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Studies on Nitro Sugars. III.[1] The Synthesis of 3-Nitrohexofuranose Derivatives

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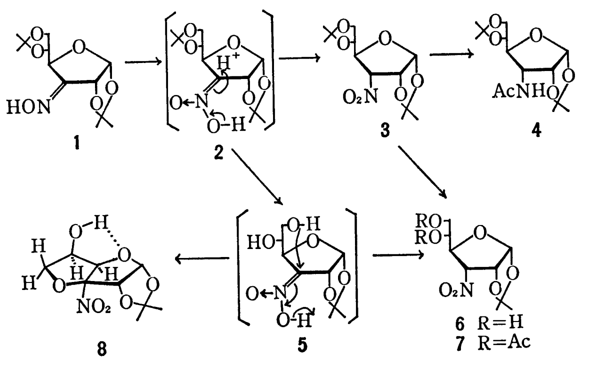
The oxidation of 1,2;5,6-di-*O*-isopropylidene-3-oximino-α-D-*ribo*-hexofuranose (**1**) with trifluoroperacetic acid at a low temperature afforded, in a 75% yield, the corresponding 3-nitro-allofuranose (**3**), but at a high temperature it gave at least three nitro compounds, *i.e.*, **3**, 3-deoxy-1,2-*O*-isopropylidene-3-nitro-α-D-allofuranose (**6**) and 3,6-anhydro-3-nitro-α-D-glucofuranose (**8**). **6** was converted to 5,6-di-*O*-acetate (**7**) and confirmed by comparison with the 3-epimer (**11**), which was prepared by the acetonation of 3-deoxy-3-nitro-D-glucose, partial hydrolysis and acetylation. The structure of **8** was instrumentally determined and supported by the fragmentation pathways in its mass spectrometry. The formation of **8** was assumed to proceed through nitronic acid (**5**) as an intermediate.

In our studies of nitro sugars for synthesizing some kinds of carbohydrate derivatives,[2,3] *e. g.*, branched sugars,[4] epoxides,[4] polyamino sugars,[5] and 2′-nucleosides,[6] a new method of synthesizing nitro sugars, particularly 2- and 3-nitro sugars, in an entirely different way had been required as a matter of course. Recently, we have presented[7] a novel route to nitro sugars with the following reaction sequence: $>CH-OH \longrightarrow >C=O \longrightarrow >C=NOH \longrightarrow >CH-NO_2$; in this route we used trifluoroperacetic acid oxidation[8] for the final step, and thus synthesized some 3-deoxy-3-nitro-α-D-pento- and hexo-furanose in excellent yields. Thie new method seems to promise a wide application, being capable of introducing a nitro group into a desired position of a furanose ring as well as of a pyranose one.[9]

In connection with the examination of this method, we now describe the oxidation of 3-oximino-hexofuranose derivative, the isolation of two by-products and the determination of their structures.

Results and Discussion

When 1,2;5,6-di-*O*-isopropylidene-3-oximino-α-D-*ribo*-hexofuranose (**1**)[10] was treated below 5 °C with trifluoroperacetic acid in the presence of dibasic sodium phosphate in acetonitrile, the corresponding 3-deoxy-3-nitroallo-furanose (**3**), $\nu_{as\ NO_2}$ 1560 cm^{-1}, was easily prepared in a 75% yield.[7] The *allo*-con-



Scheme 1.

figuration of **3** was assigned on the basis of the coupling constant, $J_{2,3}$ (4.5 Hz)[11] and a chemical identification; the catalytic reduction of **3**, followed by *N*-acetylation, gave, in an 86% yield, 3-acetamido-3-deoxy-1,2; 5,6-di-*O*-isopropylidene-α-D-allofuranose (**4**), which was characterized by comparison with an authentic sample.[12]

On the tlc of the reaction mixture, at least two by-products were detected. Under refluxing conditions, in contrast to the case with a low temperature, compound **3** was not detected, but the amounts of the by-products increased. The two by-products, 3-deoxy-1,2-*O*-isopropylidene-3-nitro-α-D-allofuranose (**6**) and 3,6-anhydro-1,2-*O*-isopropylidene-3-nitro-α-D-glucofuranose (**8**), were isolated by column chromatography, with benzene–acetone (20 : 1) as the eluent.

The structural and configurational assignments of these products rest on chemical as well as on spectroscopic evidence. The former was converted to the corresponding 5,6-di-*O*-acetate (**7**), which showed that $J_{2,3}$=3.5 Hz[11] can be assigned to the *allo*-configuration, when compared with the *gluco*-isomer (**11**), which has not coupling constant between H-2 and H-3 (see Fig. 2). The latter, $C_9H_{13}NO_7$, was unchanged by periodate oxidation and recovered. In the IR spectra, $\nu_{as\ NO_2}$ band at 1550 cm^{-1} (KBr disc) and a weak intramolecular hydrogen bond between the hydroxyl group and the ring-oxygen atom at 3555 cm^{-1} in the 0.15—0.004 mol/l concentration range in chloroform

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Table 1. The NMR data of 3-nitro-hexofuranose derivatives (TMS as an internal standard in $CDCl_3$)

Compound	Chemical shift of ring protons (τ)							Other protons (τ)	Coupling constant (Hz)						
	H-1	H-2	H-3	H-4	H-5	H-6	H-6′		J_{12}	J_{23}	J_{34}	J_{45}	J_{56}	$J_{56'}$	$J_{66'}$
3	4.09 d	4.95 q	5.1—5.3 m		5.7—6.2 m			8.45 8.60 CH_3>C< 8.65 CH_3 8.67	4	4.5	?	?	?	?	?
7	4.12 d	?	4.71 q	4.85—5.1 m		5.51 q	5.94 q	8.44 CH_3>C< 8.64 CH_3 7.94 OAc 7.97	3	3.5	7	?	3	4.5	12
8	3.94 d	5.22 d	—	4.61 d	5.42 q	5.80 q	5.95 q	8.42 CH_3>C< 8.61 CH_3 7.53 OH	4	—	—	5	5	5	10
9	3.92 d	5.02 d	4.92 d	5.66 q	5.8—6.2 m			8.47 8.56 CH_3>C< 8.64 CH_3 8.68	4	0	4	8	?	?	?
11	3.90 d	5.00 d	4.93 d	5.34 q	5.09 o	5.43 q	5.89 q	8.48 CH_3>C< 8.64 CH_3 7.94 OAc	3	0	4	8	3	4	12

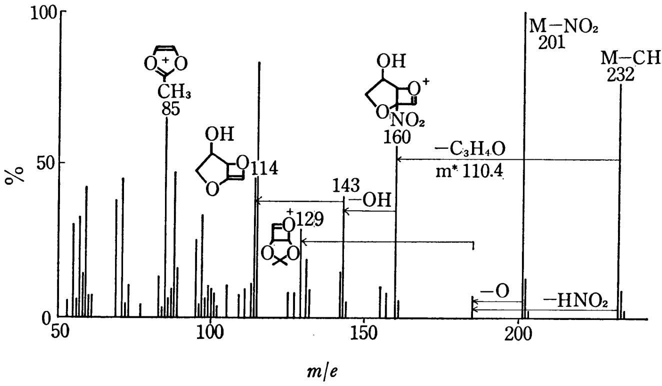

Fig. 1. Mass spectrum of 3,6-anhydro-1,2-*O*-isopropylidene-3-nitro-α-D-glucofuranose (**8**).

are observed. In the NMR spectrum, as is shown in Table 1, two methyl protons of the *O*-isopropylidene group, one hydroxyl proton, and six ring-proton signals of the sugar skeleton are observed. The NMR data suggest the absence of the ring proton at the C–3 position. Furthermore, the mass spectrum provides two significant pieces of information regarding the structure; the M–CH_3 ion peak at *m/e* 232, which is characteristic[13] of *O*-isopropylidene derivatives, and the M–NO_2 peak at *m/e* 201, which means a specific structure since no split of —NO_2 at the first step was observed[14] in the mass spectra of ten new nitro sugars which have a secondary nitro group besides nitroolefin and **8**. Consequently, the 3,6-anhydro structure of **8** was found to agree with all these data; it was also supported by the fragmentation pathways, as is shown in Fig. 1.

As is shown in Table 2, the formation of **3**, **6**, and **8** was obviously dependent on the temperature and on the ratio of trifluoroperacetic acid and dibasic sodium phosphate used as a buffer. In this reaction, as is shown in Scheme 1, the intermediary nitronic acid (**2**) may be normally converted to **3** through prototropy from the upper side of the furanose ring under mild conditions. In the presence of a smaller amount of the buffer and/or under an elevated temperature, however, **3** should be hydrolyzed to afford **6**. On the other hand, the 3,6-anhydro derivative **8** may be formed through the intermediate (**5**) which is derived from **2** by partial hydrolysis with trifluoroacetic acid under

Table 2. Reaction conditions and yields on oxidation of **1**

Mole ratio to **1**		Temperature °C	Time (hr)	Yield (%)[a]		
CF_3CO_3H	Na_2HPO_4			**3**	**6**	**8**
2.1	14	5	2	75	trace	trace
3.3	14	5	2	62	2	2
1.05	1.25	20	2	9	38	14
2.1	2.5	20	2	10	30	11
2.1	5.6	55	1	19	5	20
2.1	5.6	reflux	0.5	trace	13	15
2.1	14	reflux	0.5	1	15	18

a) As a separated product by column chromatography.

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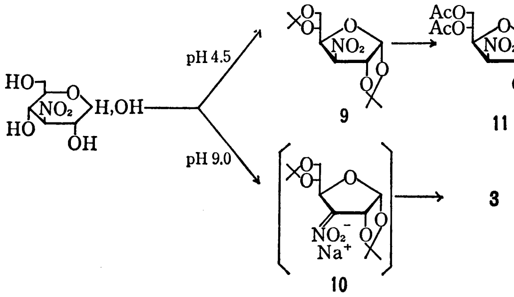
severe conditions; that is, an oxygen atom at the C–6 position of **5** attacks the cationic C–3 carbon atom to form oxidatively the 3,6-anhydro structure because of the presence of the peracid. However, the conversion of **5** to **6** through prototropy may also be possible. Under acidic conditions, nitronic acids are generally accessible to protonation, followed by a nucleophilic attack such as that of a hydroxide and bromide ion to afford nitroso compounds.[15] However, the formation of **8**, with a nitro group, can not be interpreted by a similar mechanism. Therefore, the removal of a hydride ion from the nitronic acid with the assistance of the peracid may enhance the cationic character of the C–3 carbon atom, thus making the hydroxyl oxygen atom at C–6 attack it nucleophilically.



Scheme 2.

In order to discuss NMR-spectrometrically a 3-nitrohexofuranose series, the synthesis of the *gluco*-isomer by the usual acetonation[16] was examined. However, it failed in the case of the usual neutralization, which is performed in an alkaline medium. The acetonation[17] of 3-deoxy-3-nitro-D-glucose in acetone using zinc chloride and phosphoric acid, followed by neutralization at pH 9, afforded **3** in a 15% yield, whereas at pH 4.5 3-deoxy-1,2; 5,6-di-*O*-isopropylidene-3-nitro-α-D-glucofuranose (**9**) was obtained in an 18% yield. Through the intermediary of aci-salt (**10**), **3** might be formed. The partial hydrolysis of **9**, followed by acetylation with acetic anhydride and boron trifluoride, afforded, in a 34% yield, 5,6-di-*O*-acetyl-3-deoxy-1,2-*O*-isopropylidene-3-nitro-α-D-glucofuranose (**11**), which was confirmed by the coupling constant, $J_{2,3}=0$, in the NMR spectrum (Fig. 2).

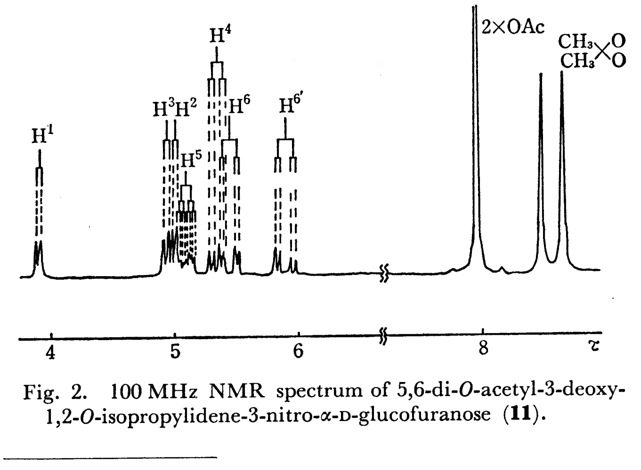


Fig. 2. 100 MHz NMR spectrum of 5,6-di-*O*-acetyl-3-deoxy-1,2-*O*-isopropylidene-3-nitro-α-D-glucofuranose (**11**).

Experimental

General. All the melting points were determined in capillaries and are uncorrected. The specific rotations were measured with a Carl Zeiss photoelectric polarimeter. The NMR spectra were recorded at 100 MHz with a JNM-4H-100 (JEOL) spectrometer in chloroform-*d*, using tetramethylsilane as the internal standard. The column chromatography was carried out on silica gel (100 mesh, Mallinckrodt, St. Louis). The tlc's were performed on silica gel (Wakogel B-5, Japan), with a solvent system of (A) benzene–acetone (30 : 1) or (B) benzene–methanol (19 : 1). All the evaporation were performed *in vacuo.*

*3-Dexoy-1,2;5,6-di-O-isopropylidene-3-nitro-α-D-allofuranose (**3**).* Into a solution of trifluoroperacetic acid in acetonitrile, prepared by mixing successively 90% hydrogen peroxide (289 mg, 7.64 mmol), trifluoroacetic anhydride (1.93 g, 9.2 mmol), acetonitrile (8 ml), dibasic sodium phosphate (7.3 g, 51.4 mmol), and urea (0.05 g), 1,2;5,6-di-*O*-isopropylidene-3-oximino-α-D-*ribo*-hexofuranose (**1**)[10] (1 g, 3.66 mmol) was slowly stirred below 5 °C. After 2 hr, the mixture was evaporated below 40 °C and extracted with chloroform (4× 20 ml); the extract was washed with water three times and evaporated. The resulting crystals were recrystallized from chloroform/petroleum ether to give 0.8 g (75%), showing a mp of 112—113 °C, $[\alpha]_D^{20}$ +106° (*c* 1, $CHCl_3$), IR(KBr): 1560 cm^{-1} (ν_{NO_2}) and tlc (solvent A): R_f 0.37.

Found: C, 50.01; H, 6.61; N, 4.81%. Calcd for $C_{12}H_{19}NO_7$: C, 49.82; H, 6.62; N, 4.84%.

*3-Acetamido-3-deoxy-1,2;5,6-di-O-isopropylidene-α-D-allofuranose (**4**).* Into a suspension of prehydrogenated 10% Pd–C (0.5 g) in methanol containing 1 M acetic acid (1.6 ml), **3** (0.45 g) was stirred in an atmosphere of hydrogen at 1 atm. After 24 hr, the reaction mixture, absorbing 138 ml of hydrogen (theoretical: 110 ml), was filtered and evaporated; then the residue was dissolved in methanol (10 ml) and acetylated with acetic anhydride (0.3 ml) at room temperature. After 1 hr, the mixture was evaporated until it became odorless. The remaining crystals were recrystallized from ethanol/petroleum ether to give 0.4 g (86%); mp 126—127 °C; $[\alpha]_D^{20}$ +73° (*c* 1, $CHCl_3$). The other data agreed completely with the authentic sample.

*5,6-Di-O-acetyl-3-deoxy-1,2-O-isopropylidene-3-nitro-α-D-allofuranose (**7**).* Into a mixture of 90% hydrogen peroxide (79.4 mg, 2.1 mmol), trifluoroacetic anhydride (525 mg, 2.5 mmol), acetonitrile (3 ml), dibasic sodium phophate (355 mg, 2.5 mmol) and urea (10 mg), **1** (273 mg, 1 mmol) was stirred at room temperature. The reaction mixture was evaporated below 40 °C and chromatographed on a silica-gel column (10×2.7 cm) with chloroform. The eluate was collected in 50-ml portions. Fractions No. 5—8 were combined and evaporated. The remaining sirup was treated with acetic anhydride (160 mg) in pyridine (4 ml) at room temperature. After the reaction mixture had stood for 1.5 hr, its evaporation gave crude crystals which were subsequently recrystallized from ether–petroleum ether. Yield, 75 mg (23%); mp 106—107 °C; $[\alpha]_D^{20}$ +110° (*c* 0.9, $CHCl_3$);

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IR(KBr): 1740 ($\nu_{C=O}$), 1560 cm^{-1} (ν_{NO_2}); tlc (solvent A): R_f 0.18.

Found: C, 46.78; H, 5.61; N, 4.08%. Calcd for $C_{13}H_{19}NO_9$: C, 46.85; H, 5.75; N, 4.20%.

3,6-Anhydro-1,2-O-isopropylidene-3-nitro-α-D-glucofuranose (8). Into a mixture of 90% hydrogen peroxide (289 mg, 7.64 mmol), trifluoroacetic anhydride (1.93 g, 9.2 mmol), acetonitrile (2 ml), dibasic sodium phosphate (2.93 g, 20.6 mmol), and urea (73 mg), **1** (1 g, 3.66 mmol) was stirred. The mixture was heated at 55 °C for 1 hr and then evaporated. The mixture was put on a silica-gel column (7.2 × 3.0 cm) with benzene. After the elution of 150 ml of benzene, **8** was eluted with benzene–acetone (19 : 1) and recrystallized from chloroform–petroleum ether. Yield, 146 mg (16%); mp 140—141 °C; $[\alpha]^{20}_{D}$ +58° (c 1, $CHCl_3$); IR(KBr): 1550 cm^{-1} (ν_{NO_2}); tlc (solvent B): R_f 0.52.

Found: C, 43.78; H, 5.10; N, 5.43%. Calcd for $C_9H_{13}NO_7$: C, 43.73; H, 5.30; N, 5.67%.

Acetonation of 3-Deoxy-3-notro-D-glucose. A mixture of 3-deoxy-3-nitro-D-glucose (200 mg), acetone (8 ml), zinc chloride (290 mg), and 85% phosphoric acid (250 mg) was stirred at room temperature for 24 hr. The reaction mixture was then slowly stirred into a diluted sodium carbonate solution, with the pH kept at 9.0 or 4.5. Chromatography on a silica-gel column with benzene, followed by recrystallization, afforded **3** (40 mg, 15%) or **9** (49 mg, 18%). **9**: mp 61—62 °C; $[\alpha]^{20}_{D}$ +7.3° (c 1, $CHCl_3$); IR(KBr): 1550 cm^{-1} (NO_2); tlc (solvent A): R_f 0.37.

Found: C, 49.96; H, 6.50; N, 4.83%. Calcd for $C_{12}H_{19}NO_7$: C, 49.82; H, 6.62; N, 4.84%.

5,6-Di-O-acetyl-3-deoxy-1,2-O-isopropylidene-3-nitro-α-D-glucofuranose (11). Into a solution of **9** (200 mg) in acetone (15 ml), 0.8% sulfuric acid (15 ml) was stirred. After 21 hr, the solution was completely neutralized with barium carbonate and filtered. The filtrate was evaporated and acetylated with acetic anhydride (0.5 ml) and boron trifluoride etherate (2 drops). Then the reaction mixture was evaporated and chromatographed with benzene. The fraction containing **11** was easily detected by tlc. The recrystallization of the residue from ether–petroleum ether afforded crystalline **11** (69 mg, 34%); mp 79—80 °C; $[\alpha]^{20}_{D}$ +17° (c 1.1, $CHCl_3$); IR(KBr): 1740 (C=O), 1550 cm^{-1} (NO_2); tlc (solvent A): R_f 0.18.

Found: C, 46.59; H, 5.76; N, 4.04%. Calcd for $C_{13}H_{19}NO_9$: C, 46.85; H, 5.75; N, 4.20%.

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