Carbohydrate Research, 26 (1973) 297–303

REACTION OF METHYL 2,3-*O*-ISOPROPYLIDENE-6-*O*-*p*-TOLYLSULFONYL-α-D-*LYXO*-HEXOFURANOSID-5-ULOSE WITH TRIETHYLAMINE–METHANOL*

A. DMYTRACZENKO†, W. A. SZAREK, AND J. K. N. JONES
Department of Chemistry, Queen's University, Kingston, Ontario (Canada)
(Received May 9th, 1972; accepted for publication, July 14th, 1972)

ABSTRACT

A synthesis of methyl 2,3-*O*-isopropylidene-6-*O*-*p*-tolylsulfonyl-α-D-*lyxo*-hexofuranosid-5-ulose (**1**) is described. Reaction of compound **1** with triethylamine–methanol yielded methyl 2,3-*O*-isopropylidene-α-D-*lyxo*-hexofuranosid-5-ulose dimethyl acetal (**2**) and methyl 6-deoxy-2,3-*O*-isopropylidene-4-methoxy-α-D-*lyxo*-hexofuranosid-5-ulose (**3**). Mechanisms for the formation of the new products (**2** and **3**) are proposed.

INTRODUCTION

Recent work in this laboratory has shown that carbohydrate α-keto *p*-toluenesulfonates can undergo several interesting transformations. Treatment of methyl 4,6-*O*-benzylidene-2-*O*-*p*-tolylsulfonyl-α-D-*ribo*-hexopyranosid-3-ulose with hydroxylamine hydrochloride in aqueous pyridine, for example, afforded a novel carbohydrate derivative, namely, *N*-(4,6-*O*-benzylidene-1-*O*-methyl-3-oximino-α-D-*ribo*(or *arabino*)-hexopyranos-2-yl)pyridinium *p*-toluenesulfonate[1]. The reaction with triethylamine–methanol has also been found to lead to some unusual compounds[2]. Thus, methyl 4,6-*O*-benzylidene-2-*O*-*p*-tolylsulfonyl-α-D-*ribo*-hexopyranosid-3-ulose gave methyl 2,3-anhydro-4,6-*O*-benzylidene-3-methoxy-α-D-allopyranoside, methyl 4,6-*O*-benzylidene-α-D-*ribo*-hexopyranosid-3-ulose dimethyl acetal, and a derivative of 3-hydroxy-2-(hydroxymethyl)-4*H*-pyran-4-one. The present article describes the reaction with triethylamine–methanol of a carbohydrate derivative containing the α-keto *p*-toluenesulfonate grouping in an exocyclic side-chain, namely, methyl 2,3-*O*-isopropylidene-6-*O*-*p*-tolylsulfonyl-α-D-*lyxo*-hexofuranosid-5-ulose (**1**).

RESULTS AND DISCUSSION

The synthesis of methyl 2,3-*O*-isopropylidene-6-*O*-*p*-tolylsulfonyl-α-D-*lyxo*-hexofuranosid-5-ulose (**1**) involved the preparation of methyl 2,3-*O*-isopropylidene-α-D-mannofuranoside as described by Randall[3], followed by selective tosylation of this

---

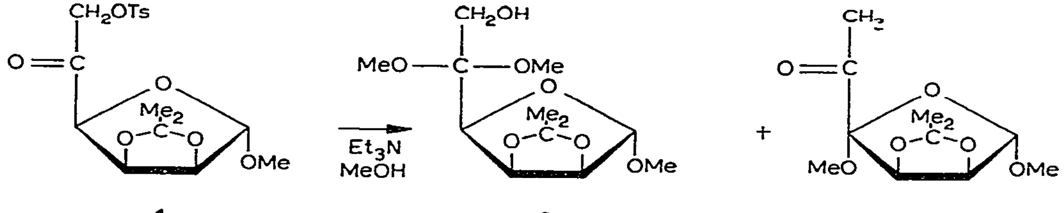
*Dedicated to Professor V. Deulofeu, in honor of his 70th birthday.

†Present address: Universidade Federal do Paraná, Instituto de Bioquimica, Curitiba, Paraná (Brasil).

compound to give the 6-*O*-*p*-tolylsulfonyl derivative, and finally oxidation with dimethyl sulfoxide–acetic anhydride.

When compound **1** was heated at reflux temperature in methanol containing 2 equiv. of triethylamine, after 15 min, t.l.c. revealed the presence of one new component having R_F 0.27 in addition to starting material (R_F 0.33); a second major new component (R_F 0.43) and only a trace of a third component (R_F 0.52) were revealed when the reaction mixture was examined by t.l.c. after 3 h. The reaction mixture was processed after 10 h, at which time t.l.c. indicated that all of the starting material had been consumed. The two major components having R_F 0.27 and R_F 0.43 were isolated in yields of 22% and 62%, respectively.

The slower-moving component was identified as methyl 2,3-*O*-isopropylidene-α-D-*lyxo*-hexofuranosid-5-ulose dimethyl acetal (**2**). The i.r. spectrum showed absorption at 3500 cm^{-1} for a hydroxyl group. The n.m.r. spectrum in chloroform-*d* showed the presence of three 3-proton singlets at τ 6.61, 6.63, and 6.69 assigned to three methoxyl groups and two 3-proton singlets at τ 8.55 and 8.72 assigned to the isopropylidene-methyl protons. The other n.m.r. parameters were ascertained by comparing the experimental spectrum with computer-simulated spectra (see Experimental). Compound **2** was unstable, but gave a stable, chromatographically homogeneous 6-methanesulfonate.

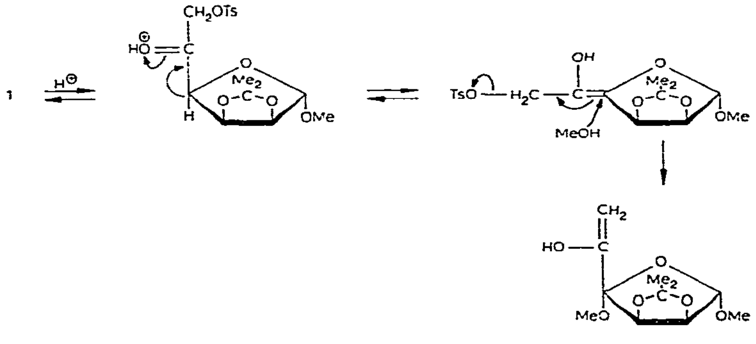


1 2 3

The dimethyl acetal **2** is presumably formed from the α-keto *p*-toluenesulfonate **1** in a manner analogous to that for the formation of methyl 4,6-*O*-benzylidene-α-D-*ribo*-hexopyranosid-3-ulose dimethyl acetal from methyl 4,6-*O*-benzylidene-2-*O*-*p*-tolylsulfonyl-α-D-*ribo*-hexopyranosid-3-ulose, namely, by way of an intermediate α-methoxy epoxide[2]. Thus, the initial step in the formation of **2** would be attack by methanol on the carbonyl carbon; an internal displacement of the *p*-tolylsulfonyloxy group by the carbonyl oxygen would then give an α-methoxy epoxide, which undergoes ring-cleavage by methanol to afford the dimethyl acetal **2**. It is interesting that, in contrast to the results obtained with the α-keto *p*-toluenesulfonate **1**, an α-methoxy epoxide could actually be isolated[2] when methyl 4,6-*O*-benzylidene-2-*O*-*p*-tolylsulfonyl-α-D-*ribo*-hexopyranosid-3-ulose was treated with triethylamine–methanol.

The other component (R_F 0.43) isolated from the reaction mixture of compound **1** with triethylamine–methanol has been identified as methyl 6-deoxy-2,3-*O*-isopropylidene-4-methoxy-α-D-*lyxo*-hexofuranosid-5-ulose (**3**). The i.r. spectrum showed absorption at 1735 cm^{-1} for a carbonyl group. The n.m.r. spectrum in chloroform-*d* showed two 3-proton singlets at τ 6.50 and 6.75 attributable to two methoxyl groups and two 3-proton singlets at τ 8.60 and 8.72 for the isopropylidene-methyl protons. A 3-proton singlet at τ 7.72 was assigned to a methyl group adjacent to a carbonyl group. The proton at C-1 was observed as a 1-proton singlet at τ 4.80, and the two protons at C-2 and C-3 were observed as a 2-proton singlet at τ 5.27; on the basis of the appearance of the latter signal, the configuration at C-4 was assigned as shown in structure **3**, since it would be reasonable to expect that the opposite configuration would result in a difference in chemical shift between the two protons at C-2 and C-3 and probably a splitting of the two signals. Further evidence for the presence of a methyl ketone was obtained by the observation of a positive iodoform test. Compound **3** also afforded a crystalline oxime. The n.m.r. spectrum of the oxime (see Experimental) suggested that this derivative was a mixture of *syn* and *anti* isomers; a doublet pattern was observed for each of the signals.

It is significant that, when methyl 2,3-*O*-isopropylidene-6-*O*-*p*-tolylsulfonyl-α-D-*lyxo*-hexofuranosid-5-ulose (**1**) was treated with triethylamine–methanol, the formation of the dimethyl acetal **2** (R_F 0.27) could be detected by t.l.c. before the formation of the methyl ketone **3** (R_F 0.43), although at the end of the reaction, the yield of **3** was greater than that of **2**. An attractive suggestion was that the formation of the methyl ketone **3** was an acid-catalyzed reaction dependent on the formation of triethylammonium *p*-toluenesulfonate by conversion of the α-keto *p*-toluenesulfonate **1** into the dimethyl acetal **2**. Accordingly, compound **1** was heated at reflux temperature in methanol containing 2 equiv. of triethylamine and 1 equiv. of *p*-toluenesulfonic acid monohydrate; in this case, after 15 min, t.l.c. revealed the presence of the methyl ketone **3** (R_F 0.43) in addition to starting material (R_F 0.33), but not of the dimethyl acetal **2**. The formation of the dimethyl acetal **2** (R_F 0.27) could be detected after 30 min, and, after 34 h, t.l.c. showed that only traces of the starting material remained. The methyl ketone **3** and the dimethyl acetal **2** were isolated in yields of 69% and 13.3%, respectively. These results implicate triethylammonium *p*-toluenesulfonate in the conversion of the α-keto *p*-toluenesulfonate **1** into the methyl ketone **3**, and the acid-catalyzed mechanism shown in Scheme 1 is proposed.



Scheme 1

EXPERIMENTAL

General. — Melting points were determined on a Fisher–Johns melting-point apparatus and are uncorrected. Optical rotations were measured with a Perkin–Elmer Model 141 automatic polarimeter at 26±3°. I.r. spectra were recorded with a Unicam SP 1000 spectrophotometer. N.m.r. spectra were recorded at 60 MHz in chloroform-*d* with tetramethylsilane as the internal standard. T.l.c. was performed with Silica Gel G as the adsorbent, with 2:3 (v/v) ethyl acetate–petroleum ether (b.p. 60–80°) as the developing solvent unless otherwise stated. The developed plates were air-dried, and compounds were located by heating the plates at about 150° after they had been sprayed with either 5% ethanolic sulfuric acid or a 10% aqueous sulfuric acid solution containing 1% cerium sulfate and 1.5% molybdic acid. Column chromatography was performed on Merck silica gel (70–230 mesh).

*Methyl 2,3-*O*-isopropylidene-6-*O*-p-tolylsulfonyl-α-*D*-mannofuranoside.* — 2,3:5,6-Di-*O*-isopropylidene-α-D-mannofuranose was prepared from D-mannose as described by Schmidt[4] and converted into methyl 2,3-*O*-isopropylidene-α-D-mannofuranoside by the method of Randall[3]. The syrupy glycoside was characterized by acetylation with pyridine–acetic anhydride to give methyl 5,6-di-*O*-acetyl-2,3-*O*-isopropylidene-α-D-mannofuranoside. After recrystallization from ethyl acetate–petroleum ether (b.p. 60–80°), the diacetate had m.p. 52–53° and $[\alpha]_D^{26}$ +56° (*c* 1.54, chloroform); lit.[3]: m.p. 54–55°, $[\alpha]_D$ +57° (*c* 1.3, chloroform). Methyl 2,3-*O*-isopropylidene-α-D-mannofuranoside (24 g) was treated with *p*-toluenesulfonyl chloride (38 g, 2 equiv.) in dry pyridine at room temperature; the progress of the reaction was followed by t.l.c. The reaction mixture was processed in the usual manner to give crystalline methyl 2,3-*O*-isopropylidene-6-*O*-*p*-tolylsulfonyl-α-D-mannofuranoside, m.p. 94–95°, $[\alpha]_D^{26}$ +4.5° (*c* 1.24, chloroform).

Anal. Calc. for $C_{17}H_{24}O_8S$: C, 52.6; H, 6.2; S, 8.3. Found: C, 52.7; H, 6.0; S, 8.3.

*Methyl 2,3-*O*-isopropylidene-6-*O*-p-tolylsulfonyl-α-*D-lyxo*-hexofuranosid-5-ulose* (**1**). — Methyl 2,3-*O*-isopropylidene-6-*O*-*p*-tolylsulfonyl-α-D-mannofuranoside (4.50 g) was treated with dimethyl sulfoxide (50 ml) and acetic anhydride (40 ml) at room temperature. After 6 h, t.l.c. [1:1 (v/v) benzene–ether] revealed that all of the starting material (R_F 0.45) had been consumed, and showed the presence of a major component having R_F 0.62 (methyl 2,3-*O*-isopropylidene-6-*O*-*p*-tolylsulfonyl-α-D-*lyxo*-hexofuranosid-5-ulose, **1**) and a small amount of a second component having R_F 0.72. The reaction mixture was concentrated *in vacuo*, and the syrupy residue was dissolved in chloroform. The chloroform solution was washed with sodium hydrogen carbonate solution and then with water, and the washed solution was concentrated to a syrup, which crystallized from propanol to afford the 5-ketone **1** (3.9 g, 85%). Recrystallization from ethyl acetate–petroleum ether (b.p. 60–80°) gave a pure sample, m.p. 79–80°, $[\alpha]_D^{26}$ −18° (*c* 1.18, chloroform); i.r. datum: ν_{max}^{Nujol} 1750 cm^{-1} (C=O), no absorption attributable to OH; n.m.r. data: τ 2.12, 2.23, 2.61 and 2.75 (A_2B_2 system, four aryl protons), 4.88–6.05 (6 protons, H-1, H-2, H-3, H-4, H-6,6′), 6.67 (3-proton singlet, OMe), 7.55 (3-proton singlet, aromatic Me), 8.67 and 8.76 (3-proton singlets, CMe_2).

Anal. Calc. for $C_{17}H_{22}O_8S$: C, 52.8; H, 5.7; S, 8.3. Found: C, 52.9; H, 5.9; S, 8.3.

*Reaction of methyl 2,3-*O*-isopropylidene-6-*O*-*p*-tolylsulfonyl-α-*D-lyxo*-hexofuranosid-5-ulose* (**1**) *with triethylamine–methanol.* — A solution of the 5-ketone **1** (2.0 g) in methanol (60 ml) and triethylamine (1.2 ml, 2 equiv.) was heated at reflux temperature. After 15 min, t.l.c. revealed the presence of a new component having R_F 0.27 in addition to the starting material (R_F 0.33); after 3 h, a second major component having R_F 0.43 and traces of a third component (R_F 0.52) were revealed in addition to the starting material and the component with R_F 0.27. After 10 h, the presence of starting material could not be detected by t.l.c. The reaction mixture was partitioned between chloroform–water; the chloroform layer was washed with 0.05M sulfuric acid, then with a 5% aqueous solution of sodium hydrogen carbonate, and finally with water, dried (magnesium sulfate), and concentrated to a syrup. This material was chromatographed on silica gel, with 2:3 (v/v) ethyl acetate–petroleum ether (b.p. 60–80°) as eluent, to yield the components having R_F 0.27 and R_F 0.43 as homogeneous syrups.

The component having R_F 0.27 (0.338 g, 22%) was identified as methyl 2,3-*O*-isopropylidene-α-D-*lyxo*-hexofuranosid-5-ulose dimethyl acetal (**2**); $[\alpha]_D^{26}$ +38° (*c* 1.55, chloroform); i.r. datum: ν_{max}^{film} 3500 cm^{-1} (OH); n.m.r. data: τ 5.07 (1-proton singlet, H-1), 5.23 (1-proton quartet, $J_{2,3}$ 5.7 Hz, $J_{3,4}$ 3.0 Hz, H-3), 5.42 (1-proton doublet, H-2), 5.85 (1-proton doublet, H-4), 6.11 (1-proton doublet, $J_{6,6'}$ 13.5 Hz, H-6), 6.31 (1-proton doublet, H-6′), 6.45 (1-proton singlet, disappeared on deuteriation, OH), 6.61, 6.63, and 6.69 (3-proton singlets, three OMe groups), 8.55 and 8.72 (3-proton singlets, CMe_2). The n.m.r. parameters for the ring protons and the hydroxymethyl protons were ascertained by comparing the experimental and computer-simulated spectra (theoretical spectra were calculated with an IBM 360 computer, equipped with a CALCOMP plotter, by use of a modification of the Laocoon II program of Castellano and Bothner-By[5]).

The component having R_F 0.43 was the major component (0.780 g, 62%) and was identified as methyl 6-deoxy-2,3-*O*-isopropylidene-4-methoxy-α-D-*lyxo*-hexofuranosid-5-ulose (**3**). The syrupy product crystallized on being kept. Recrystallization from ethyl acetate–petroleum ether (b.p. 60–80°) gave a pure sample of the methyl ketone **3**, m.p. 40–41°, $[\alpha]_D^{26}$ −1.8° (*c* 1.66, chloroform); i.r. datum: ν_{max}^{Nujol} 1735 cm^{-1} (C=O); n.m.r. data: τ 4.80 (1-proton singlet, H-1), 5.27 (2-proton singlet, H-2, H-3), 6.50 and 6.75 (3-proton singlets, two OMe groups), 7.72 (3-proton singlet, CMe), 8.60 and 8.72 (3-proton singlets, CMe_2).

Anal. Calc. for $C_{11}H_{18}O_6$: C, 53.6; H, 7.4. Found: C, 53.7; H, 7.1.

*Methyl 2,3-*O*-isopropylidene-6-*O*-methylsulfonyl-α-*D-lyxo*-hexofuranosid-5-ulose dimethyl acetal.* — Methyl 2,3-*O*-isopropylidene-α-D-*lyxo*-hexofuranosid-5-ulose dimethyl acetal (**2**) was treated with methanesulfonyl chloride in dry pyridine for 1 h at room temperature. The reaction mixture was processed in the usual manner, and the product was purified by chromatography on silica gel, with 3:1 (v/v) ethyl acetate–petroleum ether (b.p. 60–80°) as eluent, to give the 6-methanesulfonate as a homogenous syrup. The i.r. spectrum did not show any absorption attributable to hydroxyl groups; n.m.r. data: τ 5.05 (1-proton singlet, $J_{1,2}$ <0.5 Hz, H-1), 5.13 (1-proton quartet, $J_{2,3}$ 6.0 Hz, $J_{3,4}$ 3.5 Hz, H-3), 5.26 (1-proton doublet, $J_{6,6'}$ 12 Hz, H-6), 5.40 (1-proton doublet, H-6'), 5.45 (1-proton doublet, H-2), 5.78 (1-proton doublet, H-4), 6.55 and 6.63 (3-proton singlets, two OMe groups), 6.92 (3-proton singlet, mesyl group), 8.50 and 8.69 (3-proton singlets, CMe_2).

*Methyl 6-deoxy-2,3-*O*-isopropylidene-4-methoxy-α-*D-lyxo*-hexofuranosid-5-ulose oxime.* — Methyl 6-deoxy-2,3-*O*-isopropylidene-4-methoxy-α-D-*lyxo*-hexofuranosid-5-ulose (3, 100 mg) was treated with hydroxylamine hydrochloride (100 mg) in dry pyridine (5 ml) overnight at room temperature; t.l.c. [1:1 (v/v) ethyl acetate–petroleum ether (b.p. 60–80°)] revealed that all of the starting material (R_F 0.49) had reacted and a new component (R_F 0.30) had been formed. The reaction mixture was processed in the usual manner, and the oxime was isolated as a syrup which crystallized on being kept (70 mg, 66%). Recrystallization from ethyl acetate–petroleum ether (b.p. 60–80°) afforded a pure sample of methyl 6-deoxy-2,3-*O*-isopropylidene-4-methoxy-α-D-*lyxo*-hexofuranosid-5-ulose oxime, m.p. 128–129°. In the n.m.r. spectrum, the signal for the hydroxyl proton was observed as a broad band centered at τ 2.85; each of the other signals was observed as two singlets, with a spacing of ~2.5 Hz, in the ratio of ~5:4. The chemical shifts quoted are the midpoints between each pair of singlets: τ 4.91 (H-1), 5.35 (H-2 and H-3), 6.55 and 6.81 (two OMe groups), 8.11 (OMe), 8.64 and 8.74 (isopropylidene Me groups).

Anal. Calc. for $C_{11}H_{19}NO_6$: C, 50.6; H, 7.3; N, 5.4. Found: C, 50.7; H, 7.2; N, 5.2.

*Reaction of methyl 2,3-*O*-isopropylidene-6-*O-p*-tolylsulfonyl-α-*D-lyxo*-hexofuranosid-5-ulose* (**1**) *with triethylamine–methanol in the presence of* p*-toluenesulfonic acid.* — A solution of compound **1** (2.0 g) in methanol (60 ml) containing triethylamine (1.2 ml, 2 equiv.) and *p*-toluenesulfonic acid monohydrate (0.98 g, 1 equiv.) was heated at reflux temperature. After 15 min, t.l.c. revealed the presence of the methyl ketone **3** (R_F 0.43) in addition to starting material (R_F 0.33); after 30 min, the formation of the dimethyl acetal **2** (R_F 0.27) could also be detected. After 34 h, t.l.c. showed that only a trace of starting material remained. The reaction mixture was processed as described for the reaction of **1** with triethylamine–methanol to afford some of the starting material (0.050 g), the dimethyl acetal **2** (0.187 g, 13.3%), and the methyl ketone **3** (0.856 g, 69%).

ACKNOWLEDGMENT

The authors thank the National Research Council of Canada for financial support of this work.

REFERENCES

1 W. A. Szarek, B. T. Lawton, and J. K. N. Jones, *Tetrahedron Lett.*, (1969) 4867.
2 A. Dmytraczenko, W. A. Szarek, and J. K. N. Jones, *Chem. Commun.*, (1971) 1220; *Can. J. Chem.*, to be published.
3 M. H. Randall, *Carbohyd. Res.*, 11 (1969) 173.
4 O. T. Schmidt, *Methods Carbohyd. Chem.*, 2 (1963) 319.
5 S. Castellano and A. A. Bothner-By, *J. Chem. Phys.*, 41 (1964) 3863.