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STEREOSELECTIVE SYNTHESIS OF THE THERMODYNAMICALLY LESS STABLE *manno* ISOMERS FROM A NITRO SUGAR*

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ABSTRACT

Reaction of methyl 4,6-*O*-benzylidene-2,3-dideoxy-3-nitro-α-D-*erythro*-hex-2-enopyranoside (**2**) with hydrazoic acid, hydrogen cyanide, theophylline, and 2,6-dichloropurine under weakly acidic or neutral conditions resulted in the stereoselective formation of addition products having the thermodynamically less-stable *manno* configuration, whereas reaction of **2** with more-basic reagents yielded mainly products having the more stable *gluco* configuration.

INTRODUCTION

We have reported in preliminary form[1] the synthesis of compounds having the *manno* configuration from methyl 4,6-*O*-benzylidene-2,3-dideoxy-3-nitro-α-D-*erythro*-hex-2-enopyranoside (**2**) and weak acids. This paper describes complete experimental details of this research and, in addition, the remarkable solvent-effects on the reaction of **2** with hydrazoic acid.

Nucleophilic addition to a carbon–carbon double bond activated by an electron-withdrawing group is well known to produce mainly the thermodynamically more-stable product, as the reaction is reversible under conventional conditions[2]. This is especially the case with nitroalkene derivatives, owing to the effects of strong electron-withdrawal[3]†. However, if a nucleophile is added to the double bond under weakly acidic or neutral conditions, the reversible reaction might be suppressed and the addition would thus afford the kinetically controlled product. On the basis of this expectation, we have studied the reaction of nitroalkene **2** with such weak acids as hydrazoic acid or 2,6-dichloropurine, and have found that the less-stable *manno* isomers are indeed obtained in good yields.

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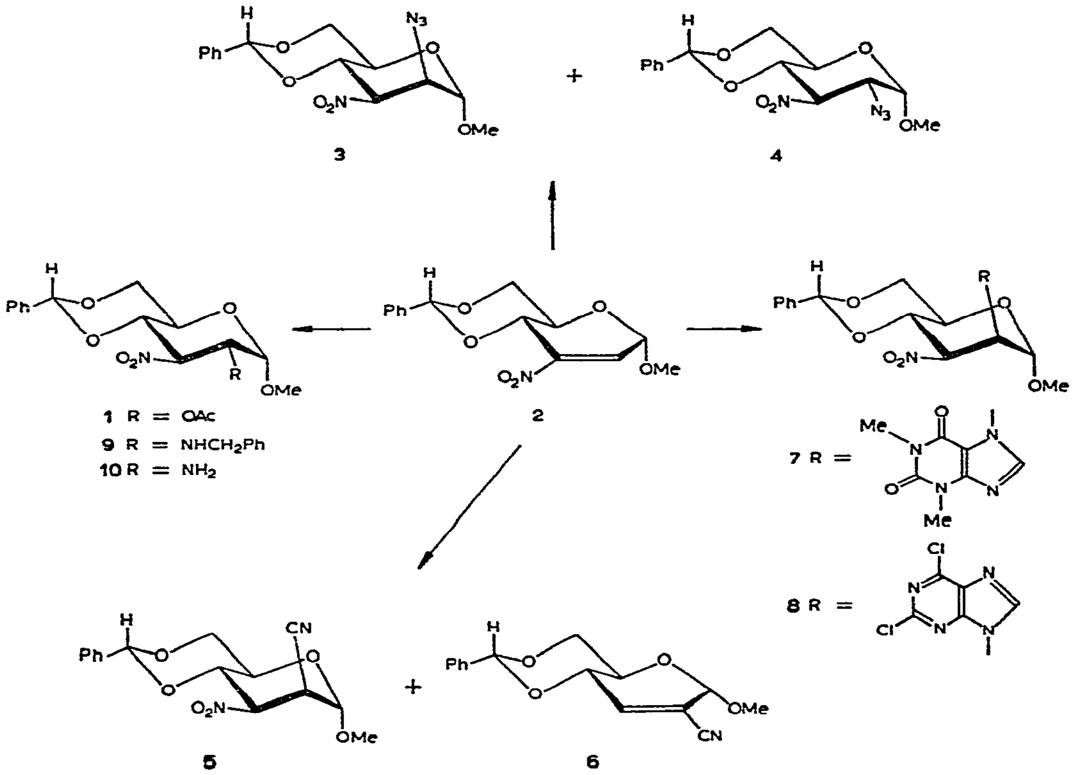
*Stereochemistry of nucleophilic addition-reactions. Part I.

†The thermodynamically less-stable *erythro* isomers were prepared by Southwick and Anderson[4] from (2-nitropropenyl)benzene and such secondary amines as morpholine under the appropriate conditions, and these results were explained by assuming stereoselective protonation to chelated forms of the *aci*-nitro intermediates. Such stereoselectivity, however, was not observed with a cyclic nitroalkene derivative[5].



RESULTS AND DISCUSSION

Treatment of methyl 2-*O*-acetyl-4,6-*O*-benzylidene-3-deoxy-3-nitro-α-D-glucopyranoside (**1**) with a small excess of sodium azide for 48 h at room temperature gave the thermodynamically more-stable isomer, namely, methyl 2-azido-4,6-*O*-benzylidene-2,3-dideoxy-3-nitro-α-D-glucopyranoside (**4**) in 60% yield, together with a small amount of the mannopyranoside (**3**) and of starting material (**1**). On the other hand, the reaction of nitroalkene **2** with hydrazoic acid in tetrahydrofuran–water for 3 h at 0° afforded methyl 2-azido-4,6-*O*-benzylidene-2,3-dideoxy-3-nitro-α-D-mannopyranoside (**3**) in 79% yield, together with a small amount of the glucopyranoside (**4**). The configurations of these compounds were determined from n.m.r. data (Table I). As shown in Table II, the rate and the stereoselectivity of the addition reaction of hydrazoic acid to **2** was found to be remarkably dependent upon the solvent used. The rate of the reaction increased progressively in the series $CDCl_3 < CH_3CN <$ tetrahydrofuran $\sim Me_2SO\text{-}d_6$ and the stereoselectivity increased according to the sequence $CDCl_3 < CH_3CN \sim$ tetrahydrofuran $< Me_2SO\text{-}d_6$. In $Me_2SO\text{-}d_6$, the reaction was complete within 10 min and gave the mannopyranoside (**3**) as the main product, whereas in $CDCl_3$, only one-half of compound **2** had reacted, even after 32.5 h, and the ratio of **3** to **4** was 1.6:1. It was noted that the latter ratio was independent of the reaction time from 10 min to 32.5 h.

TABLE I

N.M.R. DATA MEASURED AT 100 MHz IN $CDCl_3$
(FIRST ORDER, Me_4Si AS INTERNAL STANDARD)

Compound	*Chemical shift* (δ)					*Coupling constants (Hz)*			
	H-1	*H-2*	*H-3*	*H-4*	*PhCH*	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$
3[a]	4.87	4.37	4.95	4.48	5.67	1.0	4.0	10.0	?
4	4.92	3.70	5.03	4.10	5.51	3.4	10.3	9.7	9.7
5[b]	5.27	4.44	5.27	4.48	5.89	1.3	5.0	10.0	10.0
7	5.04	6.28	5.34	?	5.63	1.2	4.7	10.6	?
8	5.01	5.75	5.35	?	5.64	1.2	4.7	10.6	?
9	4.60	3.34	4.70	?	4.46	3.4	10.9	9.7	?

[a] From 60-MHz spectrum. [b] In Me_2SO-d_6.

TABLE II

SOLVENT EFFECTS ON THE REACTIONS OF 2[a] WITH HYDRAZOIC ACID

Solvent	*(ml)*	*$CDCl_3$ solution Containing HN_3*[b] *(ml)*	*Ratio* 3 *to* 4			
			10 min[c]	*2 h*[c]	*6.5 h*[c]	*32.5 h*[c]
Me_2SO-d_6	(0.2)	0.1	8:1	8:1	8:1	8:1
Me_2SO-d_6	(0.2)	0.2[d]	8:1	8:1	8:1	8:1
Tetrahydrofuran	(0.2)	0.1	5:1	5:1	5:1	5:1
CH_3CN	(0.2)	0.1	r[e]	5:1	5:1	5:1
CH_3CN	(0.2)	0.2[d]	r	r	5:1 (47% r)	5:1
$CDCl_3$	(0)	0.3	r	r	r	1.6:1 (50% r)

[a] Compound (2 0.1 mmol) was treated in an n.m.r. sample-tube at room temperature and the ratio of 3 to 4 was determined by n.m.r. spectroscopy. [b] The concentration of hydrazoic acid was ~1.6–1.8M, as determined by titration with 0.1M KOH. [c] Reaction time. [d] The concentration of hydrazoic acid was ~0.8–0.9M. [e] r Denotes the recovery of 2.

The reaction of nitroalkene 2 with hydrogen cyanide in acetonitrile at room temperature did not proceed, even after 33 h, but addition of catalytic amounts of potassium cyanide led to the formation of a mixture of methyl 4,6-*O*-benzylidene-2-cyano-2,3-dideoxy-3-nitro-α-D-mannopyranoside (5) and methyl 4,6-*O*-benzylidene-2-cyano-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside (6), in good yield. These compounds were separated by fractional crystallization from ethanol. Assignment of the *manno*-configuration to 5 was based on coupling-constant data: $J_{1,2}$ 1.3, $J_{2,3}$ 5.0, and $J_{3,4}$ 10 Hz. The cyanoalkene structure for 6 was determined from its n.m.r. (alkenic proton at δ 6.88) and i.r. spectrum (no absorption for a nitro group, absorption for a cyano group) and from the results of elemental analysis. The fact that the ratio of 5 to 6 varied with conditions (scale, the amount of catalyst used, and reaction time) prompted us to monitor the reaction by n.m.r. spectroscopy. The results are shown in Fig. 1. Either in acetonitrile solution with catalytic amounts of potassium cyanide or in dimethyl sulfoxide without the catalyst, the addition reaction was finished within 25 min and gave the 3-nitro-2-cyano derivative (5), which was gradually converted into the cyanoalkene (6).

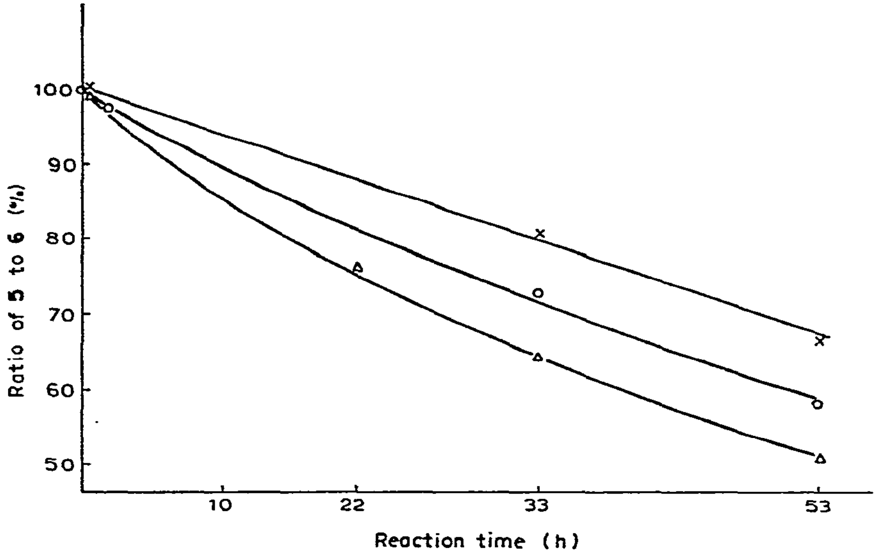


Fig. 1. Relationship between the ratios of 5 to 6 and the reaction time. The reactions of 2 (0.1 mmol) or 5 (0.1 mmol) with hydrogen cyanide were performed in an n.m.r. sample-tube at room temperature and monitored by n.m.r. spectroscopy. ×, 2 in acetonitrile in the presence of potassium cyanide (2.1 mg); ○, 5 in acetonitrile in the presence of potassium cyanide (2.1 mg); and △, 2 in Me_2SO in the absence of potassium cyanide.

When nearly equimolar amounts of 2 and anhydrous theophylline or 2,6-dichloropurine were heated under reflux for 80 h, the less-stable mannopyranosides 7 and 8, respectively, were obtained similarly in high yields. Coupling-constant data for th ring protons ($J_{1,2}$ 1.2, $J_{2,3}$ 4.7, and $J_{3,4}$ 10.6 Hz) indicated the *manno*-structure for 7 and 8. The u.v. data indicated that the sugar group had been introduced on the purine nucleus at N-7 in 7 and N-9 in 8. In contrast, treatment of nitroalkene 2 with benzylamine in acetonitrile for 4 h at room temperature gave the glucopyranoside 9 exclusively; it was isolated in 86% yield. The *gluco* configuration assigned to 9 was deduced from n.m.r. data: $J_{1,2}$ 3.4, $J_{2,3}$ 10.9, and $J_{3,4}$ 9.7 Hz. Similar reactions of 2 with aqueous ammonia had previously been shown[6] to give the glucopyranoside (10) in high yields, and this result was confirmed. The results of the present investigation suggest that the reactions of nitroalkene 2 with weak acids or purine derivatives, under the conditions described here, are controlled kinetically, whereas the reactions of 2 with more-basic reagents (such as benzylamine) are controlled thermodynamically.

EXPERIMENTAL

General methods. — Melting points were determined in capillaries and are uncorrected. I.r. spectra were recorded for KBr discs and n.m.r. spectra were determined for solutions in either $CDCl_3$ or Me_2SO-d_6 (tetramethylsilane as internal standard) with either a JNM-4H-150 (JEOL) or a Varian T-60 spectrometer. Evaporations were performed *in vacuo*. Column chromatography was carried out on silica gel (C-300, Wakogel, Japan).

Methyl 2-azido-4,6-O-benzylidene-2,3-dideoxy-3-nitro-α-D-mannopyranoside (**3**) — To a solution of **2** (ref. 7, 147 mg, 0.5 mmol) in tetrahydrofuran (4 ml) and water (0.5 ml) at 0° was added a chloroform solution of hydrazoic acid (1 ml) prepared according to the procedure of Wolff[8]. The mixture was stirred for 3 h at room temperature and then evaporated to a syrup whose n.m.r. spectrum showed that it comprised **3** and **4** in a ratio of ~5:1. The syrup was chromatographed on a column with benzene as eluant. The major component (140 mg) was recrystallized from ethanol to give **3** (133 mg, 79%), m.p. 111–112°, $[\alpha]_D^{20}$ $-18.3°$ (*c* 1, chloroform); ν_{max} 2070 (N_3) and 1555 cm^{-1} (NO_2).

Anal. Calc. for $C_{14}H_{16}N_4O_6$: C, 50.00; H, 4.80; N, 16.66. Found: C, 49.84; H, 4.91; N, 16.62.

Methyl 2-azido-4,6-O-benzylidene-2,3-dideoxy-3-nitro-α-D-glucopyranoside (**4**). — To a solution of **1** (ref. 7, 177 mg, 0.5 mmol) in acetonitrile (4 ml) and water (0.5 ml) was added sodium azide (35.8 mg, 0.55 mmol). The mixture was stirred for 48 h at room temperature and evaporated to a syrup that was washed with water and dried in air (130 mg). Its n.m.r. spectrum revealed that it contained the glucopyranoside **4** together with small amounts of the mannopyranoside **3** and starting material **1**. The syrup was chromatographed on a column with benzene as eluant. The major component was recrystallized from ethanol to give **4** (101 mg, 60%), m.p. 132.5–133.5°, $[\alpha]^{20}$ $+172°$ (*c* 0.5 chloroform); ν_{max} 2100 (N_3) and 1560 cm^{-1} (NO_2).

Anal. Calc. for $C_{14}H_{16}N_4O_6$: C, 50.00; H, 4.80; N, 16.66. Found: C, 50.12; H, 4.91; N, 16.85.

Methyl 4,6-O-benzylidene-2-cyano-2,3-dideoxy-3-nitro-α-D-mannopyranoside (**5**) *and methyl 4,6-O-benzylidene-2-cyano-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside* (**6**). — To a solution of **2** (293 mg, 1 mmol) in acetonitrile (8 ml) in the presence of potassium cyanide (2.1 mg) was added an acetonitrile solution containing hydrogen cyanide (~6 mmol). The mixture was stirred overnight and then evaporated to a solid residue (244 mg) that comprised **5** and **6**, in a ratio of 1:1, as judged by n.m.r. spectroscopy. The residue was recrystallized from ethanol to give two crystalline fractions. The first crop was platelet crystals of **5** (134 mg, 42%), m.p. 170.5–171.5°, $[\alpha]^{20}$ $-14.7°$ (*c* 1, chloroform); ν_{max} 2260 (CN) and 1560 cm^{-1} (NO_2).

Anal. Calc. for $C_{15}H_{16}N_2O_6$: C, 56.25; H, 5.04; N, 8.75. Found: C, 56.51; H, 5.03; N, 8.65.

The second crop was mainly **6**, but, according to its i.r., spectrum, it contained small amounts of **5**. Accompanying traces of **5** were removed by one more recrystallization from ethanol, to give cotton-like crystals of **6** (101 mg, 37%), m.p. 180.5–181.5°, $[\alpha]_D^{20}$ +168° (*c* 0.5, chloroform); ν_{max} 2233 (CN) cm^{-1}; n.m.r. data: δ 6.88 (1-proton singlet, H-3), 5.56 (1-proton singlet, PhCH), 4.96 (1-proton doublet, $J_{1,4}$ 1.9 Hz, H-1), and 3.50 (3-proton singlet, OMe).

Anal. Calc. for $C_{15}H_{15}NO_4$: C, 65.92; H, 5.53; N, 5.13. Found: C, 66.13; H, 5.56; N, 5.17.

The ratio of the products (**5** and **6**) varied with the reaction conditions, as has been described.

Methyl 4,6-O-benzylidene-2,3-dideoxy-3-nitro-2-(7-theophyllinyl)-α-D-manno-pyranoside (**7**). — Compound **2** (98 mg, 0.33 mmol) and theophylline (66 mg, 0.37 mmol) were gently heated for 80 h under reflux in distilled tetrahydrofuran (8 ml). The mixture was evaporated to give a residue that was pure by n.m.r. spectroscopy. The residue was recrystallized from ethanol–acetone to give **7** (143.5 mg, 91%), m.p. 206° (dec.), $[\alpha]_D^{20}$ +31.6° (*c* 1, chloroform); λ_{max} (tetrahydrofuran) 278.2 nm (ε 7980); ν_{max} 1710, 1660, 1560, and 1540 cm^{-1}.

Anal. Calc. for $C_{21}H_{23}N_5O_8$: C, 53.28; H, 4.90; N, 14.79. Found: C, 53.36; H, 4.86; N, 14.91.

Methyl 4,6-O-benzylidene-2,3-dideoxy-2-(2,6-dichloro-9-purinyl)-3-nitro-α-D-mannopyranoside (**8**). — Compound (**2**) (98 mg, 0.33 mmol) and 2,6-dichloropurine (69 mg, 0.37 mmol) were gently heated for 80 h under reflux in distilled tetrahydrofuran (8 ml). The mixture was evaporated to give a crystalline residue. N.m.r. spectroscopy revealed that the residue consisted of **8** and small amounts of a by-product; the latter has not yet been isolated. Recrystallization from ethanol gave **8** (132 mg, 82%), m.p. 194° (dec.), $[\alpha]_D^{20}$ +13.4° (*c* 1, chloroform); λ_{max} (MeOH) 273.8 nm (ε 9800); ν_{max} 1560 cm^{-1} (NO_2).

Anal. Calc. for $C_{19}H_{17}Cl_2N_5O_6$: C, 47.31; H, 3.55; N, 14.52. Found: C, 47.61; H, 3.58; N, 14.67.

Methyl 2-benzylamino-4,6-O-benzylidene-2,3-dideoxy-3-nitro-α-D-gluco-pyranoside (**9**). — To a solution of benzylamine (26 mg, ~0.24 mmol) in acetonitrile (4 ml) was added **2** (58.6 mg, 0.2 mmol). The mixture was kept for 4 h at room temperature and then evaporated to give a residue that was pure by n.m.r. spectroscopy; this was readily crystallized from ethanol to give **9** (68.8 mg, 86%), m.p. 159–160°, $[\alpha]_D^{20}$ +49.1° (*c* 1, chloroform); ν_{max} 3320 (NH) and 1560 cm^{-1} (NO_2).

Anal. Calc. for $C_{21}H_{24}N_2O_6$: C, 62.99; H, 6.04; N, 7.00. Found: C, 63.07; H, 6.00; N, 7.10.

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