RUTHENIUM TETRAOXIDE OXIDATION OF THE PRIMARY HYDROXYLIC FUNCTION TO THE CARBOXYL IN SUGAR DERIVATIVES (PREPARATION OF URONIC ACIDS)

J.Šmejkal and L.Kalvoda

Institute of Organic Chemistry and Biochemistry, Czechoslovak Academy of Sciences, Prague 6

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A solution of sodium periodate in aqueous acetone containing a catalytical amount of ruthenium tetraoxide oxidizes sugar derivatives carrying a free primary alcoholic group to uronic acids. The aliphatic glycosidic bond and the acetyl, benzoyl, isopropylidene, and benzylidene protecting groups are stable under the reaction conditions, but the benzyl group is unstable. The method may also be used in that case when the sugar molecule contains an isolated secondary hydroxylic function either free or in the form of the semiacetal.

Ruthenium tetraoxide has been recently widely used in the sugar chemistry[1] in oxidations of the secondary hydroxylic functions to the corresponding oxo derivatives. The use of this agent in oxidations of primary hydroxylic functions has not been hitherto reported. In our praxis, several oxidations were required of the primary hydroxylic function to the carboxylic group in sugar derivatives sensitive both in the acidic and basic media. Unsatisfactory results were obtained in this respect with oxidizing agents such as chromium trioxide, potassium permanganate or oxygen on platinum catalyst. On the other hand, the oxidation with sodium periodate and a catalytic amount of ruthenium tetraoxide was satisfactory in most cases.

As the reaction medium, aqueous acetone has been used since both sodium periodate and the compounds to be ozidized are fairly soluble in this solvent, whereas sodium iodate (formed by the reaction) is practically insoluble in the reaction medium. All these solubility relations favour an easy isolation of the reaction products. Because of the limited stability of acetone towards the oxidative action of the reaction mixture, an excess of sodium periodate must be used.

The aliphatic glycosidic bond and the protecting acetyl, benzoyl and isopropylidene groups are quite stable under the reaction conditions and no fission occurs. A somewhat limited stability has been observed with the benzylidene group which is slowly oxidized to the benzoyl group. This oxidation, however, occurs much more slowly than the oxidation of the primary hydroxylic function to the carboxylic group. The conversion of the protecting benzylidene group to the benzoyl group was demonstrated on the oxidation of 1,2-isopropylidene-3,5-O-benzylidene-D-glucofuranose to 1,2-isopropylidene-6-benzoyl-D-glucofuranose. The O-benzyl group proved un-

suitable as the protecting group in this method since its oxidation occurs approximately by the same rate as the oxidation of the primary hydroxylic function to the carboxylic group. The phenomenon that the oxidation of the secondary hydroxylic function (including the semiacetal secondary hydroxylic function) proceeds considerably slower than the oxidation of the primary alcoholic function to carboxyl, can be made use of in the selective oxidation of the primary alcoholic function in the presence of a secondary one provided that the reaction is interrupted in due time.

EXPERIMENTAL

Melting points were taken on a heated microscope stage (Kofler block) and are uncorrected. Infrared spectra were measured in chloroform on a Zeiss UR-10 apparatus. NMR spectra (tetramethylsilane as internal standard) were taken in deuteriochloroform on a Varian HA-100 (100 MHz) apparatus. Thin-layer chromatography was performed on silica gel according to Stahl (Lachema LSL_{254}, Czechoslovakia).

Oxidation of the Primary Alcoholic Group to the Carboxylic Group

A solution of the sugar derivative (25 mmol) in 70% aqueous acetone (200 ml) is treated with glacial acetic acid (1·0 ml) and a catalyst solution prepared by fusing a mixture of powdered ruthenium (100 mg), sodium hydroxide (2 mmol), and sodium nitrate (2 mmol) to the dark-red heat and dissolving the melt in water (3 ml) containing sodium periodate (100 mg). After the addition of the catalyst, the reaction mixture was stirred at 0°C. The reaction course was checked by thin-layer chromatography and the oxidation was interrupted as soon as the starting alcohol disappeared (30 min to 3 h) by the addition of ethanol (10 ml). When the starting compound contained an additional (isolated) free hydroxylic function, the oxidation was interrupted after disappearance of 90% of the starting compound (as shown by chromatography).

Methyl 2,3,4-Tri-O-benzoyl-D-glucuronate

A suspension of 1,6-anhydro-2,3,4-tri-O-benzoyl-β-D-glucopyranose[2] (2·5 g; 5·3 mmol), acetic anhydride (10 ml), and boron trifluoride etherate (0·2 ml) was shaken at room temperature for 90 minutes and then decomposed with water (30 ml). The reaction product (1,6-di-O-acetyl-2,3,4-tri-O-benzoyl-D-glucopyranose) was extracted with benzene, the extract washed with dilute aqueous ammonia, dried, and evaporated under diminished pressure. The residue was diluted with methanol (25 ml) and concentrated hydrochloric acid (1·5 ml), the solution kept at room temperature for 24 h, and evaporated under diminished pressure. The residual crude 2,3,4-tri-O-benzoyl-D-glucose was then oxidized without any previous purification. The reaction mixture was processed as stated above and the uronic acid converted to the methyl ester which was chromatographed on a column of silica gel (150 g) in 9 : 1 benzene–acetone solvent mixture. Yield, 1·05 g (38%) of methyl 2,3,4-tri-O-benzoyl-D-glucuronate, m. p. 157 −162°C (benzene) $[\alpha]_D^{25}$ + 21·9° (*c* 0·54, chloroform). NMR spectrum: δ 3·64 (singl. 3 H, $-COCH_3$); 4·88 (dubl. 1 H, $C_{(5)}$—H); 5·35 (dubl. 1 H, $C_{(2)}$—H); 5·67 (tripl. 1 H, $C_{(4)}$—H); 5·87 (dubl. 1 H, $C_{(1)}$—H); 6·26 (tripl. 1 H, $C_{(3)}$—H). For $C_{28}H_{24}O_{20}$ (520·5) calculated: 64·61% C, 4·65% H; found: 64·31% C, 4·48% H.

Methyl 1,2-Isopropylidene-D-xyluronate

1,2-Isopropylidene-D-xylofuranose[3] (1·00 g; 5 mmol) was oxidized according to the standard procedure and the resulting uronic acid esterified with diazomethane. The methyl ester was extrac-

ted with ethyl acetate and purified by chromatography on a column of silica gel (30 g) in 2 : 1 benzene–acetone solvent mixture. Yield, 0·25 g (23%) of methyl 1,2-isopropylidene-D-xyluronate, m.p. 102—104°C (chloroform–light petroleum); reported[4], m.p. 103—104°C. Optical rotation: $[\alpha]_D^{25}$ —34·1° (*c* 0·12, methanol); reported[4], $[\alpha]_D^{20}$ —32·8°. NMR spectrum: δ 1·32 (singl. 3 H); 1·48 (singl. 3 H, isopropylidene); 3·80 (singl. 3 H, —$COOCH_3$); 4·46 (dubl. 1 H, $C_{(3)}$—H); 4·56 (dubl. 1 H, $C_{(2)}$—H); 4·76 (dubl. 1 H, $C_{(4)}$—H), 6·06 (dubl. 1 H, $C_{(1)}$—H).

Methyl Methyl-2,3,4-tri-O-acetyl-α-D-glucopyranosiduronate

A suspension of methyl 2,3,4-tri-O-acetyl-6-O-trityl-α-D-glucopyranoside[5] (5·2 g; 10 mmol) in 75% aqueous acetic acid (52 ml) was refluxed for 30 min and cooled down. The precipitate of triphenylmethylcarbinol was filtered off and washed with 75% aqueous acetic acid. The filtrate and washings were combined and evaporated under diminished pressure. The residue was coevaporated with two 30 ml portions of dioxane, oxidized by the standard procedure, and the resulting uronic acid esterified with diazomethane. The methyl ester was purified by chromatography on silica gel (100 g) in 19 : 1 benzene–acetone solvent mixture. Yield, 1·7 g (50%) of methyl-2,3,4-tri-O-acetyl-α-D-glucopyranosiduronate, $[\alpha]_D^{25}$ +129·5° (*c* 1·0; chloroform), For $C_{14}H_{20}O_{10}$ (348·3) calculated: 48·28% C, 5·79% H; found: 48·48% C, 5·60% H.

Methyl 2,3:4,5-Di-O-isopropylidene-2-oxo-D-gluconate

2,3:4,5-Di-O-isopropylidene-D-fructopyranose[6] (2·60 g; 10 mmol) was oxidized under standard conditions and the resulting acid esterified with diazomethane. The sirupous methyl ester was purified by chromatography on a column of silica gel (50 g) in 9 : 1 benzene–acetone solvent mixture. Yield, 1·8 g (63%) of methyl 2,3:4,5-di-O-isopropylidene-2-oxo-D-gluconate, $[\alpha]_D^{25}$ 37·1° (*c* 0·90; chloroform). Infrared spectrum: ν(C=O) 1 753 cm^{-1}. NMR spectrum: δ 3·83 (singl., 3 H, —$COOCH_3$), 3·89 (dubl. 2 H, $C_{(6)}$—H_2); 4·24 (dubl. of tripl. 1 H, $C_{(5)}$—H), 4·62 (dubl. of dubl. 1 H, $C_{(4)}$—H), 4·78 (dubl. 1 H, $C_{(3)}$—H). For $C_{13}H_{20}O_7$ (288·2) calculated: 54·21% C, 7·00% H; found: 54·09% C, 7·16% H. A sample of the ester was hydrolyzed with 0·1M-KOH, the potassium salt passed through Dowex 50 (H^+) ion exchange resin, and the aqueous effluent taken down to afford the free 2,3:4,5-di-O-isopropylidene-2-oxo-D-gluconic acid, m.p. 97—98°C (reported[7], m.p. 98°C).

Methyl Methyl-2,3-O-isopropylidene-β-D-ribofuranosiduronate

Methyl 2,3-O-isopropylidene-β-D-ribofuranoside[8] (1·02 g; 5 mmol) was oxidized by the standard procedure and the resulting uronic acid esterified with diazomethane. The methyl ester was purified by chromatography on a column of silica gel (30 g) in 9 : 1 benzene–acetone solvent mixture. Yield, 0·70 g (60%) of the sirupous methyl methyl-2,3-O-isopropylidene-β-D-ribofuranosiduronate, $[\alpha]_D^{25}$ —80·0° (methanol, *c* 0·13); reported[9], $[\alpha]_D^{25}$ —74° (methanol). Infrared spectrum: ν(C=O) 1 737 cm^{-1}. For $C_{10}H_{16}O_6$ (232·2) calculated: 51·71H C, 6·96% H; found: 51·79% C, 6·75% H.

Methyl 1,2-O-Isopropylidene-3,5-O-benzylidene-D-glucuronate

A. 1,2-O-Isopropylidene-3,5-O-benzylidene-D-glucofuranose[10] (1·8 g) was oxidized under standard conditions and the resulting uronic acid esterified with diazomethane. The methyl ester was extracted with chloroform, the extract dried, and evaporated to afford 1,0 g (51%) methyl 1,2-O-isopropylidene-3,5-O-benzylidene-D-glucuronate, m.p. 105°C (chloroform–light petroleum), $[\alpha]_D^{25}$ +16·1° (*c* 0·50, chloroform). Infrared spectrum: ν(C=O) 1 747 cm^{-1}. For $C_{17}H_{20}O_7$ (336·3) calculated: 60·72% C, 5·99% H; found: 60·68% C, 5·96% H.

B. 1,2-O-Isopropylidene-3,5-O-benzylidene-D-glucofuranose[10] (0·9 g; 6 mmol) was oxidized with potassium permanganate according to Zervas[10]. The resulting 1,2-O-isopropylidene-3,5-O-benzylidene-D-glucuronic acid was esterified with diazomethane to afford 0·4 g (49%) of the methyl ester, m.p. 105°C, undepressed on admixture with the specimen obtained by procedure *A*. The IR spectra of both specimens were identical.

1,2-O-Isopropylidene-6-O-benzoyl-D-glucofuranose

1,2-O-Isopropylidene-5,6-O-benzylidene-D-glucofuranose[10] (3·1 g; 10 mmol) was oxidized under standard conditions until the starting compound disappeared. The excess oxidizing agent was decomposed, the acetone evaporated, the residue extracted with chloroform, the extract dried, and evaporated to afford 2·0 g (63%) of a substance, m.p. 195°C (chloroform–light petroleum), $[\alpha]_D^{25}$ +5·4° (*c* 0·50, methanol). Infrared spectrum: ν(C=O) 1 690; ν(OH) 3 490; 3 450; ν(C—H) 1 601; 1 584; 3 060; 3 035 cm^{-1}. This IR spectrum is identical with that of 1,2-O-isopropylidene-6-O-benzoyl-D-glucofuranose prepared according to Coleman and coworkers[11] and the mixed melting point determination does not show any depression.

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