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REACTION OF 1-*O*-ACETYL-4,6-*O*-BENZYLIDENE-2,3-DIDEOXY-3-NITRO-α-D-*ERYTHRO*-HEX-2-ENOPYRANOSE AND ITS ANOMER WITH HYDRAZOIC ACID*

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ABSTRACT

The title compounds (**6** and **7**) were prepared by acetylation of 4,6-*O*-benzylidene-3-deoxy-3-nitro-α-D-glucopyranose (**3**) followed by elimination of acetic acid. Reaction of the β anomer (**7**) with hydrazoic acid gave the thermodynamically more-stable glucopyranose **8** exclusively, whereas similar reaction of the α anomer (**6**) afforded the less-stable mannopyranose **10** as the major product and the *gluco* isomer **11** as the minor product. Striking solvent-effects were observed in the latter reaction, including the epimerization of **10** to **11** in dimethyl sulfoxide and *N*,*N*-dimethylformamide, but not in other solvents (chloroform, ethyl acetate, and tetrahydrofuran). The reaction of **6** with hydrogen cyanide also gave the mannopyranose **9** in good yield.

INTRODUCTION

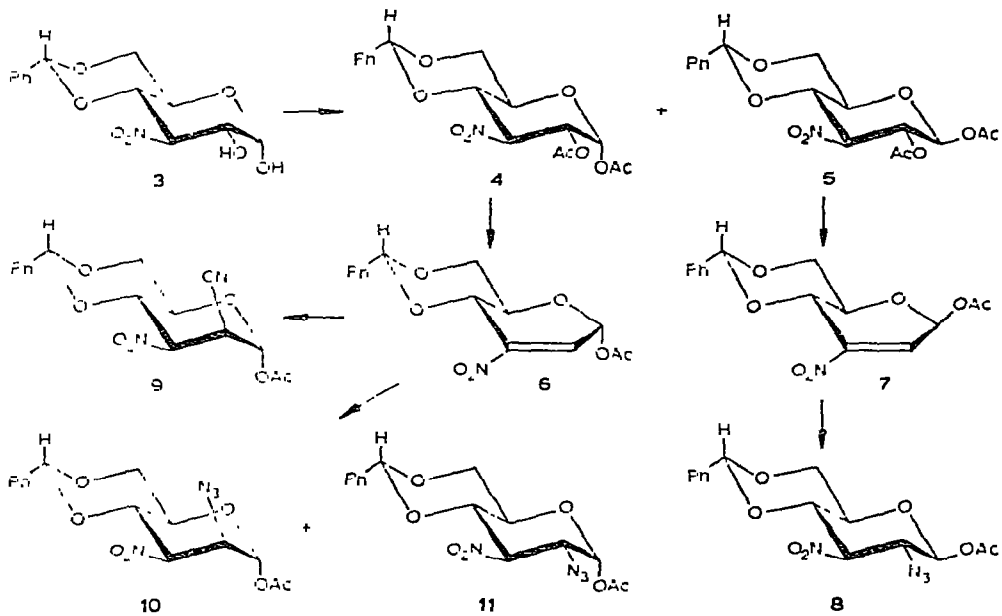
We have shown that the reaction of methyl 4,6-*O*-benzylidene-2,3-dideoxy-3-nitro-α-D-*erythro*-hex-2-enopyranoside (**1**) with hydrogen cyanide affords the thermodynamically less-stable, mannopyranoside in good yield[1], but similar reaction of the β anomer **2** gave the more-stable glucopyranoside[2a] exclusively*†; both reactions were proved to be kinetically controlled. Although the possibility of reversible reactions was not completely excluded, similar stereochemical results were observed in the reactions of **1** and **2** with hydrogen peroxide[3], *S*-ylids[4], *N*-bromoacetamide[5], and active methylene compounds in heterogeneous reactions[6]. In order to determine whether or not the behavior of **1** and **2** was representative of the mode of addition, we have prepared 1-*O*-acetyl-4,6-*O*-benzylidene-2,3-dideoxy-3-nitro-α-D-*erythro*-hex-2-enopyranose (**6**) and its β anomer **7**, and have studied their addition reactions with hydrazoic acid and/or hydrogen cyanide.

*Stereochemistry of Nucleophilic Addition-Reactions. Part III. For related work, see ref. 1. For Part II in this series, see ref. 2a.

†Paulsen and Greve found that a similar reaction of **2** with hydrogen cyanide in the presence of catalytic amounts of triethylamine gave the adducts having the *gluco* and *manno* configurations, as well as the cyanoalkene derivative; see ref. 2b.

RESULTS AND DISCUSSION

Acetylation of **3** with acetic anhydride in pyridine, as described previously[7], gave a quantitative yield of 1,2-di-*O*-acetyl-4,6-*O*-benzylidene-3-deoxy-3-nitro-α-D-glucopyranose (**4**). Treatment of **3** with acetic anhydride in the presence of catalytic amounts of anhydrous sodium acetate for 45 min at 85° afforded a mixture of the α acetate **4** and the β acetate **5** in the approximate ratio of 13:7 as determined by n.m.r. spectroscopy, and these were separated by fractional crystallization. Assignment (Tables I and II) of the β configuration to **5** was based on the magnitude (8.5 Hz) of $J_{1,2}$. Treatment of **4** and **5** with sodium hydrogencarbonate in refluxing benzene readily afforded the nitroalkenes **6** and **7**, respectively. It is noteworthy that the n.m.r. spectra of **6** and **7** showed the presence of long-range couplings: $J_{1,4}$ 1.2 and $J_{2,4}$ 1.9 Hz, and $J_{1,4}$ 2.8 and $J_{2,4}$ 2.2 Hz, respectively.



Treatment of the β anomer **7** with hydrazoic acid in tetrahydrofuran for 25 min at 0° or in chloroform for 3 h at room temperature gave exclusively 1-*O*-acetyl-2-azido-4,6-*O*-benzylidene-2,3-dideoxy-3-nitro-β-D-glucopyranose (**8**), the configuration of which was deduced from coupling-constant data: $J_{1,2}$ 8.8 and $J_{2,3} = J_{3,4}$ 10.0 Hz.

Treatment of the α anomer **6** with hydrogen cyanide in acetonitrile in the presence of catalytic amounts of potassium cyanide for 3 h at 0° afforded the manno-pyranoside **9** in 83% yield, together with small amounts of byproduct. The *manno* configuration of **9** was assigned by n.m.r. spectroscopy: $J_{1,2}$ 1.2, $J_{2,3}$ 5.0, and $J_{3,4}$ 10.6 Hz. When the α anomer **6** was treated with hydrazoic acid in chloroform for 3.5 h at room temperature, a mixture of 1-*O*-acetyl-2-azido-4,6-*O*-benzylidene-2,3-dideoxy-

TABLE I

CHEMICAL SHIFTS (δ) OF 3-NITRO DERIVATIVES AT 100 MHz IN CHLOROFORM-*d* (Me_4Si AS INTERNAL STANDARD)

Compd.	*H-1*	*H-2*	*H-3*	*H-4*	*H-5*	*H 6a*	*H-6e*
5	5.77	5.52	4 83	4.22	3 63	3 79	4 38
6[a]	6.52	7.07		4 96	[b]	[b]	[b]
7	6.63	6.79		4.83	[b]	[b]	[b]
8	5.66	4.14	4.57	4 07	3 66	3.77	4.36
9	6 39	3.76	5.06	4.03	[b]	[b]	[b]
10	6.23	4 37	4.92	4 50	[b]	[b]	[b]
11[a]	6.41	4 59	5 19	[b]	[b]	3.94	4 29

[a]In dimethyl sulfoxide-d_6. [b]Not amenable to first-order analysis

TABLE II

FIRST-ORDER COUPLING-CONSTANTS (Hz) FOR 3-NITRO DERIVATIVES, MEASURED AT 100 MHz IN CHLOROFORM-*d*

Compd.	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6a}$	$J_{5,6e}$	$J_{6a,6e}$
5	8.5	10.0	10 0	10 0	10 0	4.5	10.0
6[a]	3.1			6.3	[b]	[b]	[b]
7	1.3			7.5	[b]	[b]	[b]
8	8 8	10 0	10.0	9.0	9.4	4 4	9 4
9	1.2	5 0	10 6	8.8	[b]	[b]	[b]
10	1.6	3.8	10 0	8.8	[b]	[b]	[b]
11[a]	3.8	11 3	10 0	[b]	10.0	3.8	10 0

[a]In dimethyl sulfoxide-d_6. [b]Not amenable to first-order analysis.

3-nitro-α-D-mannopyranose (**10**) and its 2-epimer **11** was obtained in 95% yield. These were separated by fractional crystallization. The i.r. spectra of both compounds showed the presence of an azido group (2100–2110 cm^{-1}) and of a nonconjugated nitro group (1560 cm^{-1}). The *manno* configuration of **10** and the *gluco* configuration of **11** were assigned from n.m.r. data: $J_{1,2}$ 1.6, $J_{2,3}$ 3.8, and $J_{3,4}$ 10.0 Hz, and $J_{1,2}$ 3.8, $J_{2,3}$ 11.3, and $J_{3,4}$ 10.0 Hz, respectively.

As shown in Table III, this reaction was greatly affected by solvents. In such nonpolar solvents as benzene, the starting material **6** was recovered after 5 h (Expts. 1 and 7), but in more-polar solvents such as tetrahydrofuran and dimethyl sulfoxide, the reaction proceeded readily within 0.5 h to give **10** as the major product and **11** as the minor one (Expts. 2–6). In a tetrahydrofuran (0.15 ml)–chloroform-*d* (0.4 ml) solution, compound **6** (0.1 mmol) reacted with hydrazoic acid (~0.18 mmol) within 30 min (Expt. 11), but in tetrahydrofuran (0.05 ml)–chloroform-*d* (0.4 ml) it did not react even after 71 h (Expt. 10). Furthermore, in chloroform-*d* solution, the ratio of **11** to **10** increased with an increase of the concentration of hydrazoic acid (Expts. 8 and 9). These solvent-effects are explicable as follows. Activation of hydrazoic acid is

TABLE III

SOLVENT EFFECTS ON THE REACTIONS OF 6[a] WITH HYDRAZOIC ACID

Expt.	*Solvent (ml)*	*$CDCl_3$ solution of HN_3[b] (ml)*	*Reaction time (h)*	*Ratio of* **11** *to* **10** + **11** (%)
1	Benzene (0.4)	0.1	5	recovery of **6**
2	Ethyl acetate (0.5)	0.1	0.5	12[c]
3	THF (0.5)	0.1	0.5	13
4	THF (0.2)	0.1	0.5	11[c]
5	Me_2SO-d_6 (0.2)	0.1	0.5	20[d]
6	$HCONMe_2$ (0.2)	0.1	0.6	25[d]
7	$CDCl_3$ (0.3)	0.1	74	recovery of 6[e]
8	$CDCl_3$ (0.2)	0.2	3.5	50
9	$CDCl_3$ (0)	0.4	3.5	70[c]
10	$CDCl_3$ (0.3)–THF (0.05)	0.1	71	recovery of **6**
11	$CDCl_3$ (0.3)–THF (0.15)	0.1	0.5	13

[a]Compound **6** (0.1 mmol) was treated in an n.m.r. sample-tube at room temperature, and the ratio was determined by n.m.r. spectroscopy, which revealed the absence of other products. [b]The concentration of HN_3 was about 1.8M, as determined by titration with 0.1M potassium hydroxide. [c]The ratio was independent of reaction time between 0.5 h to 1 day. [d]The ratio depended on the reaction time; see Fig. 1. [e]Crystals of **6** still remained.

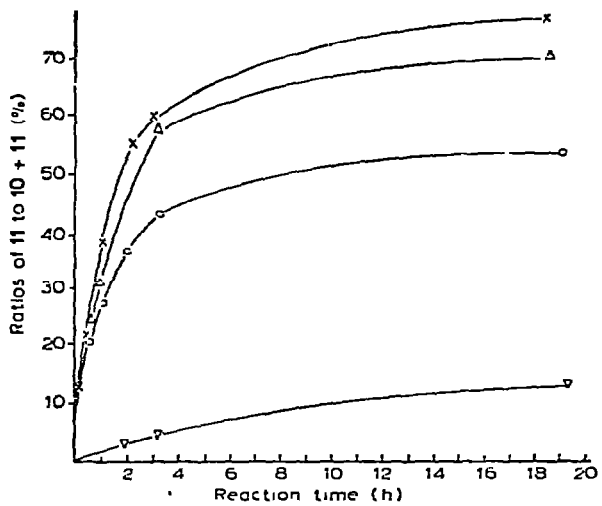


Fig. 1. Relationship between the ratios of **11** to **10** + **11** and the reaction time. The reactions of **6** (0.1 mmol) with hydrazoic acid (~1.8M $CDCl_3$ solution, 0.1 ml) were performed in an n.m.r. sample-tube at room temperature, and monitored by n.m.r. spectroscopy: ×, **6** in Me_2SO-d_6 (0.2 ml); △, **6** in $HCONMe_2$ (0.2 ml); ○, the 3-deuterated derivative of **10** in Me_2SO-d_6 (0.2 ml); and ▽, the 3-deuterated derivative of **10** in Me_2SO-d_6 (0.2 ml) in the absence of hydrazoic acid. Except for the last example (▽), only **11** was observed by n.m.r. spectroscopy after 7 days.

required to initiate the reaction. In polar solvents, hydrazoic acid is activated by solvation, giving the mannopyranose, which is kinetically favored owing to stereoelectronic control and steric hindrance. However, in nonpolar solvents, instead of solvation, hydrogen-bonding is operative between hydrazoic acid and the acetoxyl group at C-1 to afford the *gluco* isomer **11**. As almost the same solvent-effects had been observed in the reaction of α-pyranoside[1] **1**, the presumed hydrogen bond would be formed with the alkyl-oxygen atom of the acetoxyl group. In dimethyl sulfoxide, the stereoselectivity of **1**, however, unlike that of **6**, is higher than in tetrahydrofuran. To elucidate this discrepancy, the reaction was monitored by n.m.r. spectroscopy. In ethyl acetate, chloroform, and tetrahydrofuran, the ratio of **11** to **10** was not changed during the period of 0.5 to 24 h; however, in dimethyl sulfoxide and *N*,*N*-dimethylformamide, it increased together with the reaction time (Fig. 1), showing that epimerization of **10** to **11** took place in such polar aprotic solvents*. In fact, when 1-*O*-acetyl-2-azido-4,6-*O*-benzylidene-2,3-dideoxy-3-deuterio-3-nitro-α-D-mannopyranose was treated with hydrazoic acid in dimethyl sulfoxide-d_6, epimerization of the *manno* isomer to the *gluco* isomer was observed. An extrapolated value of formation of about 10% of *gluco* isomer **11** in these aprotic, polar solvents is in good agreement with that obtained in the similar reaction of **1**. It is noteworthy that epimerization was accelerated in the presence of hydrazoic acid.

In contrast to the reactions of the pyranoside **1** with either an excess of ammonia[8] or of sodium azide[1], each of which gave the *gluco* adduct in high yield, similar reaction of **6** afforded complicated results; these might arise through hydrolysis of the acetoxyl group followed by further transformation.

EXPERIMENTAL

General methods. — Melting points were determined in capillaries and are uncorrected. I.r. spectra were recorded for potassium bromide discs with a Hitachi 215 i.r. spectrophotometer. N.m.r. spectra were determined at 100-MHz with a JNM-4H-100 (JEOL) spectrometer for solutions in chloroform-*d*, with tetramethylsilane as internal standard.

*1,2-Di-*O*-acetyl-4,6-*O*-benzylidene-3-deoxy-3-nitro-β-*D*-glucopyranose* (**5**). — The benzylidene acetal[7] **3** (1.485 g, 5 mmol) and sodium acetate (750 mg) in acetic anhydride (15 ml) were heated for 45 min at 85°. The mixture was poured into ice–water (200 ml) and the precipitate that separated was collected and washed thoroughly with cold water. The n.m.r. spectrum of the product revealed that it was a 13:7 mixture of **4** and **5**. Recrystallization from ethyl acetate furnished two crystalline fractions. The first crop began to deposit quickly; it was isolated, and washed with ethyl acetate after being kept for 15 h at room temperature. This crop (1.038 g) was pure **4**, identical with an authentic sample[7] by melting point, and by i.r., and n.m.r. spectra. The second crop (1.0 g), obtained by partial concentration of the mother

*In a similar reaction of the methyl pyranoside **1**, the product-ratio was nearly constant from 10 min to 32.5 h in acetonitrile, tetrahydrofuran, chloroform, and dimethyl sulfoxide[1].

liquors was **5**, together with an appreciable amount of **4**. After three recrystallizations from ethyl acetate, pure **5** was isolated: m.p. 224–225°, $[\alpha]_D^{20}$ −29.0° (*c* 1, chloroform); ν_{max} 1770 and 1760 (CO), and 1560 cm^{-1} (NO_2).

Anal. Calc. for $C_{17}H_{19}NO_9$: C, 53.54; H, 5.02; N, 3.67. Found: C, 53.83; H, 5.03; N, 3.87.

*1-O-Acetyl-4,6-O-benzylidene-2,3-dideoxy-3-nitro-α-*D*-erythro-hex-2-enopyranose* (**6**). — The acetate **4** (14 g) and dry sodium hydrogencarbonate (14 g) in distilled benzene (130 ml) were boiled for 36 h under reflux, with stirring. The mixture was cooled and filtered, and the filtrate was evaporated to give a crystalline residue. Recrystallization from benzene afforded 8.4 g (71%) of **6**; m.p. 204° (dec.), $[\alpha]_D^{20}$ −152° (*c* 1, chloroform); ν_{max} 1730 (CO) and 1530 cm^{-1} (alkenic nitro group).

Anal. Calc. for $C_{15}H_{15}NO_7$: C, 56.07; H, 4.71; N, 4.36. Found: C, 56.33; H, 4.92; N, 4.38.

*1-O-Acetyl-4,6-O-benzylidene-2,3-dideoxy-3-nitro-β-*D*-erythro-hex-2-enopyranose* (**7**). — Treatment of **5** (280 mg) with sodium hydrogencarbonate (280 mg) in distilled benzene (12 ml) for 20 h under the conditions used for the preparation of **6** gave a crystalline residue. Recrystallization from hexane–ethyl acetate afforded 215 mg 91%) of **7**, m.p. 135–136°, $[\alpha]_D^{20}$ −120° (*c* 1, chloroform); ν_{max} 1760 (CO) and 1530 cm^{-1} (alkenic nitro group).

Anal. Calc. for $C_{15}H_{15}NO_7$: C, 56.07; H, 4.71; N, 4.36. Found: C, 56.29; H, 4.82; N, 4.33.

*1-O-Acetyl-2-azido-4,6-O-benzylidene-2,3-dideoxy-3-nitro-β-*D*-glucopyranose* (**8**). — To a solution of **7** (107 mg, 0.33 mmol) in distilled tetrahydrofuran (11 ml) at 0° was added a chloroform solution of hydrazoic acid (0.4 ml, ~1.8M). The mixture was stirred for 25 min at 0° and then evaporated *in vacuo* to give an n.m.r.-spectroscopically pure, crystalline residue, which was recrystallized from ethanol to give 102 mg (84%) of **8**: m.p. 130–131°, $[\alpha]_D^{20}$ −37.2° (*c* 1, chloroform); ν_{max} 2110 (N_3), 1765 and 1760 (CO), and 1560 cm^{-1} (NO_2).

Anal. Calc. for $C_{15}H_{16}N_4O_7$: C, 49.45; H, 4.43; N, 15.38. Found: C, 49.48; H, 4.48; N, 15.34.

Compound **8** was obtained in 86% yield when **7** was treated with hydrazoic acid in chloroform for 3 h at room temperature.

*1-O-Acetyl-4,6-O-benzylidene-2-cyano-2,3-dideoxy-3-nitro-α-*D*-mannopyranose* (**9**). — To a solution of **6** (161 mg, 0.5 mmol) in acetonitrile (8 ml) in the presence of a catalytic amount of potassium cyanide (1.1 mg) at 0° was added a solution of hydrogen cyanide (~3 mmol) in acetonitrile. The mixture was stirred for 3 h at 0° and then evaporated *in vacuo*. The residue (177 mg) was washed with water and crystallized from ethanol to give 145 mg (83%) of **9**: m.p. 207° (dec.), $[\alpha]_D^{20}$ +10.8° (*c* 1, chloroform); ν_{max} 1750 (CO) and 1560 cm^{-1} (NO_2).

Anal. Calc. for $C_{16}H_{16}N_2O_7$: C, 55.17; H, 4.63; N, 8.04. Found: C, 55.29; H, 4.59; N, 8.01.

*1-O-Acetyl-2-azido-4,6-O-benzylidene-2,3-dideoxy-3-nitro-α-*D*-mannopyranose* (**10**). — To a solution of **6** (161 mg, 0.5 mmol) in distilled tetrahydrofuran (16 ml) at

0° was added a chloroform solution of hydrazoic acid (0.5 ml, ~1.8M). The mixture was stirred for 25 min at 0° and then evaporated to give a crystalline residue, which was recrystallized from ethanol, affording 150 mg (82%) of **10**: m.p. 132–133°, $[\alpha]_D^{20}$ +12.0° (*c* 1, chloroform); ν_{max} 2110 (N_3), 1750 (CO), and 1560 cm^{-1} (NO_2).

Anal. Calc. for $C_{15}H_{16}N_4O_7$: C, 49.45; H, 4.43; N, 15.38. Found: C, 49.49; H, 4.45; N, 15.19.

1-O-Acetyl-2-azido-4,6-O-benzylidene-2,3-dideoxy-3-nitro-α-D-glucopyranose (**11**). — A chloroform solution of hydrazoic acid (0.4 ml, ~1.8M) was added to **6** (32.1 ml, 0.1 mmol). The crystals dissolved immediately. The mixture was kept for 3.5 h at room temperature and then evaporated *in vacuo* to give a crystalline residue consisting of **10** and **11** in the approximate ratio of 3:7 (as determined by its n.m.r. spectrum), in 95% yield (34.6 mg). Recrystallization of the crude product (104 mg) from ethanol gave two crystalline fractions. The first crop was **11** (66 mg), m.p. 186.5–187.5°, $[\alpha]_D^{20}$ +105° (*c* 1, chloroform); ν_{max} 2100 (N_3), 1757 (CO), and 1560 cm^{-1} (NO_2).

Anal. Calc. for $C_{15}H_{16}O_7$: C, 49.45; H, 4.43; N, 15.38. Found: C, 49.64; H, 4.52; N, 15.25.

The second crop (26 mg) was **10**, identical by i.r. and n.m.r. spectroscopy with the product already described

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