Branched-chain Sugars. Part 14.† Synthesis of New Branched-chain Cyclitols having *myo*- or *scyllo*-, and *muco*-Configuration from 3-*O*-Benzyl-5,6-dideoxy-5-*C*-(1,3-dithian-2-yl)-6-nitro-L-idofuranose and -D-glucofuranose

By **Masuo Funabashi** *‡ and **Juji Yoshimura**, Laboratory of Chemistry for Natural Products, Faculty of Science, Tokyo Institute of Technology, Nagatsuta, Midori-ku, Yokohama 227, Japan

Michael addition of 2-lithio-1,3-dithian to 3-*O*-benzyl-5,6-dideoxy-1,2-*O*-isopropylidene-6-nitro-α-D-*xylo*-hex-5-enofuranose (1) gives 3-*O*-benzyl-5,6-dideoxy-5-*C*-(1,3-dithian-2-yl)-1,2-*O*-isopropylidene-6-nitro-β-L-idofuranose (2) and -α-D-glucofuranose (3) in the ratio 4 : 3, respectively. Removal of the isopropylidene group and intramolecular cyclization in weak basic conditions gives branched-chain cyclitols having *myo*- or *scyllo*-configuration from (2) and *muco*-configuration from (3). The mechanism of cyclization is discussed.

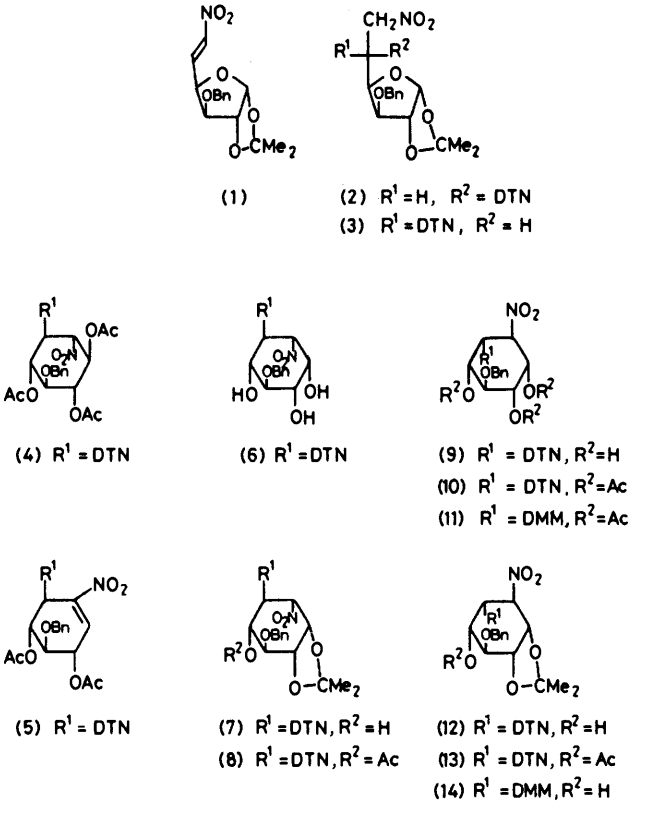
SOME biologically active branched-chain cyclitols and analogous compounds such as validamycin A,[1] crotepoxide,[2] simmondsin,[3] and glyoxylase I inhibitor[4] as well as rancinamycin[5] have successively been found, whereas there are few methods available for the synthesis of such optically active branched-chain cyclitols.

As part of a series of synthetic and stereochemical studies on branched-chain sugars and cyclitols,[6] we now describe a simple procedure for the synthesis of optically active branched-chain *myo*- or *scyllo*-, and *muco*-nitroinositol derivatives by (i) the Michael addition of 2-lithio-1,3-dithian[7] to 3-*O*-benzyl-5,6-dideoxy-1,2-*O*-isopropylidene-6-nitro-α-D-*xylo*-hex-5-enofuranose,[6] (ii) removal of the isopropylidene group, and (iii) intramolecular cyclization of 3-*O*-benzyl-5,6-dideoxy-5-*C*-(1,3-dithian-2-yl)-6-nitro-L-idofuranose and -D-glucofuranose in weak basic conditions.

Several methods have been reported so far for the introduction of carbon-branching into inositols: the Grignard reaction or diazoalkane condensation to several inososes,[8] nitroethane condensation with 1,5-dialdehyde,[9] the Diels–Alder reaction for the synthesis of DL-pseudosugars,[10] an unusual cyclization of bis(diazo)ketone,[11] and syntheses of DL-crotepoxide.[12] Unfortunately, the former two methods are limited mainly for the introduction of R–C(–)(–)–OH (R = alkyl), and the latter four methods are not always practicable, especially in view of the synthesis of optically active branched-chain cyclitols having carbon-branching such as RCH_2–C(–)–H (R = H or OH).

We have therefore tried to develop a simple method to obtain potentially versatile compounds for the synthesis of optically active pseudosugar-type cyclitols.

It is known[13] that 6-deoxy-6-nitro-D-glucose and -L-idose cyclize easily in basic conditions to give an equilibrium mixture of *myo*-, *scyllo*-, and *muco*-nitroinositols, in which the formation ratio of these two or three inositols is kinetically or thermodynamically controlled. It would therefore be reasonable to think that introduction of a bulky substituent instead of the hydroxy-group at C-5 of 6-deoxy-6-nitro-D-glucose or -L-idose would control or limit the stereochemistry of intramolecular cyclization of nitroalkanecarbaldehyde between C-6 and -1. Theoretically, a *scyllo*- or *myo*-inositol derivative would be expected from the 5,6-dideoxy-5-*C*-substituted-6-nitro-L-idose derivative (2), compared to a *muco*- or a *chiro*-inositol derivative from the corresponding 6-deoxy-6-nitro-D-glucose (3), presupposing that both a nitro-group and a bulky carbon-branching occupy predominantly equatorial orientations. From a thermodynamic point of view, however, *scyllo*- and



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‡ *Present address:* Chiba University, College of Arts and Sciences, Yayoi-cho, Chiba-shi 280, Japan.

muco-inositol, respectively, could be expected to be preferentially formed. In fact, the following data support this speculation. Although the introduction of an alkyl group at C-5 of 6-nitro-hexoses is not easy, this could be overcome by Michael addition of 2-lithio-1,3-dithian to 3-*O*-benzyl-5,6-dideoxy-1,2,-*O*-isopropylidene-6-nitro-α-D-*xylo*-hex-5-enofuranose (1). The reaction of (1) with 1.2 mol equiv. of 2-lithio-1,3-dithian at −45 to −50 °C in dry tetrahydrofuran gave 3-*O*-benzyl-5,6-dideoxy-5-*C*-(1,3-dithian-2-yl)-1,2-*O*-isopropylidene-6-nitro-β-L-idofuranose (2) and -α-D-glucofuranose (3) in 60% yield, the ratio (2) : (3) being *ca.* 4 : 3 (n.m.r., g.l.c.). Both n.m.r. spectra were very similar, and they gave no information on the configuration at C-5. The intramolecular cyclization between C-1 and C-6 of (2) and (3), however, clearly demonstrates that (2) and (3) correspond to the L-*ido*- and D-*gluco*-isomers, respectively. Though the L-*ido*-isomer should give *scyllo*- and/or *myo*-inositol derivatives, the following experiment shows that the basic condition of the reaction might control the stereochemistry of the cyclization reaction kinetically or thermodynamically.

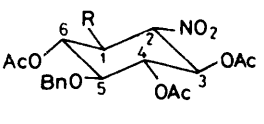
Hydrolysis of the 1,2-*O*-isopropylidene group of (2) with 90% trifluoroacetic acid at room temperature or by refluxing (2) in 75% acetic acid, and treatment of the free sugar with an equimolar amount of sodium carbonate in aqueous methanol at room temperature for 15 h gave a syrupy mixture showing two main spots on t.l.c. The less polar component showed i.r. absorptions typical of a nitro-olefin (at 1 650 and 1 520 cm^{-1}). The syrupy mixture was further acetylated with acetic anhydride in the presence of toluenesulphonic acid to give a crystalline triacetate (4) and a syrupy nitro-olefin diacetate (5) in the ratio *ca.* 1 : 1. N.m.r. data of the triacetate (4) (Table) clearly demonstrate that (4) must be a *scyllo*-inositol derivative since all coupling constants of the ring protons were 7.5—10 Hz, indicating a *trans*-diaxial relationship in a rigid chair conformation. The chemical shifts of the acetoxy-protons [14] (δ 1.85, 1.88, and 2.00; all equatorial) also support this conclusion. In other words, the stereochemical relationship between C-4 and -5 of (2) should be *threo*, and hence the L-idose derivative has structure (2).

On the other hand, when the free sugar of (2) was

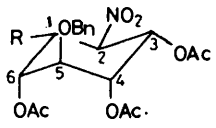
N.m.r. data of branched-chain *scyllo*-, *myo*-, and *muco*-nitroinositol derivatives

Compound		H-1	H-2	H-3	H-4	H-5	H-6	H-1′	Acetyl	Isopropyl
(4)	δ	2.95	5.06	5.61	5.15	3.70	5.43	3.98	1.88	
(*scyllo*)									1.95	
		td	t	q	t	t	q	d	2.00	
	J	10	10	7.5	7.5	7.5	$J_{1,6}$ 10			
(8)	δ	3.21	5.25	4.83	4.42	3.79	5.44	4.44	2.10	1.30
(*myo*)										1.53
		o	q	q	o	t	s	d		
	J	12	3.2	7.0	3.0	2.4		$J_{1,6}$ 5.6, $J_{4,6}$ 1.6		
(10)	δ	3.20	5.35	5.70	~5.5	3.78	~5.5	4.13	1.97	
(*muco*)									2.05	
		o	t	d		t		d	2.09	
	J	10.5	10.5	3.0	2.5	2.5		$J_{1,6}$ 2.5		
(12)	δ	2.88	5.10	~4.6	4.34	3.98	~4.6	4.23		1.32
(*muco*)										1.55
		o	q	q	q	t	q	d		
	J	12.0	8.0	3.7	2.5	2.0		$J_{1,6}$ 2.5		
(14)	δ	2.60	4.88	4.61	~4.4	3.95	~4.3	~4.4		1.31
(*muco*)										1.52
		o	q	q		q				
	J	12.5	9.0	3.8	2.5	2.0		$J_{1,6}$ 2.5		

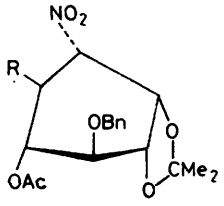
J Values quoted in Hz; d = doublet, t = triplet, q = quartet, s = sextet, o = octet



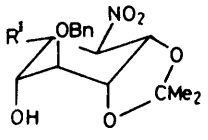
(4)



(10)



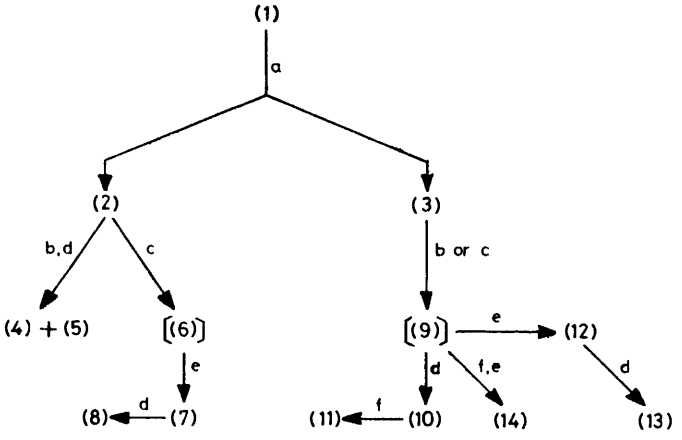
(8) R = DTN



(12) R^1 = DTN
(13) R = DMM

subjected to similar cyclization in the presence of sodium hydrogen carbonate, a *myo*-inositol derivative (6) was predominantly formed. Acetylation of (6) in the presence of boron trifluoride–ether or toluene-*p*-sulphonic acid failed to give the corresponding triacetate, but a nitro-olefin diacetate (5). Acetonation of (6) with a mixture of acetone and dimethoxypropane in the presence of toluene-*p*-sulphonic acid and anhydrous copper(II) sulphate, however, gave the corresponding mono-*O*-isopropylidene derivative (7) in good yield. Acetylation of (7) gave a crystalline monoacetate (8), seemingly having a twist-boat comformation.

Similar cyclization of (3) was also effected in the presence of sodium carbonate or sodium hydrogen carbonate to afford a *muco*-inositol derivative (9) in good yield. N.m.r. parameters of the triacetate (10) (Table) disclose that H-1, -2, and -3 are all axial while the others are all equatorial. Thus it is clear that compound (10)

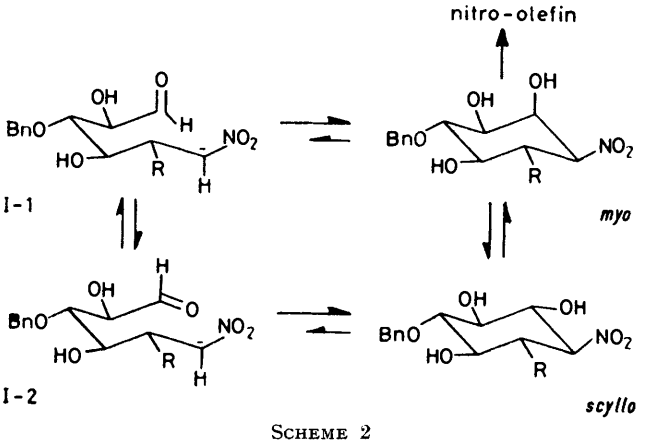


SCHEME 1 Reagents: a, 1,3-dithian–Bu^{n}Li; b, aq. Na_2CO_3–MeOH; c, aq. $NaHCO_3$–MeOH; d, Ac_2O–TsOH; e, 2,2-dimethoxypropane–TsOH; f, HgO–$HgCl_2$–BF_3OEt_2–MeOH

has the typical rigid chair conformation of *muco*-inositol (aaaeee). Furthermore, the chemical shifts of the acetoxy-methyl protons (at δ 1.97, 2.05, and 2.09) also support the presence of one equatorial and two axial acetoxy-groups. Thus, a D-*gluco*-configuration can be assigned to compound (3). Another isomer, a *chiro*-inositol derivative, was not isolated.

On the other hand, acetonation of (9) with the same procedure as mentioned above gave the 3,4-*O*-isopropylidene derivative (12) in excellent yield. Acetal exchange of the dithian group of (10) and (12) with methanol in the presence of mercuric chloride was efficiently effected to give the corresponding dimethylacetal derivatives (11 and 14). The reaction sequence is shown in Scheme 1.

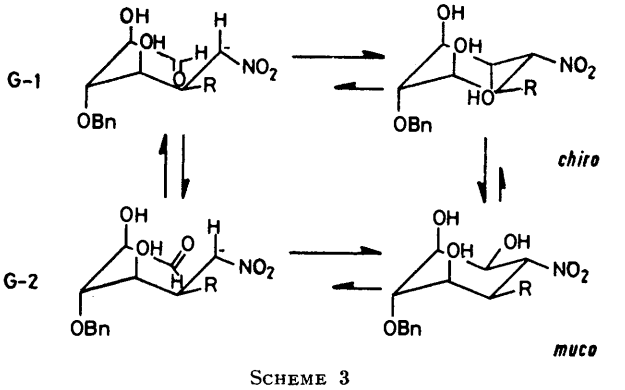
Although there are no clear explanations at present for the reasons why such different basic conditions of cyclization (aq. $NaHCO_3$–MeOH, pH 10 ± 0.5; aq. Na_2CO_3–MeOH, pH 12 ± 0.5) do influence the stereochemistry of the cyclization of (2), and not that of (3), these phenomena could be understood on the following assumptions: (i) the *myo*-inositol derivative (6) is a kinetically-controlled product and epimerization to the *scyllo*-inositol derivative is very slow at low pH but faster at higher pH, where the *myo*-inositol derivative is more labile than the *scyllo*-derivative, giving a nitro-olefin, and (ii), in the case of (3), the *muco*-inositol derivative is



SCHEME 2

both a kinetically- and thermodynamically-controlled product and rather stable in such a basic condition (pH 10—12).

Schemes 2 and 3 are helpful in understanding the transition state of cyclization of (2) and (3). In the case of (2), an acyclic conformation I-1 seems to be more favoured than I-2 to give a *myo*-inositol derivative kinetically. In the case of (3), an acyclic conformation G-2 seems to be more favoured than G-1, because G-2 has no crucial 1,3-non-bonded interaction between the *O*-benzyl and the carbonyl group. Therefore, a *muco*-inositol derivative forms much faster, and does not epimerize to the thermodynamically unstable chiro-inositol derivative.



SCHEME 3

EXPERIMENTAL

Melting points were determined on a Yanagimoto micro-melting-point apparatus. Solvents were evaporated off *in vacuo* below 40 °C. N.m.r. spectra (100 MHz) were recorded with a JNM-PS-100 spectrometer in solutions of deuteriochloroform with tetramethylsilane as internal reference. Optical rotations were measured with a Carl Zeiss LEP A1 spectrophotometer using a 0.5 dm tube. T.l.c. and preparative t.l.c. were effected on silica gel

(Merck type 60) with the following solvent systems: A, 2 : 1 benzene/ethyl acetate; B, 8 : 1 benzene/ethyl acetate.

3-O-*Benzyl*-5,6-*dideoxy*-5-C-(1,3-*dithian*-2-*yl*)-1,2,O-*isopropylidene*-6-*nitro*-β-L-*idofuranose* (2) and -α-D-*glucofuranose* (3).—To a solution of (1) (3.2 g, 10 mmol) in dry tetrahydrofuran (15 ml) cooled at −45 °C was added a solution of 2-lithio-1,3-dithian prepared at −45 °C from 1,3-dithian (1.68 g) and butyl-lithium (10% solution in hexane, 7.7 ml, 14 mmol) in dry tetrahydrofuran (20 ml). The reaction mixture was kept at −45 °C for 45 min and then acidified with acetic acid. Work-up gave a crude syrup (4.8 g) which was washed three times with hot hexane, and then treated with methanol to deposit crystals (1.5 g). Recrystallization from ethanol gave fine *needles* of (2), m.p. 165—166°, $[\alpha]_D^{22}$ −34° (*c* 1.0, acetone), $\nu_{max.}$ 1 550 and 1 365 cm^{-1} (C–NO_2), δ 1.27, 1.46 (s, 6 H, isopropyl), 1.6—2.2 and 2.6—2.9 (m, 6 H, dithian-methylene), 3.45 (m, 1 H, H-5), 4.00 (d, 1 H, H-3, $J_{3,4}$ 3.2 Hz), 4.15 (d, 1 H, H-5′, $J_{5,5'}$ 5.0 Hz), 4.31—4.82 (m, 4 H, H-2, H-4, and benzyl), 5.88 (d, 1 H, H-1, $J_{1,2}$ 3.8 Hz), and 7.2—7.45 (m, 5 H, phenyl). (Found: C, 54.4; H, 6.15; N, 3.1. $C_{20}H_{27}NO_6S_2$ requires C, 54.42; H, 6.17; N, 3.17%).

The residue after evaporation of the filtrate of (2) was then purified by chromatography on a silica gel (Wako-gel C-200, 50 g) column to give a syrup (1.3 g), a portion of which was purified (preparative t.l.c.) to yield the *glucofuranose* (3); $[\alpha]_D^{22}$ −45° (*c* 1.3, acetone), $\nu_{max.}$ 1 550 and 1 370 cm^{-1} (C–NO_2), δ 1.31, 1.48 (s, 6 H, isopropyl), 1.6—2.2 and 2.5—2.9 (m, 6 H, dithian-methylene), 3.36 (m, 1 H, H-5), 3.97 (d, 1 H, H-5′, $J_{5,5'}$ 5.0 Hz), 4.00 (d, 1 H, H-3, $J_{3,4}$ 3.2 Hz), 4.35—4.80 (m, 4 H, H-2, H-4, and benzyl), 5.87 (d, 1 H, H-1, $J_{1,2}$ 3.8 Hz), and 7.3—7.5 (m, 5 H, phenyl). (Found: C, 54.15; H, 6.45; N, 3.0%).

Conversion of (2) *into* 1L-(1,3,5/2,4,6)-3,4,6-*tri*-O-*acetyl*-5-O-*benzyl*-2-*nitro*-3,4,5,6-*tetrahydroxycyclohexanecarbaldehyde propylene dithioacetal* (4) and 1L-(1,5/4,6)-4,6-*di*-O-*acetyl*-5-O-*benzyl*-2-*nitro*-4,5,6-*trihydroxycyclohex*-2-*enecarbaldehyde propylene dithioacetal* (5).—A solution of (2) (300 mg, 0.68 mmol) in 75% acetic acid (18 ml) was refluxed for 2.5 h and concentrated to a pale yellow syrup (270 mg), which was then dissolved in a mixture of methanol (20 ml) and aqueous sodium carbonate (2%, 6 ml). The solution was kept at room temperature overnight and deionized with IR-120 (H^+). The resin was then removed by filtration and washed with methanol. The filtrate and washings were concentrated to a syrup (250 mg, two spots on t.l.c.), which was then treated with acetic anhydride in the presence of toluene-*p*-sulphonic acid at room temperature overnight. After the usual work-up, the syrup obtained was subjected to preparative t.l.c. (solvent system B) to give a crystalline *scyllo*-inositol derivative (4) (100 mg, 30%), which was recrystallized from ethanol; m.p. 208—210°, $[\alpha]_D^{22}$ −6.7° (*c* 1.0, acetone) (Found: C, 52.4; H, 5.45; N, 2.75. $C_{23}H_{29}O_9NS_2$ requires C, 52.37; H, 5.52; N, 2.66%. An amorphous nitro-olefin (5) (90 mg, 31%) was separated along with (4) as the less polar component; $[\alpha]_D^{22}$ −45° (*c* 1.0, acetone) (Found; C, 53.75; H, 5.5; N, 2.95. $C_{21}H_{25}O_7NS_2$ requires C, 53.96; H, 5.39; N, 3.00%).

1L-(1,5/2,3,4,6)-5-O-*Benzyl*-3,4-O-*isopropylidene*-2-*nitro*-3,4,5,6-*tetrahydroxycyclohexanecarbaldehyde propylene dithioacetal* (7) and 1L-(1,5/2,3,4,6)-6-O-*acetyl*-5-O-*benzyl*-3,4-O-*isopropylidene*-2-*nitro*-3,4,5,6-*tetrahydroxycyclohexanecarbaldehyde propylene dithioacetal* (8).—The hydrolyzed syrup (250 mg, 0.62 mmol) obtained as above from (2) was dissolved in a mixture of methanol (20 ml) and water (6 ml) containing sodium hydrogen carbonate (135 mg, 1.6 mmol), kept at room temperature for 12 h, and deionized with IR-120. The resin was removed by filtration and washed twice with methanol. The filtrate and washings were concentrated to a hard syrup (220 mg) [R_F 0.42 (major) and 0.58 (minor) on t.l.c. (solvent system A)]. The major component was isolated with preparative t.l.c. (solvent system A) to give a clear syrup (6) (150 mg). A solution of (6) (150 mg) in dry acetone (5 ml) and 2,2-dimethoxypropane (5 ml) was then stirred in the presence of a catalytic amount of toluene-*p*-sulphonic acid and anhydrous copper(II) sulphate (100 mg) at room temperature for 20 h. The insoluble material was filtered off and the filtrate was immediately concentrated to a pale brown syrup, which was dissolved in chloroform, and washed with aqueous sodium hydrogen carbonate. The chloroform layer was washed with aqueous sodium chloride and water, dried ($MgSO_4$), and concentrated to a syrup. A portion (100 mg) was subjected to preparative t.l.c. to give (7) (70 mg); $[\alpha]_D^{24}$ −9.3° (*c* 1.14, $CHCl_3$). On the other hand, another part of the syrup (50 mg) was treated with acetic anhydride (3 ml) in the presence of toluene-*p*-sulphonic acid overnight at room temperature. After the usual work-up, the crystalline *monoacetate* (8) was obtained; m.p. 188—189° (from EtOH), $[\alpha]_D^{24}$ −25° (*c* 1.0, acetone) (Found: C, 54.45; H, 6.15; N, 2.8. $C_{22}H_{29}O_7S_2$ requires C, 54.65; H, 6.05; N, 2.90%).

1L-(2,5/1,3,4,6)-3,4,6-*Tri*-O-*acetyl*-5-O-*benzyl*-2-*nitro*-3,4,5,6-*tetrahydroxycyclohexanecarbaldehyde propylene dithioacetal* (10).—A suspension of (3) (220 mg, 0.5 mmol) in 75% acetic acid (12 ml) was refluxed for 2.5 h, and concentrated to a pale yellow syrup, which was then dissolved in methanol (15 ml) and aqueous sodium carbonate (2%; 5 ml). The mixture was then kept at room temperature for 15 h and deionized with IR-120. The resin was removed by filtration, washed with methanol, and concentrated to a crude syrup (9) (200 mg). A solution of the syrup in acetic anhydride (5 ml) was kept in the presence of toluene-*p*-sulphonic acid at room temperature overnight, then poured into ice–water containing sodium hydrogen carbonate and extracted with chloroform. The extracts were then washed with water, dried ($MgSO_4$), and evaporated to a syrupy mass, which was finally subjected to preparative t.l.c. (solvent system B) to give a crystalline residue (120 mg). Recrystallization from ethanol gave *needles*, m.p. 187—188°, $[\alpha]_D^{22}$ +33° (*c* 1.18, $CHCl_3$) (Found: C, 52.5; H, 5.5; N, 2.6. $C_{23}H_{29}NO_9S_2$ requires C, 52.37; H, 5.52; N, 2.66%).

1L-(2,5/3,4,6)-3,4,6-*Tri*-O-*acetyl*-5-O-*benzyl*-2-*nitro*-3,4,5,6-*tetrahydroxycyclohexanecarbaldehyde dimethyl acetal* (11).—A mixture of compound (9) (50 mg), mercuric oxide (50 mg), mercuric chloride (100 mg), and boron trifluoride–ether (15 mg) in dry methanol (3 ml) and methyl orthoformate (3 ml) was stirred at room temperature for 24 h. The insoluble materials were filtered off and washed with methanol (5 ml × 2). The filtrate and washings were concentrated to a pale yellow syrup, which was immediately dissolved in chloroform, and washed with aqueous sodium hydrogen carbonate. The chloroform layer was then washed with aqueous sodium chloride, dried ($MgSO_4$), and concentrated to a syrup. Purification with preparative t.l.c. (solvent system B) gave the *dimethylacetal* (11) (30 mg); $[\alpha]_D^{22}$ +2.5° (*c* 1.0, acetone) (Found: C, 54.5; H, 6.2; N, 2.75. $C_{22}H_{29}O_{11}N$ requires C, 54.65; H, 6.05; N, 2.88%).

1L-(2,5/1,3,4,6)-5-O-*Benzyl*-3,4,O-*isopropylidene*-2-*nitro*-3,4,5,6-*tetrahydroxycyclohexanecarbaldehyde propylene dithioacetal* (12) *and* 1L-(2,5/1,3,4,6)-6-O-*acetyl*-5-O-*benzyl*-3,4-O-*isopropylidene*-2-*nitro*-3,4,5,6-*tetrahydroxycyclohexanecarbaldehyde propylene dithioacetal* (13).—The syrup (9) (100 mg) was dissolved in acetone (3 ml) and 2,2-dimethoxypropane (3 ml) and kept at room temperature for 24 h in the presence of toluene-*p*-sulphonic acid (23 mg) and copper(II) sulphate (50 mg). The insoluble materials were filtered off and washed with acetone (2 × 5 ml). The filtrate and washings were concentrated to a brown syrup, which was immediately dissolved in chloroform and washed with aqueous sodium hydrogen carbonate. The chloroform layer was further washed with aqueous sodium chloride, dried ($MgSO_4$), and concentrated to a crystalline residue. Recrystallization from ethanol gave fine *needles* of (12) (70 mg), m.p. 183—184°, $[\alpha]_D^{22}$ −36° (*c* 1.0, acetone) (Found: C, 54.85; H, 6.35; N, 3.15. $C_{20}H_{27}O_6NS_2$ requires C, 54.42; H, 6.17; N, 3.17%).

Acetylation of (12) (50 mg) with acetic anhydride (3 ml) in the presence of toluene-*p*-sulphonic acid gave the *monoacetate* (13) (40 mg), m.p. 147—148° (Found: C, 54.6; H, 5.95; N, 3.0. $C_{22}H_{29}O_7NS_2$ requires C, 54.65; H, 6.05; N, 2.90%).

1L-(2,5/1,3,4,6)-5-O-*Benzyl*-3,4-O-*isopropylidene*-2-*nitro*-3,4,5,6-*tetrahydroxycyclohexanecarbaldehyde dimethyl acetal* (14).—A mixture of the syrup (9) (160 mg, 0.4 mmol), mercuric oxide (190 mg, 0.88 mmol), and mercuric chloride (250 mg, 0.92 mmol) in absolute methanol (10 ml) was stirred at room temperature for 24 h in the presence of boron trifluoride–ether (*ca.* 10 mg). The insoluble materials were then filtered off, and the filtrate was concentrated to a pale brown syrup, which was then dissolved in dry acetone (2 ml) and 2,2-dimethoxypropane (3 ml). The solution was kept at room temperature for 5 h in the presence of toluene-*p*-sulphonic acid and anhydrous copper(II) sulphate (300 mg). Work-up as for (12) and recrystallization from ethanol gave *needles*, m.p. 122—123°, $[\alpha]_D^{18}$ −70.9° (*c* 1.01, CCl_4) (Found: C, 57.2; H, 6.9; N, 3.65. $C_{19}H_{27}O_8N$ requires C, 57.42; H, 6.85; N, 3.52%).

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