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STUDIES ON NITRO SUGARS

PART II*. SYNTHESIS OF BENZYL 3,5-DI-*O*-BENZYL-2-DEOXY-2-NITRO-α-D-XYLOFURANOSIDE AND ITS TRANSGLYCOSYLATION WITH ALKALI

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ABSTRACT

Oxidation of benzyl 3,5-di-*O*-benzyl-2-oximino-α-D-*threo*-pentofuranoside (**6**) with trifluoroperoxyacetic acid afforded benzyl 3,5-di-*O*-benzyl-2-deoxy-2-nitro-α-D-xylofuranoside (**8**) in 83% yield. Transglycosylation of **8** to give the corresponding methyl xyloside (**10**) was achieved in alkaline methanol at room temperature, proceeding probably via an intermediate 2-nitroglycal (**9**). The structures of **8** and **10** were determined from their specific rotations and p.m.r. spectra.

INTRODUCTION

Recently we have presented[1] a novel route to nitro sugars by the following reaction sequence: $>CH-OH \rightarrow >C=O \rightarrow >C=NOH \rightarrow >CH-NO_2$, applying trifluoroperoxyacetic acid oxidation[2] for the final step, and have synthesized some 3-deoxy-3-nitrofuranoses in excellent yields. This new method gives promise of wide application, being useful for introducing a nitro group into a desired position of a furanose ring as well as a pyranose one[3].

In continuation of these studies, we now describe the synthesis of the title 2-deoxy-2-nitrofuranoside, a compound inaccessible by conventional means[4,5], and also its facile transglycosylation with alkali.

RESULTS AND DISCUSSION

Treatment of oily 3,5-di-*O*-benzyl-1,2-*O*-isopropylidene-α-D-xylofuranose (**2**), derived from 1,2-*O*-isopropylidene-α-D-xylofuranose[6] (**1**) in the usual way, with hydrogen chloride-saturated benzyl alcohol at room temperature, gave syrupy benzyl 3,5-di-*O*-benzyl-α-D-xylofuranoside (**3**), which was isolated and characterized as the

*We designate Ref. 1 as Part 1.

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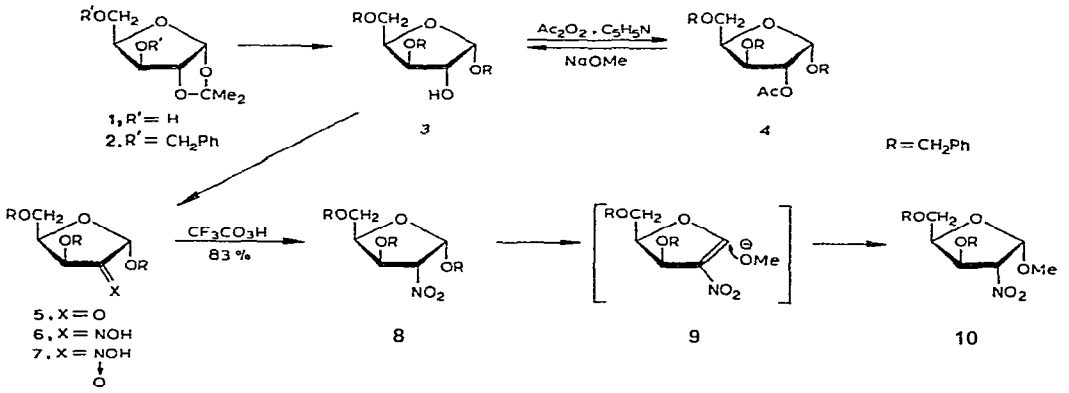
corresponding crystalline 2-acetate (**4**). A chromatographically pure sample of **3** was obtained when **4** was deacetylated with sodium methoxide in methanol.



Assignment of the α-anomeric configuration to **3** and to **4** is based upon the following observations: (*a*) their specific rotations (in chloroform) are positive, being +56.0° and +63.2° (ref. 7), respectively; (*b*) an i.r. absorption band (ν_{OH}) of **3** in chloroform is observed at 3540 cm^{-1} in the concentration range 0.2~0.007 moles per liter, indicating the existence of an intramolecular hydrogen-bond, which can be expected only for the α-D-xylofuranoside **3** and not for its β-anomer; (*c*) $J_{1,2}$ values of 4.8 and 4.3 Hz, for **3** and **4**, respectively, indicate that H-1 and H-2 are oriented in *cis*-relationship on the furanose ring[8]. Oxidation[9] of **3** with dimethyl sulfoxide, followed by column chromatography on silica gel with benzene as an eluent, afforded the unstable 2-ulose **5**, $\nu_{C=O}$ 1775 cm^{-1} (neat), which was immediately converted into syrupy benzyl 3,5-di-*O*-benzyl-2-oximino-α-D-*threo*-pentofuranoside (**6**) in the usual manner, in 67% overall yield from **3**.

Treatment of the oxime **6** with trifluoroperoxyacetic acid, prepared according to Emmons *et al.*[2], in the presence of excess dibasic sodium phosphate and a small amount of urea for 2 h at room temperature, gave the syrupy benzyl 3,5-di-*O*-benzyl-2-deoxy-2-nitro-α-D-xylofuranoside (**8**) in over 83% yield, ν_{asNO_2} 1550 cm^{-1} (neat), and no other product was detected by p.m.r. and t.l.c. This highly selective formation of **8** is indeed surprising, as the benzyloxy groups at C-1 and C-3 would seem to have nearly equivalent steric dispositions with respect to the sp^2-hybridized C-2 in the intermediary nitronic acid[2] (**7**), so that a mixture of **8** and its 2-epimer might reasonably have been expected to arise. The mechanism of this reaction is to be further investigated.

In determining the structure of **8**, the failure of an attempted reduction to the authentic 2-amino sugar in the presence of palladium on carbon necessitated assignment of the configuration by p.m.r. data only. From the p.m.r. spectra of many nitro sugars, it is known[10,11] that the nitro group does not materially influence the coupling constants but does affect the chemical shifts. Therefore, the coupling constants for the nitro sugar should be similar to those for common sugars. When H-1 and H-2 on the

furanose ring are *trans*-oriented, the $J_{1,2}$ value would range from 0~1.9 Hz[8,12–14]. The observed $J_{1,2}$ value of 4.0 Hz in **8** there for indicates a *cis*-relationship, and thus the α-D-*xylo* configuration ($[\alpha]_D^{20}$ +65.0° in chloroform).

The position β to the nitro group in the 3-nitroglycoside series is accessible to various nucleophiles[4,5,10,15,16], including purines[17] and pyrimidines[18], with weakly basic catalysts such as sodium hydrogen carbonate. On the other hand, alkaline cleavage of acetals[19,20,21] including glycosidic bonds, through activation by a nitro group in the β-position has been observed on several occasions. Furthermore, Baer has predicted[22] that glycosides carrying a nitro group on the ring, in the position β to the ring oxygen atom, namely 2-nitroglycosides, might be labile to glycosidic fission. Therefore, the chemical behavior of the anomeric center of 2-nitro sugars in alkaline media may offer interesting possibilities especially for new synthetic routes to glycosides by way of nucleophilic elimination–addition reactions. In fact, it was observed that treatment of **8** with a 1:1 mixture of 6M sodium hydroxide and methanol at room temperature, followed by column chromatography on silica gel with benzene as an eluent, afforded crystals of the corresponding methyl xyloside (**10**), m.p. 83–85°, in 48% yield. The formation of a trace of the β-anomer was detected by p.m.r. spectroscopy of the unpurified reaction mixture, but it was not isolated.

Assignment of the α-D configuration to **10** was based upon the positive $[\alpha]_D^{20}$ value[7] of +30° (in chloroform), the $J_{1,2}$ value of 3.8 Hz, and the similarity of the spectra of **8** and **10**. Furthermore, the anomeric benzyl methylene group of **8** resonates as an AB quartet in the region of τ 5.33–5.38 (Table I), whereas the benzyl methylene signals of the groups at C-5 and C-3 appear as a singlet and an AB quartet*, respectively, about 0.1 p.p.m. higher than that for the anomeric substituent. Hence the signals of the two benzyl methylene groups of **10** appearing at τ 5.48 (quartet) and τ 5.49 (singlet) were assigned to the substituents at C-3 and C-5, respectively. No signal appeared in the region of τ 5.33–5.38, indicating that the exchange reaction had occurred at the anomeric position.

EXPERIMENTAL

General. — Melting points were determined in capillaries and are uncorrected. Specific rotations were measured with a Carl Zeiss photoelectric polarimeter. P.m.r. spectra were recorded at 100 MHz with a spectrometer JNM-4H-100 (JEOL), and tetramethylsilane as an internal standard. Column chromatography was carried out on silica gel (100 mesh powder, Mallinckrodt, St. Louis) developed with benzene. T.l.c. were performed on silica gel (Wakogel B-5, Japan) with a solvent system of 30:1 benzene–acetone.

3,5-Di-O-benzyl-1,2-O-isopropylidene-α-D-xylofuranose (**2**). — A mixture of 1,2-*O*-isopropylidene-α-D-xylofuranose[6] (**1**) (38 g) and benzyl chloride (328 g) was stirred vigorously for 2 h at 150° in the presence of potassium hydroxide (190 g). After

*It is reasonable[23] to assume that the benzyl methylene group in an assymmetric environment (C-1, C-3) resonates as an AB quartet, whereas the one remote from it (C-5) gives rise to a singlet.

TABLE I

P.M.R. DATA FOR 3,5-DI-*O*-XYLOFURANOSES IN CHLOROFORM-*d* (Me_4Si AS AN INTERNAL STANDARD)

Compound	*Chemical shift* (τ)						*Coupling constant* (*Hz*)						*Chemical shift of benzyl methylene proton* (τ) *at*		
	H-1	*H-2*	*H-3*	*H-4*	*H-5*	*H-5'*	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{4,5'}$	$J_{5,5'}$	*C-1*	*C-3*	*C-5*
2	4.11	?	6.07	?	6.27	6.27	4.0	0	3.3	6.5			—	5.48 *q*	5.49 *s*
3	4.88	5.79	6.02	?	6.27	6.40	4.8	3.6	6.0	4.8	6.0	10.5	5.33 *q*	5.44 *q*	5.48 *s*
4	4.62	4.98	?	?	6.23	6.37	4.3	4.3	?	4.8	5.5	10.7	5.38 *q*	5.51 *q*	5.45 *s*
8	4.29	5.09	?	?	?	?	4.0	5.8	?	?	?	?	5.37 *q*	5.47 *q*	5.48 *s*
10	4.38	5.00	?	5.68	6.31	6.31	3.8	6.5	3.8	7.0			—	5.48 *q*	5.49 *s*

cooling, the reaction mixture was poured into ice and water with stirring, and the mixture was extracted with dichloromethane (4 × 100 ml). The extract was washed with water five times and dried over calcium chloride. The oily residue obtained on evaporation of the solvent *in vacuo* was purified by distillation; yield 32 g (45%), b.p. 183° at 0.03 mm Hg, $[\alpha]_D^{20}$ −51° (*c* 1, chloroform); R_F 0.40 (t.l.c.).

Anal. Calc. for $C_{22}H_{26}O_5$:C, 71.33; H, 7.08. Found: C, 71.04; H, 7.00.

*Benzyl 2-*O*-acetyl-3,5-di-*O*-benzyl-α-*D*-xylofuranoside* (**4**). — A mixture of **2** (20.4 g) and benzyl alcohol (66 ml) was stirred at 3° and hydrogen chloride gas was passed through for 35 min. The reaction mixture was poured with vigorous stirring into an excess of a 1:1 mixture of acetone and aqueous saturated sodium hydrogen carbonate. After removal of inorganic material, the filtrate was evaporated *in vacuo* and the residue chromatographed on silica gel with benzene as eluant. The eluate was evaporated and the residue (14.6 g) acetylated with acetic anhydride (7 ml) and pyridine (25 ml) for 1 h at room temperature. The reaction mixture was evaporated *in vacuo* until it became odorless, and the residue was recrystallized twice from ethanol; yield 6.7 g (42%), m.p. 72–73°, $[\alpha]_D^{20}$ +63.2° (*c* 1, chloroform), ν_{max}^{KBr} 1730 cm^{-1} ($\nu_{C=O}$); R_F 0.51 (t.l.c.).

Anal. Calc. for $C_{28}H_{30}$: C, 72.71; H, 6.54. Found: C, 72.99; H, 6.54.

*Benzyl 3,5-di-*O*-benzyl-α-*D*-xylofuranoside* (**3**). — To a suspension of **4** (5.6 g) in methanol (100 ml), M sodium methoxide (5 ml) was added with occasional stirring. After 23 h, the solution was neutralized with cation-exchange resin (Mitsubishi Diaion SK 1, H^+ form, Japan) and evaporated *in vacuo*. The remaining crude syrup (5.1 g, 100%) showed $[\alpha]_D^{20}$ +56° (*c* 1, chloroform); R_F 0.31 (t.l.c.); p.m.r. spectrum see Table I).

*Benzyl 3,5-di-*O*-benzyl-2-oximino-α-*D*-*threo*-pentofuranoside* (**6**). — Chromatographically pure syrupy **3** (5.1 g) was dissolved in distilled dimethyl sulfoxide (68 ml) and acetic anhydride (40 ml). After 24 h at room temperature, the solution was evaporated *in vacuo* below 60°. An extract of the residue obtained with ethyl acetate was washed four times with water and evaporated *in vacuo* to give syrupy **5**; ν_{max}^{film} 1775 cm^{-1} ($\nu_{C=O}$). A mixture of the 2-ulose **5**, hydroxylamine hydrochloride (4.9 g), pyridine (59 ml), and ethanol (59 ml) was heated under reflux for 2 h and evaporated *in vacuo*. The solution of the residue in dichloromethane was washed three times with water and then evaporated. The remaining syrup was chromatographed on a column of silica gel with benzene as eluant, and the eluate was evaporated *in vacuo* to give syrupy **6**; yield (3.5 g (67%), ν_{OH} 3300 cm^{-1} $\nu_{C=O}$ absent) and R_F 0.23.

Anal. Calc. for $C_{26}H_{27}NO_5$: C, 72.04; H, 6.28; N, 3.23. Found: C, 71.65; H, 6.36; N, 3.14.

*Benzyl 3,5-di-*O*-benzyl-2-deoxy-2-nitro-α-*D*-xylofuranoside* (**8**). — To a mixture of 90% hydrogen peroxide (0.166 g), trifluoroacetic anhydride (1 g), acetonitrile (8 ml), dibasic sodium phosphate (1.37 g) and urea (5 mg), was added a solution of **6** (0.233 g) in acetonitrile (3 ml). The reaction mixture was stirred for 2 h at room temperature and then filtered, and the filtrate was evaporated *in vacuo* below 40°. Chromatography of the syrup on a column of silica gel with benzene as eluent gave

syrupy **8**; yield 0.203 g (83%), $[\alpha]_D^{20}$ +65° (*c* 0.7, chloroform); R_F 0.80 (t.l.c.): ν_{max}^{film} 1550 cm^{-1} (ν_{asNO_2}).

Anal. Calc. for $C_{26}H_{27}NO_6$: C, 69.47; H, 6.05; N, 3.12. Found: C, 69.25; H, 5.92; N, 3.10.

Methyl 3,5-di-O-benzyl-2-deoxy-2-nitro-α-D-xylofuranoside (**10**). — Compound **8** (0.2 g) was dissolved in a mixture of methanol (3 ml) and 6M aqueous sodium hydroxide (3 ml) with stirring at room temperature. After 24 h, the solution was deionized with cation-exchange resin (Mitsubishi Diaion SK 1, H^+ form, Japan) and then evaporated. The resulting syrup was dissolved in a small amount of benzene and put on a column of silica gel (2.5 × 7.0 cm). The eluate was collected in 30-ml portions. Fraction 5 and 6 were combined and evaporated *in vacuo* to give crystals of **10**; yield 80 mg (48%), showing m.p. 83–85°, $[\alpha]_D^{20}$ +30° (*c* 0.9, chloroform); R_F 0.68 (t.l.c.); ν_{max} 1545 cm^{-1} (ν_{asNO_2}).

Anal. Calc. for $C_{20}H_{23}NO_6$: C, 64.33; H, 6.21; N, 3.75. Found: C, 64.11; H, 6.27; N, 3.83.

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