A solution of the residue in ether was successively washed with 5% aqueous sodium hydrogencarbonate, and water, dried, and evaporated, and the residue was purified by column chromatography using solvent *B* for elution. On evaporation, the fractions having R_F 0.85 gave crude **21**, which was recrystallized from ether–light petroleum (94 g, 55%), m.p. 89–91°, $[\alpha]_D^{20}$ +8.8°.

Anal. Calc. for $C_{23}H_{26}O_8$: C, 64.17; H, 6.09. Found: C, 64.14; H, 6.15.

1,6-Di-O-benzoyl-3,4-O-isopropylidene-2,5-di-O-p-tolylsulfonyl-L-iditol (**22**). — To a solution of compound **21** (94 g) in pyridine (500 mL) was added tosyl chloride (130 g), and the mixture was kept for 4 days at room temperature, poured into water, and the precipitated oil extracted into ethyl acetate. The extract was processed in the usual way, to yield, after evaporation, **22** as a syrup (147 g, 90%), which was pure enough for the next step; $[\alpha]_D^{20}$ −67°; R_F 0.85 (*D*).

Anal. Calc. for $C_{37}H_{38}O_{12}S_2$: C, 60.15; H, 5.18; S, 8.68. Found: C, 59.82; H, 5.02; S, 8.32.

2,5-Diazido-1,6-di-O-benzoyl-2,5-dideoxy-3,4-O-isopropylidene-D-mannitol (**23**). — To a stirred solution of the ditosylate **22** (147 g) in *N*,*N*-dimethylformamide (1 L) was added sodium azide (35 g). The mixture was stirred for 1 h at 120°, cooled, and evaporated. The residue was extracted with ethyl acetate, and the extract washed with water, dried, and evaporated. On recrystallization from methanol, the residue gave pure **23** (85.5 g, 88%), m.p. 72–74°, $[\alpha]_D^{20}$ +37.6°; R_F 0.85 (*E*).

Anal. Calc. for $C_{23}H_{24}N_6O_6$: C, 57.49; H, 5.04; N, 17.49. Found: C, 57.40; H, 5.19; N, 17.46.

2,5-Diazido-1,6-di-O-benzoyl-2,5-dideoxy-D-mannitol (**24**). — A solution of **23** (85 g) in acetic acid (400 mL) and M hydrochloric acid (80 mL) was heated on a steam bath for 30 min and then kept for 2 h at room temperature. The precipitated crystals were filtered off, washed successively with cold acetic acid (30 mL) and water, and

dried over potassium hydroxide, to give pure **24** (67 g, 85%), m.p. 189–191° (dec.), $[\alpha]_D^{20}$ −17° (pyridine); R_F 0.5 (*D*). The m.p. was not altered on recrystallization from benzene.

Anal. Calc. for $C_{20}H_{20}N_6O_6$: C, 54.54; H, 4.58; N, 19.08. Found: C, 54.59; H, 4.68; N, 18.99.

2,5-Diazido-2,5-dideoxy-D-*mannitol* (**25**). — A solution of dibenzoate **24** (67 g) in dry methanol (1 L) was treated, in the presence of phenolphthalein, with 4.5M methanolic sodium methoxide to persistent alkalinity, kept for 30 min at 50°, and the reaction monitored by t.l.c. (*A*). When the starting material (R_F 0.95) and the monobenzoate formed (R_F 0.85) had been completely converted into **25** (R_F 0.30), the solution was cooled, made neutral with carbon dioxide, and evaporated. The residue was dissolved in water, and methyl benzoate was removed by extraction with chloroform. The residue obtained on evaporation of the aqueous solution was dissolved in ethyl acetate, the solution dried, the suspension filtered, and the filtrate evaporated. The residue was filtered with the aid of ethyl acetate, to yield pure **25** (30 g, 85%), m.p. 98–100°, $[\alpha]_D^{20}$ −38.5° (water).

Anal. Calc. for $C_6H_{12}N_6O_4$: C, 31.03; H, 5.21; N, 36.20. Found: C, 30.97; H, 5.17; N, 36.14.

1,4:3,6-Dianhydro-2,5-diazido-2,5-dideoxy-D-*mannitol* (**27**). — To a stirred solution of diazide **25** (23.2 g) in pyridine (150 mL) was added tosyl chloride (40 g) during 30 min at +5°. The mixture was kept overnight at room temperature, and then processed in the usual way. The chloroform solution containing the ditosylate **26** as the main component (R_F 0.5, *C*) was concentrated to 300 mL, cooled to +5°, and treated with 5M methanolic sodium methoxide (50 mL). The mixture was kept for 1 h at room temperature, washed with water, dried, and evaporated. The residue was purified by column chromatography, using solvent *D* for elution. The fractions having R_F 0.6 were evaporated, and the residue was extracted with carbon tetrachloride. The insoluble component (having the same R_F value) was filtered off, and the filtrate was evaporated, to yield pure **27** (7.65 g, 39%), $[\alpha]_D^{20}$ +338°.

Anal. Calc. for $C_6H_8N_6O_2$: C, 36.73; H, 4.11; N, 42.84. Found: C, 36.59; H, 4.00; N, 42.73.

2,5-Diazido-2,5-dideoxy-L-*iditol* (**28**). — A solution of the 1,6-dibenzoate **16** (12 g) in dry methanol (120 mL) was treated, in the presence of phenolphthalein, with 4.5M methanolic sodium methoxide to persistent alkalinity. The mixture was kept for 4 h at room temperature, made neutral with solid carbon dioxide, and evaporated. The residue was dissolved in water, and the solution extracted twice with carbon tetrachloride to remove the methyl benzoate. The aqueous layer was evaporated, the residue was dissolved in ethyl acetate (100 mL), and the solution dried, and concentrated to 20 mL. On cooling, the diazide **28** crystallized out. Evaporation of the mother liquor afforded a second crop. Recrystallization of the combined material from ethyl acetate (20 mL) gave pure **28** (5 g, 79%), m.p. 90–92°, $[\alpha]_D^{20}$ +11.4° (water); R_F 0.35 (*A*).

Anal. Calc. for $C_6H_{12}N_6O_4$: C, 31.03; H, 5.21; N, 36.20. Found: C, 31.11; H, 5.26; N, 36.13.

2,5-Diazido-2,5-dideoxy-1,3,4,6-tetra-O-*methyl*-L-*iditol* (**29**). — To a stirred solution of diazide **28** (4.65 g) in acetone (120 mL) were simultaneously added dropwise a solution of sodium hydroxide (12 g) in water (12 mL) and dimethyl sulfate (12 mL) during 2 h at 40°. Stirring was continued for 1 h at 50°, and then water (100 mL) was added, and the mixture was stirred for 2 h at 50°. The solution was concentrated to about half its volume, and extracted with chloroform (2 × 50 mL). The extract was washed with water, dried, and evaporated, to give pure **29** (5.4 g, 94%), $[\alpha]_D^{20}$ +38°; R_F 0.65 (*D*).

Anal. Calc. for $C_{10}H_{20}N_6O_4$: C, 41.66; H, 6.99; N, 29.15. Found: C, 41.40; H, 6.82; N, 28.85.

2,5-Diazido-2,5-dideoxy-1,3,4,6-tetra-O-(*methylsulfonyl*)-L-*iditol* (**30**). — To a stirred solution of diazide **28** (7 g) in dry pyridine (80 mL) at +20° was added mesyl chloride (15 mL) during 30 min. The mixture was kept for 4 h at room temperature, and then processed in the usual way, to give, after evaporation, compound **30** as a colorless syrup (15.4 g, 94%), $[\alpha]_D^{20}$ +5.7° (pyridine); R_F 0.35 (*B*).

Anal. Calc. for $C_{10}H_{20}N_6O_{12}S_4$: C, 22.06; H, 3.70; N, 15.44; S, 23.56. Found: C, 21.88; H, 3.45; N, 15.12; S, 23.31.

1,4:3,6-Dianhydro-2,5-diazido-2,5-dideoxy-1(4),3(6)-dithio-L-*mannitol* (**33**). — A solution of tetramesylate **30** (47 g) and potassium thiobenzoate (36 g) in acetone (1.5 L) was boiled on a steam bath for 1 h, cooled, the mixture filtered, and the filtrate evaporated. A solution of the residue in chloroform was washed with water, dried, and concentrated to 500 mL. This solution, containing the 1,6-bis(thiobenzoate) **31** as the main component (R_F 0.50, *D*), was treated with 4.65M methanolic sodium methoxide (50 mL), and kept for 15 min at 40°. It was then washed with water, dried, and evaporated. The resulting, semicrystalline material was filtered off with the aid of carbon tetrachloride, to give, after two recrystallizations from benzene, pure dithiodianhydride **33** (7.25 g, 37%), m.p. 171–173°, $[\alpha]_D^{20}$ −183.4°; R_F 0.85 (*F*).

Anal. Calc. for $C_6H_8N_6S_2$: C, 31.56; H, 3.53; N, 36.81; S, 28.09. Found: C, 31.62; H, 3.59; N, 36.72; S, 27.88.

ACKNOWLEDGMENTS

The authors are indebted to I. Pelczer for the evaluation of the n.m.r. spectra, and to Drs. F. Andràsi and P. Berzsenyi for the biological data.

REFERENCES

1 J. KUSZMANN AND G. MEDGYES, *Carbohydr. Res.*, 64 (1978) 135–142.
2 R. C. HOCKETT, H. G. FLETCHER, JR., E. L. SHEFFIELD, AND R. M. GOEPP, JR., *J. Am. Chem. Soc.*, 68 (1946) 927–930, 930–935.
3 L. F. WIGGINS AND D. J. C. WOOD, *J. Chem. Soc.*, (1951) 1180–1184.
4 N. K. MATHESON AND S. J. ANGYAL, *J. Chem. Soc.*, (1952) 1133–1138.
5 A. C. COPE AND T. Y. SHEN, *J. Am. Chem. Soc.*, 78 (1956) 3177–3181, 5912–5916.

6 J. A. MILLS, *Adv. Carbohydr. Chem.*, 10 (1955) 1–53.
7 R. MONTGOMERY AND L. F. WIGGINS, *J. Chem. Soc.*, (1946) 393–396.
8 V. G. BASHFORD AND L. F. WIGGINS, *J. Chem. Soc.*, (1950) 371–374.
9 P. BRIGL AND H. GRÜNER, *Ber.*, 67 (1934) 1969–1973.
10 L. VARGHA AND E. KASZTREINER, *Chem. Ber.*, 92 (1959) 2506–2515.
11 E. SCHRÖDER, C. RUFER, AND R. SCHMIECHEN, *Arzneimittelchemie*, Vol. I, Thieme Verlag, Stuttgart, 1976, p. 33.
12 P. SOHÁR AND J. KUSZMANN, *Org. Magn. Reson.*, 6 (1974) 407–412.
13 P. SOHÁR, G. MEDGYES, AND J. KUSZMANN, *Org. Magn. Reson.*, 11 (1978) 357–359.