Carbohydrate Research, 60 (1978) 97–103

C-GLYCOSYL DERIVATIVES IN NITRO SUGAR CHEMISTRY: SYNTHESIS OF D-RIBOFURANOSYLNITROMETHANE DERIVATIVES AND THEIR EPIMERIZATION UNDER NEUTRAL CONDITIONS*

TETSUYOSHI TAKAMOTO, HIROSHI OMI, TOSHIHIKO MATSUZAKI, AND ROKURO SUDOH
Department of Chemistry, Faculty of Science, Tokyo Institute of Technology, Ookayama, Meguro-ku, Tokyo 152 (Japan)
(Received March 15th, 1977; accepted for publication in revised form, May 24th, 1977)

ABSTRACT

The nitromethane condensation-product (**3**) from 2,3-*O*-isopropylidene-D-ribose (**2**) underwent dehydration and subsequent thermal cyclization in dimethyl sulfoxide to give a mixture of α- and β-D-ribofuranosylnitromethane derivatives (**5** and **6**) in a ratio of 7:2. Heating of 6-*O*-benzoyl-1-deoxy-1-nitro-D-altritol (**10**) in water afforded α- and β-*C*-glycosyl derivatives (**11** and **12**) in a ratio of 2:3. Pure **11** and **12** gave the same mixture of **11** and **12** when heated in water, and similar epimerization of the isopropylidene acetals **5**, **6**, **13**, and **14** proceeded readily upon heating, leading mainly to the thermodynamically more-stable α anomers.

INTRODUCTION

The natural occurrence of a number of *C*-nucleosides[1] has led to considerable work on the synthesis of anomeric C–C bonds[2]. Recently, Ohrui *et al.*[3] have demonstrated that 2,3-*O*-isopropylidene-D-ribofuranosylalkanes having electron-withdrawing substituents, such as cyano, carboxyl, and the like, at the α position are readily prepared by Wittig reactions on 2,3-*O*-isopropylidene-D-ribose. The α anomers of these compounds are thermodynamically more-stable than their β counterparts under conditions of alkaline equilibration. On the other hand, recent interest in nitro sugar chemistry in our laboratory[4] has extended to synthetic studies on *C*-glycosyl derivatives involving nitromethyl groups at C-1, as the highly reactive nitro group may have wide applications for C–C bond-formation[5,6]. Such *C*-glycosyl derivatives are also very interesting with respect to the stereochemical considerations already mentioned. It was previously reported that 1-deoxy-1-nitro-D-alditols undergo dehydration and subsequent Michael-type addition and cyclization to afford mainly glycopyranosylnitromethanes under gentle reflux in water[7,8] or in 1% aqueous

*Reported at the VIIIth International Symposium on Carbohydrate Chemistry, Kyoto, Japan, August 19, 1976.

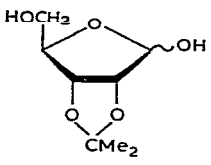
sulfuric acid[9]. We now describe the synthesis of D-ribofuranosylnitromethane derivatives via introduction of a 3,4-acetal function or a 6-*O*-benzoyl group into the 1-deoxy-1-nitro-D-hexitols derived from D-ribose. The strong electron-withdrawing power of the nitro group leads to facile epimerization under neutral conditions.

RESULTS AND DISCUSSION

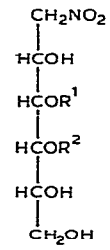
Condensation of nitromethane with 2,3-*O*-isopropylidene-D-ribose[10] (**2**) in the conventional manner[11] gave 3,4-*O*-isopropylidene-1-deoxy-1-nitro-D-allitol and -D-altritol* (**3** and **4**) in 15 and 9% yields, respectively, with recovery of **2** in 62% yield. Higher yields could not be obtained from this reaction by variation of the conditions. These facts indicate that the reversible nature of the nitromethane condensation plays a crucial role. Although, at this stage, application of an irreversible Wittig reaction might be considered, ylides of nitromethane have not been prepared[12].

Determination of the configuration at C-2 of **3** and **4** is based on the circular dichroism† spectra of the corresponding deprotected nitroalditols **9** and **8**, and indicates the (*S*) and (*R*) chiralities, respectively.

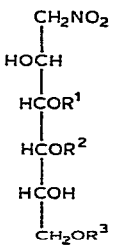
Heating **3** in dimethyl sulfoxide for 12 h at 100° caused the anticipated ring-closure via the nitroalkene intermediate (**7**), providing in 88% yield a mixture of



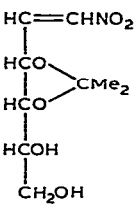
2



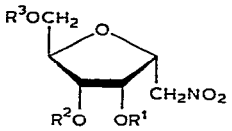
3 $R^1 = R^2 = CMe_2$
9 $R^1 = R^2 = H$



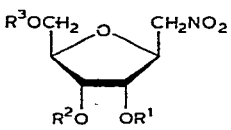
4 $R^1 = R^2 = CMe_2, R^3 = H$
8 $R^1 = R^2 = R^3 = H$
10 $R^1 = R^2 = H, R^3 = Bz$



7



5 $R^1 = R^2 = CMe_2, R^3 = H$
11 $R^1 = R^2 = H, R^3 = Bz$
13 $R^1 = R^2 = CMe_2, R^3 = Bz$



6 $R^1 = R^2 = CMe_2, R^3 = H$
12 $R^1 = R^2 = H, R^3 = Bz$
14 $R^1 = R^2 = CMe_2, R^3 = Bz$

*Compound **4** was very unstable; a degradation product showing no nitro bands in its i.r. spectrum and giving a strongly positive spot with sulfuric acid on t.l.c. was obtained when column purification was attempted.

†1-Deoxy-1-nitro-alditols having the (*S*) configuration at C-2 show positive c.d. curves, whereas the (*R*) isomers give negative curves[13–15].

2,5-anhydro-1-deoxy-3,4-*O*-isopropylidene-1-nitro-D-altritol and D-allitol (**5** and **6**) in a ratio of 7:2, as determined by integration of the acetal carbon atoms in the ^{13}C n.m.r. spectrum and the isopropylidene methyl protons (δ 1.51 and 1.58) in the ^{1}H n.m.r. spectrum. These products showed the same R_F values in several solvent systems and could not be separated. The cyclization also proceeded in acetonitrile after boiling for 78 h under reflux to give the same ratio of products, but the reaction did not occur in 1,4-dioxane or toluene, and gave a complicated mixture when water or *N*,*N*-dimethylformamide were used.

When a 4:1 epimeric mixture of **8** and **9** [obtained by direct condensation of D-ribose (**1**) with nitromethane] was treated with an equimolar amount of benzoyl chloride–pyridine in 1,4-dioxane, crystalline 6-*O*-benzoyl-1-deoxy-1-nitro-D-altritol (**10**) was isolated in 8% overall yield. The structure of **10** was elucidated by catalytic hydrogenation followed by saponification with sodium methoxide to give a ninhydrin-positive spot that had the same chromatographic R_F value as that of the hydrogenation product of **8**, but was different from that derived from **9**.

Compound **10** also cyclized in the same manner in water or dimethyl sulfoxide to afford crystalline 2,5-anhydro-6-*O*-benzoyl-1-deoxy-1-nitro-D-altritol and -D-allitol (**11** and **12**), in 68% total yield. In contrast to the behavior of **5** and **6**, the β isomer **12** preponderated over the α isomer **11** (ratio of 3:2). Although the cyclization of **3** and **10** thus proceeded smoothly in polar solvents, it was extremely slow (taking $>$ 80 h) in acetonitrile, and did not take place at all in such less-polar solvents as 1,4-dioxane and toluene. Thus, polar solvents are required for the dehydration and cyclization steps.

The considerable influence of the isopropylidene group (which makes the conformation rigid), on the formation of thermodynamically favored α isomers, has been shown in other examples[3,16]. On the other hand, in the absence of the acetal function, epimerizable β-*C*-glycosyl derivatives are known[3,17,18] to be thermodynamically more-stable than their α counterparts. As a rationalization for such configurational questions, Ohrui *et al.*[19,20] have recently proposed an anomeric effect in furanoses, based upon *cis* 1,2- and 1,3-interactions between O and H substituents.

When the mixture of **11** and **12** was treated with acetone in the presence of *p*-toluenesulfonic acid, followed by chromatography, 2,5-anhydro-6-*O*-benzoyl-1-deoxy-3,4-*O*-isopropylidene-1-nitro-D-altritol and -D-allitol (**13** and **14**) were obtained in 90% total yield. Treatment of a 2:3 mixture of **13** and **14** with sodium methoxide for 3 h afforded **5** and **6** (3:1) through debenzoylation and epimerization, with opening and reclosure of the furanose ring. The ^{13}C n.m.r. spectrum of the *C*-glycosyl derivatives **5**, **6**, **13**, and **14** showed clearly distinguishable signals for the isopropylidene group* (Table I).

Although, of course, the equilibrium between "α" and "β" isomers was readily

*^{13}C-Chemical shift values of isopropylidene methyl and acetal carbon atoms may be conveniently employed for determination of glycosylic configuration in appropriate *C*-glycosyl derivatives[3].

TABLE I

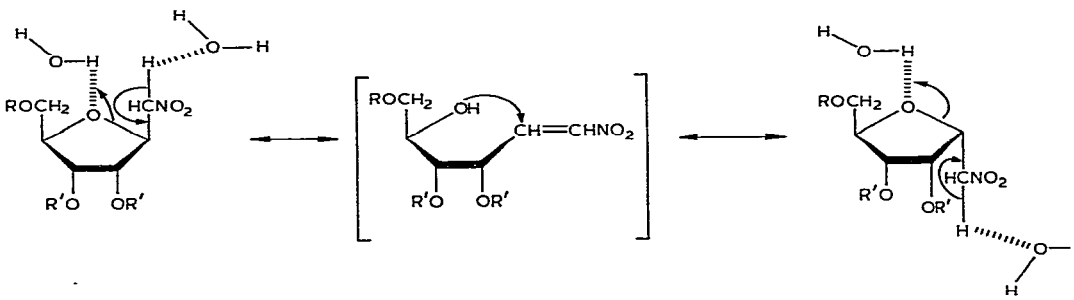
^{13}C-N.M.R. DATA IN CHLOROFORM-*d*: CHEMICAL SHIFTS (p.p.m.) OF ISOPROPYLIDENE CARBON ATOMS

Compound	*Isopropylidene methyl*		*Acetal carbon atom*
5	24.61	26.04	113.30
6	25.32	27.27	114.73
13	24.68	26.11	113.62
14	25.50	27.74	115.28

TABLE II

NOTEWORTHY SOLVENT-EFFECTS ON THE EPIMERIZATION OF β-**14** INTO THE α ANOMER **13** AT 85–90° WITHOUT BASE

Solvent	*Time (h)*	*Ratio (α:β)*
Dry Me_2SO	23	3:2
Commercial Me_2SO	8	4:1
Me_2SO + H_2O (3:1)	3	4:1
Dry MeCN	23	recovered
MeCN + H_2O (3:1)	8	4:1



achieved under basic conditions, it is noteworthy that it could also be realized by thermal equilibration under neutral conditions. Under anhydrous conditions, as shown in Table II, epimerization of the β isomer **14** took place relatively slowly in dimethyl sulfoxide and not at all in acetonitrile. Compounds **11** and **12** also gave mixtures of the epimers in water (3 h) or dry dimethyl sulfoxide (20 h), but not in toluene. From the foregoing effects, it is clear that water, even in traces is highly effective in promoting rapid epimerization in dimethyl sulfoxide. As no such epimerization was observed at room temperature, thermal factors must be quite important and a possible push–pull mechanism aided by water is shown in the accompanying scheme. Starting from 1-deoxy-1-nitro-D-alditols, water formed first during the dehydration step probably plays a significant role in such epimerization, after initial formation of the kinetic products.

EXPERIMENTAL

General methods. — Melting points are uncorrected. Solutions were evaporated *in vacuo*. Optical rotations were measured with a Carl Zeiss photoelectric polarimeter. Circular dichroism spectra of the nitroalditols were recorded with a JASCO Model ORD/UV-5 automatic recording spectropolarimeter, Japan Spectroscopic Manufacturing Co. (Nippon Bunko). ^{1}H-N.m.r. spectra were recorded with a Varian T-60 or a JNM-4H-100 (JEOL) spectrometer with tetramethylsilane as the internal standard. ^{13}C-N.m.r. spectra were recorded with a JEOL FX-60 spectrometer. Column chromatography and t.l.c. were performed with 100-mesh silica gel (Mallinckrodt, St. Louis) and DC-Fertig Platten Kieselgel 60 F_{254}, Merck Co. Darmstadt, respectively, with the solvent systems (*A*) 2:1 carbon tetrachloride–acetone, (*B*) 10:1 carbon tetrachloride–acetone, (*C*) 20:1 ethyl acetate–methanol, (*D*) 30:1 ethyl acetate–methanol, (*E*) 20:1 chloroform–methanol, (*F*) 10:1 ethyl acetate–methanol, and (*G*) 4:3:4 methanol–conc. ammonium hydroxide–chloroform.

*1-Deoxy-3,4-*O*-isopropylidene-1-nitro-*D*-allitol* (**3**) *and* -D-*altritol* (**4**) *and their hydrolysis for circular-dichroism measurements.* — 2,3-*O*-Isopropylidene-D-ribose[10] (**2**, 2.25 g, 13.5 mmol) was treated with nitromethane (1.7 g, 27 mmol) in the presence of M sodium methoxide (15 ml) in methanol (30 ml) for 1.5 h at room temperature. After deionization with Amberlite IR-120 (H^+) resin, the mixture was evaporated and the residue put on a column (18 × 2.8 cm) with solvent *B* as the eluant. Evaporation of fractions having R_F 0.37 (solvent *A*) gave **2** (1.6 g, 62% recovered), followed by chromatographically homogeneous, semicrystalline **3** (0.51 g, 15%); R_F 0.26 (*A*); $[\alpha]_D^{20}$ +10.4° (*c* 1.8, methanol); ν_{max}^{KBr} 1560 cm^{-1} (NO_2); ^{13}C n.m.r. ($CDCl_3$) 25.32 and 27.76 p.p.m. (CMe_2-methyls), 109.65 (acetal carbon), 78.97 (C-1), and 64.12 (C-6); and almost pure **4** (0.3 g, 9%) as a syrup having R_F 0.19 (solvent *A*). Compound **3** (100 mg) was treated with 5M sulfuric acid (1.3 ml) in methanol (3 ml) for 10 h at room temperature. After deionization with Amberlite IRA-410 (OH^-) resin, the residue obtained by evaporation was put on a column (9.5 × 1.7 cm) and eluted with solvent *C* to give pure **9** as a syrup; R_F 0.19 (*D*); $[\alpha]_D^{20}$ −45° (*c* 0.3, water). Similar treatment of **4** (100 mg) gave **8** having R_F 0.19 (*D*) containing a very small proportion of an impurity (t.l.c.). Aqueous solutions (10 mM) of **9** and **8** were prepared for c.d. spectra; for **9** (*c* 0.01)[15] $[\theta]_{290-298}$ 1250, $[\theta]_{284}$ 1263; for **8** (*c* 0.00854): $[\theta]_{286-291}$ −1785, $[\theta]_{280}$ −1841.

*2,5-Anhydro-1-deoxy-3,4-*O*-isopropylidene-1-nitro-*D*-altritol* (**5**) *and* -D-*allitol* (**6**). — A solution of **3** (0.5 g) in dimethyl sulfoxide (2 ml) was heated for 12 h at 100° and evaporated below 40°. The residue was purified by column chromatography (18 × 2.8 cm) with solvent *B* as eluant. Fractions having R_F 0.30 (solvent *E*) were combined and evaporated to give a syrupy mixture of **5** and **6** (0.41 g, 88%) in a ratio of 7:2 (by ^{13}C n.m.r. and ^{1}H n.m.r. spectroscopy). Further purification under the same chromatographic conditions gave fractions enriched in **5** (ratio of 10:1) (220 mg) and in **6** (1:2) (150 mg).

*6-*O*-Benzoyl-1-deoxy-1-nitro-*D*-altritol* (**10**). — A mixture of D-ribose (10 g),

nitromethane (50 ml), M sodium methoxide (75 ml), and methanol (75 ml) was stirred vigorously for 3 h at room temperature and then deionized with Amberlite IR-120 (H^+) resin. The residue obtained by evaporation was put onto a column (12 × 3.5 cm) and eluted with solvent *F*. Fractions containing mainly a mixture of **8** and **9** (in the ratio of 4:1 as determined by ^{13}C n.m.r. spectroscopy) were combined and evaporated. To a solution of the products in pyridine (80 ml) and 1,4-dioxane (50 ml) was added benzoyl chloride (9 ml) below 5°. The solvents were removed and the residue was washed with water and petroleum ether several times to give a syrup that was crystallized from methanol; yield of **10**; 1.68 g (8%), m.p. 150° (dec.), $[\alpha]_D^{20}$ +1.3° (*c* 1.1, methanol); ν_{max}^{KBr} 1710 (C=O) and 1550 cm^{-1} (NO_2).

Anal. Calc. for $C_{13}H_{17}NO_8$: C, 49.52; H, 5.44; N, 4.44. Found: C, 49.47; H, 5.48; N, 4.39.

Compound **10** was hydrogenated over 5% palladium-on-carbon in methanol for 1 h in the presence of an equimolar amount of hydrochloric acid to give a syrup that was treated with sodium methoxide. The mixture showed a ninhydrin-positive spot (R_F 0.18, solvent *G*) that was identical to that obtained by hydrogenation of **8** but different from that (R_F 0.23) from **9**.

*2,5-Anhydro-6-*O*-benzoyl-1-deoxy-1-nitro-*D*-allitol* (**12**) *and -*D*-altritol* (**11**). — Compound **10** (1.25 g) was heated in water (240 ml) for 8 h at 85–90°. The mixture was filtered and the water was evaporated to give a white solid that was recrystallized from water, affording a 3:2 mixture of **12** and **11**; R_F 0.35 and 0.38 (solvent *A*), respectively; yield 0.796 g (68%). Pure **12** and **11** were obtained by preparative t.l.c. followed by recrystallization from water. Compound **12** had m.p. 115–115.5°, $[\alpha]_D^{20}$ −2.5° (*c* 1.1 methanol); ν_{max}^{KBr} 1715 (C=O) and 1560 cm^{-1} (NO_2).

Anal. Calc. for $C_{13}H_{15}NO_7$: C, 52.52; H, 5.09; N, 4.71. Found: C, 52.40; H, 5.11; N, 4.65.

Compound **11** had m.p. 117–118°, $[\alpha]_D^{20}$ +43.8° (*c* 1.1, methanol); ν_{max}^{KBr} 1710 (C=O) and 1550 cm^{-1} (NO_2).

Anal. Found: C, 52.49; H, 5.10; N, 4.68.

*2,5-Anhydro-6-*O*-benzoyl-1-deoxy-3,4-*O*-isopropylidene-1-nitro-*D*-allitol* (**14**) *and -*D*-altritol* (**13**). — The mixture of **12** and **11** (0.3 g) was stirred in acetone (30 ml) in the presence of anhydrous *p*-toluenesulfonic acid (60 mg) for 20 h and then treated with Amberlite IRA-410 (OH^-) resin. Removal of acetone gave a solid that was recrystallized from ethanol to afford a mixture of **14** and **13** [R_F 0.22 and 0.28 (solvent *B*), respectively]; yield 0.33 g (90%). Pure **14** and **13** were obtained by preparative t.l.c. or by column chromatography with carbon tetrachloride as an eluant. Compound **14** had m.p. 66–67.5°, $[\alpha]_D^{20}$ −16.2° (*c* 1.5, chloroform); ν_{max}^{KBr} 1720 (C=O) and 1545 cm^{-1} (NO_2).

Anal. Calc. for $C_{16}H_{19}NO_7$: C, 56.97; H, 5.68; N, 4.15. Found: C, 57.11; H, 5.76; N, 4.15.

Compound **13** had m.p. 84–85°, $[\alpha]_D^{20}$ −10.5° (*c* 0.9, chloroform); ν_{max}^{KBr} 1720 (C=O) and 1545 cm^{-1} (NO_2).

Anal. Found: C, 57.01; H, 5.66; N, 4.11.

Epimerization by base. — From **5** *and* **6**. The 10:1 mixture of cyclized products **5** and **6** (80 mg, 0.3 mmol) was kept in 0.04M sodium methoxide (4 ml) at room temperature. After 24 h, evaporation of the deionized mixture provided a syrup showing **5** and **6** in the ratio of 3:1, as determined by the intensities of the acetal methyl signals at δ 1.51 (**5**) and 1.58 (**6**) in the ^{1}H-n.m.r. spectrum.

From **13** *and* **14**. The 1:1 mixture of **13** and **14** (24 mg) was treated with 0.09M sodium methoxide (5 ml) for 40 h. Following processing as just described, a syrupy mixture of **5** and **6** in the ratio of 3:1 was obtained.

Epimerization by heating. — From **11** *or* **12**. Pure **11** was heated in water for 3 h at 85–90° to give a mixture of **11** and **12** in the ratio of 2:3. Compound **12** also gave the same mixture under the same conditions.

From **13** *or* **14**. Pure **13** gave a 4:1 mixture of **13** and **14** when heated in commercial dimethyl sulfoxide for 8 h at 80–90°. Compound **14** also gave the same mixture under the same conditions. Such epimerizations occurred in other solvents, as summarized in Table II.

ACKNOWLEDGMENTS

The authors are grateful to Prof. H. Kobayashi and Dr. Y. Kaizu, Tokyo Institute of Technology, for recording the c.d. spectra and Mr. K. Kosaka, Japan Electric Optical Laboratories, for recording the ^{13}C-n.m.r. spectra. They also thank the Ministry of Education, Japanese Government, for a Scientific Research Grant-in-aid.

REFERENCES

1 R. J. SUHADOLNIK, *Nucleoside Antibiotics*, Wiley–Interscience, New York, 1970, pp. 354–404.
2 For example, M. BOBEK AND J. FARKAŠ, *Collect. Czech. Chem. Commun.*, 34 (1969) 247–252; S. HANESSIAN AND A. G. PERNET, *Adv. Carbohydr. Chem. Biochem.*, 33 (1976) 111–188.
3 H. OHRUI, G. H. JONES, J. G. MOFFATT, M. L. MADDOX, A. T. CHRISTENSEN, AND S. K. BYRAN, *J. Am. Chem. Soc.*, 97 (1975) 4602–4613.
4 For example, T. TAKAMOTO AND R. SUDOH, *Bull. Chem. Soc. Jpn.*, 48 (1975) 3413–3414.
5 H. L. FINKBEINER AND G. W. WAGNER, *J. Org. Chem.*, 28 (1963) 215–217.
6 J. YOSHIMURA, T. IIDA, AND M. FUNABASHI, *Bull. Chem. Soc. Jpn.*, 43 (1970) 3887–3891.
7 J. C. SOWDEN, C. H. BOWERS, L. HOUGH, AND S. H. SHUTE, *Chem. Ind. (London)*, (1962) 1827–1828.
8 L. HOUGH AND S. H. SHUTE, *J. Chem. Soc.*, (1962) 4633–4637.
9 J. C. SOWDEN AND M. L. OFTEDAHL, *J. Org. Chem.*, 26 (1961) 1974–1976.
10 P. A. LEVENE AND R. S. TIPSON, *J. Biol. Chem.*, 102 (1936) 731–747.
11 J. C. SOWDEN AND H. O. L. FISCHER, *J. Am. Chem. Soc.*, 69 (1947) 1048–1050.
12 S. TRIPPETT AND D. M. WALKER, *J. Chem. Soc.*, (1959) 3874–3876.
13 C. SATOH AND A. KIYOMOTO, *Chem. Pharm. Bull.*, 12 (1964) 615–619.
14 C. SATOH AND A. KIYOMOTO, *Carbohydr. Res.*, 3 (1966) 248–251.
15 C. SATOH, A. KIYOMOTO, AND T. OKUDA, *Carbohydr. Res.*, 5 (1967) 140–148.
16 S. D. BERNARDO AND M. WEIGELE, *J. Org. Chem.*, 42 (1977) 109–112.
17 C. K. CHU, I. WEMPEN, K. A. WATANABE, AND J. J. FOX, *J. Org. Chem.*, 41 (1976) 2793–2797.
18 J. G. BUCHANAN, A. R. EDGAR, M. J. POWER, AND P. D. THEAKER, *Carbohydr. Res.*, 38 (1974) C22–C24.
19 H. OHRUI, S. EMOTO, G. H. JONES, AND J. G. MOFFATT, *Abstr. Int. Symp. Carbohydr. Chem., 8th, (Kyoto)*, 1976, p. 29.
20 H. OHRUI AND S. EMOTO, *J. Org. Chem.*, 42 (1977) 1951–1957.