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PREPARATION OF METHYL 4,6-*O*-BENZYLIDENE-2-DEOXY-2-NITRO-β-D-GLUCOPYRANOSIDE FROM THE CORRESPONDING 3-DEOXY-3-NITRO DERIVATIVES WITH SODIUM NITRITE

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ABSTRACT

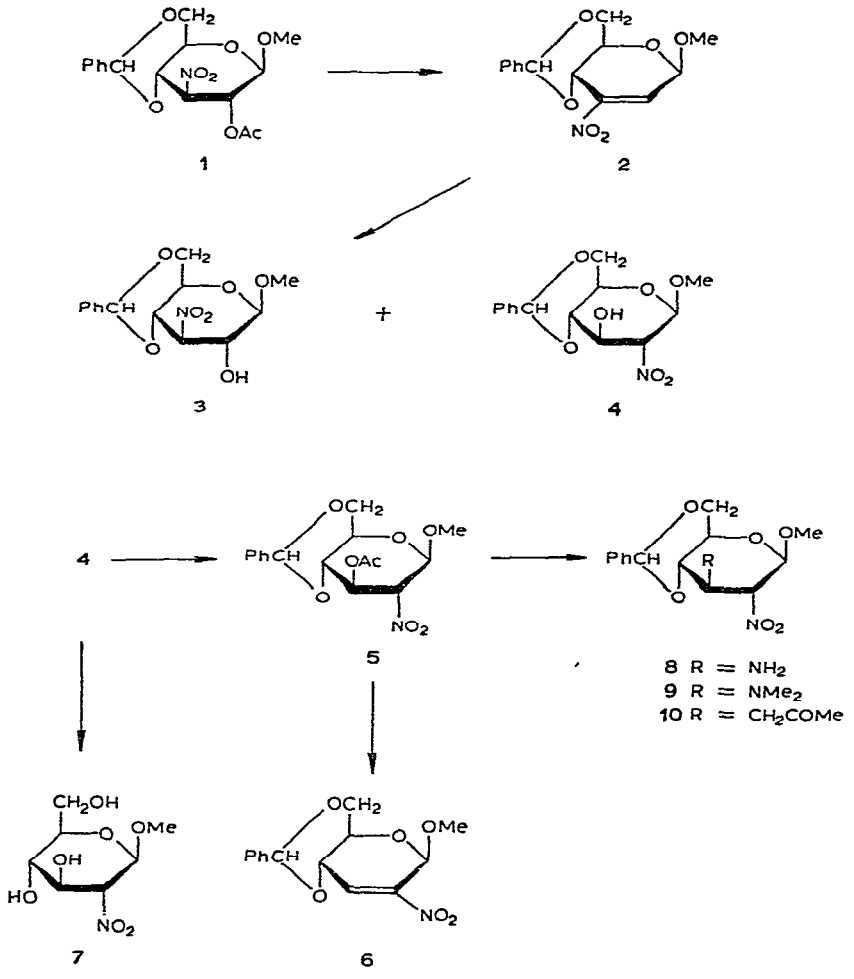
Treatment of methyl 4,6-*O*-benzylidene-2,3-dideoxy-3-nitro-β-D-*erythro*-hex-2-enopyranoside (**2**) with nitrous acid afforded the title 2-nitro sugar (**4**). The same product was also prepared by heterogeneous reaction of methyl 2-*O*-acetyl-4,6-*O*-benzylidene-3-deoxy-3-nitro-β-D-glucopyranoside (**1**) with sodium nitrite in the presence of a phase-transfer catalyst. Acid hydrolysis of **4** gave methyl 2-deoxy-2-nitro-β-D-glucopyranoside (**7**). Acetylation of **4**, followed by elimination of acetic acid, afforded a 2-nitroalkene (**6**). The 3-acetate **5** reacted with ammonia, dimethylamine, and 2,4-pentanedione to give the products **8**, **9**, and **10**, respectively, having the *gluco* configuration.

INTRODUCTION

The observation that methyl 4,6-*O*-benzylidene-2,3-dideoxy-3-nitro-β-D-*erythro*-hex-2-enopyranoside (**2**) and its anomer react with 2,6-dichloropurine[1,2] and active-methylene compounds[3–5] under mild conditions to give good yields of the 2-purinyl pyranoside and 2-*C*-branched chain sugars, respectively, prompted us to apply the same reactions to 2-nitro sugars in order to develop a novel synthetic route for *N*- and *C*-nucleosides. Therefore, we have attempted the preparation of 2-nitro sugars[6]. In this paper, we describe preparation of the title compound by transposition of the nitro group, and also reactions of the 2-nitro-3-acetate (**5**) with various nucleophiles.

RESULTS AND DISCUSSION

Treatment of the 3-nitroalkene **2** with sodium nitrite in acetonitrile–water at room temperature or at 0° gave a brown–red solution, from which no nitro derivative could be isolated. However, the fact[2,7] that such weak acids as hydrogen cyanide readily add to **2** or its anomer suggests that nitrous acid, which is also a weak acid, may likewise react with **2**. When **2** was treated with sodium nitrite in the presence of



strong cation-exchange resin (Mitsubishi Diaion SK1, Japan), almost all of the mixture dissolved in water. Small amounts of a mixture of methyl 4,6-*O*-benzylidene-3-deoxy-3-nitro-β-D-glucopyranoside (**3**) and methyl 4,6-*O*-benzylidene-2-deoxy-2-nitro-β-D-glucopyranoside (**4**) were obtained, accompanied by the odor of benzaldehyde, suggesting that debenzylidenation had occurred under these conditions. Decationization of sodium nitrite by passing it through a column of the strong cation-exchange resin was not applicable, because evolution of gas in the column was observed. Treatment of **2** with sodium nitrite in the presence of weak cation-exchange resin (Amberlite IRC-50) gave a mixture of the 3-nitro alcohol **3** (major product) and the 2-nitro alcohol **4** (minor product), in good yield. The latter product (**4**) was readily isolated in 14% yield as a first crop by fractional crystallization. Frankel and Klager[8] obtained 2,2,3-trinitrobutane from 2-nitro-2-butene and 70% nitric acid; however, the formation of **4** seems not to involve a trinitro intermediate but a dinitro

intermediate, derived by addition of nitrous acid, followed by cleavage of the nitro group from C-3 as nitrous acid.

An alternative preparation of **4** was accomplished by employing a heterogeneous system. Methyl 2-*O*-acetyl-4,6-*O*-benzylidene-3-deoxy-3-nitro-β-D-glucopyranoside (**1**), which is the precursor of **2**, was treated with sodium nitrite in the presence of hexadecyltributylphosphonium bromide as a phase-transfer catalyst[9] for 4 days at room temperature to give the 2-nitro alcohol **4** in up to 20% yield, together with starting material **1** (20%) and the 3-nitro alcohol **3** (40%). This reaction was very slow, and only **1** was recovered after 18 h. In homogeneous reactions of **1** with sodium nitrite, however, compound **4** was not isolated, suggesting that the heterogeneous system differs from the homogeneous one in suppressing the potentially disadvantageous contact of sodium nitrite with the starting and/or intermediary nitro sugars. Although the yield of **4** is low, these two methods appear to be useful, because **3** may be readily converted[10] into **1** and **2**.

Elemental analysis of **4** corresponded to $C_{14}H_{17}NO_7$ and its i.r. spectrum showed strong absorption for a hydroxyl (3400) and a nitro (1550 cm^{-1}) group. The n.m.r. spectrum of **4** was not completely assigned, but it was clearly different from that of **3**. Acetylation of **4** with acetic anhydride and pyridine furnished nearly equal amounts of methyl 3-*O*-acetyl-4,6-*O*-benzylidene-2-deoxy-2-nitro-β-D-glucopyranoside (**5**) and another product. Furthermore, treatment of **4** with acetic anhydride in the presence of catalytic amounts of boron trifluoride etherate gave a different product; those findings will be published elsewhere. Acetylation of **4** with acetic anhydride and sodium acetate at low temperature led to recovery of starting material, but **5** was obtained in 70% yield when **4** was heated for 45 min at 90° in acetic anhydride–sodium acetate. Assignment of the *gluco* configuration to **5** was deduced from the coupling-constant data; $J_{1,2}$ 7.8, $J_{2,3}$ 10, and $J_{3,4}$ 9.1 Hz. Treatment of **5** with sodium hydrogencarbonate in refluxing benzene gave methyl 4,6-*O*-benzylidene-2,3-dideoxy-2-nitro-β-D-*erythro*-hex-2-enopyranoside (**6**). Acid hydrolysis of **4** afforded methyl 2-deoxy-2-nitro-β-D-glucopyranoside (**7**). Physical data of the 2-nitro derivatives are quite different from those of the corresponding 3-nitro derivatives[10].

TABLE I

CHEMICAL SHIFTS (δ) OF 2-NITRO DERIVATIVES AT 100 MHz IN CHLOROFORM-*d* (Me_4Si AS INTERNAL STANDARD)

Compound	*H-1*	*H-2*	*H-3*	*H-4*	*H-5*	*H-6a*	*H-6e*	*PhCH*	*OMe*	*Others*
5	4.94	4.53	5.79	←	3.60–3.85	→	4.38	5.49	3.53	2.05 (OAc)
6	5.75		7.3–7.5[a]	4.46	3.64	3.87	4.36	5.57	3.52	
8	4.87	4.28	3.33	3.77	3.59	3.67	4.36	5.53	3.52	1.54 (NH_2)
9	4.81	4.41	←	3.55–3.83		→	4.35	5.53	3.48	2.46 (NMe_2)
10[b]	4.90	4.63	2.84	3.77	3.5–3.8	3.62	4.33	5.48	3.52	2.08 ($COCH_3$)

[a]The signal was hidden in the signals of the aromatic protons. [b]Assignment of H-3 was carried by comparison with the spectrum of the 3-acetonyl (-d_5) derivative but assignments of H-4 and H-6a are tentative.

TABLE II

FIRST-ORDER COUPLING CONSTANTS (Hz) FOR 2-NITRO DERIVATIVES, MEASURED AT 100 MHz IN CHLOROFORM-*d*

Compound	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6a}$	$J_{5,6e}$	$J_{6a,6e}$
5	7.8	10	9.1	?	?	3.1	10
6[a]			1.9	7.5	9.1	3.8	10
8	8.1	10	8.8	10	10	3.8	9.4
9	7.8	10.6	?	?	?	3.8	10
10	7.5	11.3	10	8.8	8.8	3.8	9.5

[a]Compound 6 showed long-range coupling: $J_{1,3}$ or $J_{1,4}$ 2.5 Hz.

As observed with the 3-nitro acetate[11] **1**, the 2-nitro acetate **5** is very reactive to nucleophiles. For example, it reacted readily with ammonia and dimethylamine to give the 3-amino-2-nitro-glucopyranoside (**8**) and the 3-dimethylamino-2-nitro-glucopyranoside (**9**), respectively, in good yield. Phase-transfer catalyzed addition of 2,4-pentanedione[4] to **5** was accompanied by acetyl fission in the primary product to give the 2-nitro-3-*C*-(2-oxopropyl)-glucopyranoside (**10**) in 71% yield. Coupling-constant data for ring protons indicate the *gluco* configuration for **8**, **9**, and **10** (Table I).

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 chloroform-*d* (tetramethylsilane as internal standard) with a JNM-4H-100 (JEOL) spectrometer. Solutions were evaporated *in vacuo*. Column chromatography was performed on silica gel (C-300, Wakogel, Japan).

Methyl 4,6-O-benzylidene-2-deoxy-2-nitro-β-D-glucopyranoside (**4**). — (*a*) *From the 3-nitroalkene* **2**. To a solution of **2** (ref. 10, 879 mg, 3 mmol) in acetonitrile (16 ml)–water (2 ml) in the presence of Amberlite IRC-50 (880 mg) was added sodium nitrite (414 mg, 6 mmol). The mixture was stirred for 3 h and then evaporated to a syrup, that crystallized from ethanol. The product was recrystallized from ethanol to give **4** as colorless plates (131 mg, 14%), m.p. 220–221° (dec.), $[\alpha]_D^{20}$ −52.4° (*c* 1, acetone); ν_{max} 3400 (OH) and 1550 cm^{-1} (NO_2).

Anal. Calc. for $C_{14}H_{17}NO_7$: C, 54.02; H, 5.51; N, 4.50. Found: C, 54.19; H, 5.60; N, 4.56.

The ethanolic mother liquor was evaporated to a syrup that was chromatographed on silica gel, with benzene as eluant, to afford crystalline **3** (653 mg, 70%). Recrystallization from ethanol gave **3**, identical with an authentic sample[7].

(*b*) *From the 3-nitro acetate* **1**. To a solution of **1** (ref. 10, 530 mg, 1.5 mmol) in benzene (20 ml)–water (4 ml) containing hexadecyltributylphosphonium bromide (51 mg) was added sodium nitrite (414 mg, 6 mmol). The mixture was stirred for 24 h

at room temperature. Additional sodium nitrite (414 mg) was then added, and the mixture was stirred for further 3 days. The mixture was washed with water and the organic layer evaporated to give 420 mg of residue. Semicrystalline material that precipitated upon addition of ethanol consisted of **4** together with a small amount of **1**. Recrystallization from ethanol gave 93 mg (20%) of **4** as the first crop. Evaporation of the ethanolic mother liquor gave a syrup that was chromatographed on silica gel with benzene as eluant. Concentration of the eluate containing the faster-moving component afforded unreacted **1** (106 mg, 20%). Evaporation of the eluate containing the slower-moving component yielded **3** (187 mg, 40%) together with small amounts of **4**.

Methyl 3-O-acetyl-4,6-O-benzylidene-2-deoxy-2-nitro-β-D-glucopyranoside (**5**). — The benzylidene glucoside **4** (300 mg) and sodium acetate (200 mg) in acetic anhydride (4 ml) were heated for 45 min at 80–90°. The mixture was cooled and then poured into ice–water. The crude acetate, that separated was collected, washed thoroughly with water, and dried in a desiccator (262 mg, 77%). Recrystallization from ethanol gave 238 mg (70%) of **5**, m.p. 155.5–156.0°, $[\alpha]_D^{20}$ −67.7° (*c* 1, chloroform); ν_{max} 1755 (CO) and 1550 cm^{-1} (NO_2).

Anal. Calc. for $C_{16}H_{19}NO_8$: C, 54.39; H, 5.42; N, 3.96. Found: C, 54.27; H, 5.41; N, 3.83.

*Methyl 4,6-O-benzylidene-2,3-dideoxy-2-nitro-β-D-*erythro*-hex-2-enopyranoside* (**6**). — Compound **5** (428 mg) and dry sodium hydrogencarbonate (428 mg) in distilled benzene (20 ml) were heated for 40 h under reflux, with stirring. The mixture was cooled, filtered, and the filtrate evaporated to give a crystalline residue. Recrystallization from ethyl acetate afforded 295 mg (83%) of **6**, m.p. 98°, $[\alpha]_D^{20}$ −75.0° (*c* 1, chloroform); ν_{max} 1660 (C=C) and 1530 cm^{-1} (NO_2).

Anal. Calc. for $C_{14}H_{15}NO_6$: C, 57.33; H, 5.16; N, 4.78. Found: C, 57.43; H, 5.19; N, 4.72.

Methyl 2-deoxy-2-nitro-β-D-glucopyranoside (**7**). — To a solution of **4** (440 mg) in methanol was added strong cation-exchange resin (Mitsubishi Diaion SK1 Japan, 530 mg). The mixture was stirred for 14 h at room temperature and then filtered. The filtrate was evaporated to a syrup that was washed with petroleum ether. The syrup crystallized from ethanol to give **7** (262 mg). Recrystallization from ethanol gave 246 mg (78%) of **7** as colorless plates, m.p. 198–199° (dec.), $[\alpha]_D^{20}$ −29.7° (*c* 1, methanol); ν_{max} 3500, 3350, 3250 (OH) and 1550 cm^{-1} (NO_2).

Anal. Calc. for $C_7H_{13}NO_7$: C, 37.67; H, 5.87; N, 6.28. Found: C, 37.63; H, 5.85; N, 6.22.

Methyl 3-amino-4,6-O-benzylidene-2,3-dideoxy-2-nitro-β-D-glucopyranoside (**8**). — To a solution of **5** (35.3 mg, 0.1 mmol) in tetrahydrofuran (3 ml) was added aqueous ammonia (25%, 60 mg). The mixture was stirred for 5 h at room temperature and then evaporated to a solid residue, which was washed with water and then recrystallized from isopropyl alcohol to give 26 mg (84%) of **8**, m.p. 147° (dec.), $[\alpha]_D^{20}$ −53.0° (*c* 0.4, chloroform); ν_{max} 3350 (NH) and 1540 cm^{-1} (NO_2).

Anal. Calc. for $C_{14}H_{18}N_2O_6$: C, 54.19; H, 5.85; N, 9.03. Found: C, 54.40; H, 5.81; N, 9.18.

Methyl 4,6-O-benzylidene-2,3-dideoxy-3-dimethylamino-2-nitro-β-D-gluco-pyranoside (**9**). — Similar treatment of **5** (35.3 mg) with dimethylamine (110 mg) as just described gave 28.7 mg (85%) of **9**, m.p. 144–145°, $[\alpha]_D^{20}$ −51.8° (*c* 1, chloroform); ν_{max} 1560 cm^{-1} (NO_2).

Anal. Calc. for $C_{16}H_{22}N_2O_6$: C, 56.79; H, 6.55; N, 8.28. Found: C, 56.89; H, 6.51; N, 8.24.

Methyl 4,6-O-benzylidene-2,3-dideoxy-2-nitro-3-C-(2-oxopropyl)-β-D-gluco-pyranoside (**10**). — To a solution of **5** (70.6 mg, 0.2 mmol), 2,4-pentanedione (36 mg, 0.36 mmol), hexadecyltributylphosphonium bromide (6 mg), and benzene (3 ml) was added 0.5M sodium hydroxide (1.6 ml). The mixture was stirred for 23 h at room temperature and then washed with water. The benzene layer was evaporated and the residue recrystallized from ethanol to afford 49.8 mg (71%) of **10**, m.p. 109.5–110°, $[\alpha]_D^{20}$ −66.9° (*c* 1, chloroform); ν_{max} 1715 (CO) and 1555 cm^{-1} (NO_2).

Anal. Calc. for $C_{17}H_{21}NO_7$: C, 58.11; H, 6.02; N, 3.99. Found: C, 58.26; H, 6.02; N, 4.13.

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