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SYNTHESIS OF METHYL ETHERS OF METHYL (METHYL β-D-GALACTOPYRANOSID)URONATE

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The oxidation of methyl β-D-galactopyranoside with oxygen in the presence of platinum and carbon gave methyl (methyl β-D-galactopyranosid)uronate (I) with a yield of 20%. The partial methylation of (I) with methyl iodide in the presence of silver oxide followed by preparative liquid chromatography on silica gel provided a convenient method for obtaining all the methyl ethers in the individual state.

Syntheses of the methyl ethers of methyl (methyl α-D-galactopyranosid)uronate have been described previously (1) in which the key stage is the oxidation of the primary hydroxy group in partially methylated, partially benzylated, methyl α-D-galactopyranosides. To obtain methyl ethers of D-galacturonic acid, in the present work we have used the simpler approach proposed previously for obtaining methyl ethers of methyl (methyl α-D-glucopyranosid)uronate [2]. It is based on the catalytic oxidation of methyl β-D-galactopyranoside with oxygen in the presence of platinum on carbon, which takes place with the participation of the primary hydroxyl. The resulting uronic acid methyl glycoside is converted under the action of methanol into methyl (methyl β-D-galactopyranosid)uronate (I), by the partial methylation of which, followed by preparative liquid chromatography, the individual methyl ethers of (I) have been obtained.

The differences in the chromatographic mobilities of the methyl ethers of (I) enabled all the methyl ethers of (I) with the exception of the 2,3- and 2,4-di-O-methyl ethers to be obtained by liquid column chromatography. These ethers are readily crystallized from the usual solvents. The total yield of methyl ethers on chromatotraphy was 95%. The separation was monitored by TLC and GLC. Below we give the R_f and R_T values of the methyl ethers of (I) (* — retention times of the acetates of the methyl ethers):

	Positions of the methyl groups							
	2	3	4	2,3	2,4	3,4	2,3,4	—
R_f	0,31	0,25	0,28	0,45	0,46	0,42	0,63	0,08
R_T, NPGS, 210°	1,23	1,09	1,00 (13,2 min)	0,35	0,33	0,50	0,16	—
R_T^*, NPGS, 190°	0,68	1,00 (23,1 min)	1,08	0,30	0,44	0,74	0,19	1,40
R_T, QF-1, 175°	0.90	1,24	1,00 (12,3 min)	0,71	0,61	0.85	0,46	—
R_T^*, QF-1, 155°	1,00 (10,2 min)	1,38	2,00	0,35	0,70	1,24	0,26	2,29

^{13}C NMR spectroscopy was used for the identification of the methyl ethers of (I). The assignment of the signals in (I) was made by comparison with the spectrum of methyl β-D-galactopyranoside [3]. The assignment of the signals in the methyl ethers of (I) was made in the light of known laws [4]. The signals of the carbon atoms in the ^{13}C NMR spectra of the methyl ethers of (I) are given at the top of the next page.

EXPERIMENTAL

Melting points were measured on a Boëtius instrument. Specific rotations were determined on a Perkin-Elmer M 141 automatic polarimeter using methanol as the solvent. ^{13}C NMR spectra were obtained on a Bruker HX-90E spectrometer. Chemical shifts are given in parts per million

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^{13}C chemical shifts	Positions of the methyl groups							
	—	2	3	4	2,3	2,4	3,4	2,3,4
C-1	104,2	104,2	104,2	104,1	104,1	104,1	104,1	103,9
C-2	70,8	80.5	69,7	71,0	79,6	80,9	70.1	79,9
C-3	72,9	72,5	82,0	73,4	81,7	73.1	82,7	82,5
C-4	70.3	70.4	66,1	80,7	66,3	80,9	76,4	76,6
C-5	74,9	74,7	74,8	73,8	74.7	73,8	73.8	73,5
C-6	171.2	171,0	171.1	171,1	171,1	171,1	171,1	171,0
MeO-1	58,0	57,9	58,0	58.0	58,0	58,0	58,0	57.9
MeO-2		60,9			60.8	61,0		60,9
MeO-3			57.0		57.1		58.0	57,9
MeO-4				61.8		61,8	61.2	61.2
MeO-6	53.6	53.4	53,6	53,6	53,6	53,1	53,6	53,5

(ppm) and were measured relative to CH_3OH as internal standard, δ_{CH_3} being taken as 49.6 ppm. D_2O was used as solvent. TLC was performed on silica gel L 5-40 μ (Chemapol) in the chloroform–methanol (95:5) system. GLC was performed on a Tsvet-106 instrument fitted with a flame-ionization detector and double columns (0.3 × 200 cm). The filling was 1.5% of NPGS and 2% of QF-1 on Chromaton N-AW-HMDS (0.125-0.160 mm, Chemapol). The rate of flow of argon was 60 ml/min. Column chromatography was performed on silica gel L 100-160 μm (Chemapol).

Methyl β-D-galactopyranoside [5]. A solution of 90 g of tetra-O-acetyl-α-D-galactopyranosyl bromide in 900 ml of absolute methanol was kept for a day at room temperature and was then neutralized with AV-17 resin (OH^-), and evaporated in vacuum, and the residue was crystallized from ethanol. Yield 27.8 g (65%), mp 175-176°C, $[\alpha]_D^{20}$ −0.9° (c 0.9). According to the literature [5]: mp 175°C, $[\alpha]_D^{20}$ −0.6° (water).

Methyl (methyl β-D-galactopyranoside)uronate (I). With vigorous stirring, oxygen was passed through a solution of methyl β-D-galactopyranoside (9.0 g) in water (150 ml) in the presence of platinum on carbon (10%, 1.8 g) at 90°C for 3 h. Sodium bicarbonate (3.8 g) was added in four portions to maintain a weakly alkaline medium. The solution was de-ionized with KU-2 cation-exchange resin (H^+) and was evaporated. The resulting syrup was dissolved in absolute methanol, and the solution was boiled under reflux for 1 h and was evaporated. The reaction product so obtained was purified by chromatography on a silica gel column using a gradient of methanol in chloroform. The yield of (I) was 2.0 g (20%), mp 186-188°C, $[\alpha]_D^{20}$ −6.5° (c 1.0; water).

Partial Methylation of (I). A solution of 4.0 g of (I) in 40 ml of methanol was treated with 8 g of silver oxide and 8 ml of methyl iodide, and the mixture was stirred in the dark with a magnetic stirrer for 1 h. Then it was filtered and evaporated, the yield of syrup being 4.3 g.

Separation of the Methyl Ethers of (I). The mixture of methyl ethers of (I) (4.2 g) was deposited on a column (3 × 45 cm) of silica gel. Elution was performed with a gradient of solvents: hexane → chloroform → methanol. As a result, the following compounds were obtained: the 2,3,4-tri-O-methyl ether of (I) — 0.3 g, mp 100-101°C, $[\alpha]_D^{20}$ −18.3° (c 0.9); the 3,4-di-O-methyl ether of (I) — 0.35 g, mp 107-108°C, $[\alpha]_D^{20}$ −5.0° (c 1.0); a mixture of the 2,3- and 2,4-di-O-methyl ethers — 0.8 g the 2-O-methyl ether of (I) — 1.0 g, mp 162-163°C, $[\alpha]_D^{20}$ −38.6° (c 1.0); the 4-O-methyl ether of (I) — 0.2 g mp 182-183°C, $[\alpha]_D^{20}$ −49.3 (c 0.7); and the 3-O-methyl ether of (I) 0.5 g, mp 156-157°C, $[\alpha]_D^{20}$ −38.4° (c 1.2). When the mixture of di-O-methyl ethers of (I) was crystallized from ethyl acetate, the 2,4-di-O-methyl ether of (I) was obtained with a yield of 0.24 g, mp 166-167°C, $[\alpha]_D^{20}$ −49.1° (c 0.7). Crystallization from hexane gave the 2,3-di-O-methyl ether of (I) — 0.33 g, mp 105-106°C, $[\alpha]_D^{20}$ −21.9° (c 0.9).

SUMMARY

A convenient method is proposed for synthesizing all the methyl ethers of methyl (methyl β-D-galactopyranosid)uronate.

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POSSIBILITY OF USING THE PERIODATE OXIDATION REACTION IN COMBINATION WITH PMR SPECTROSCOPY FOR ESTABLISHING THE STRUCTURES OF NUCLEOSIDES AND MONOSACCHARIDES, AND THEIR ANALOGS

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A convenient method is proposed for establishing the structures of analogs and derivatives of nucleosides and monosaccharides which consists in performing the periodate oxidation reaction directly in the ampul for recording the PMR spectrum. It has been shown that the PMR spectra of the products of the periodate oxidation reaction are substantially simpler than the spectra of the initial compounds in the case of compounds with terminal diol groupings and of 1-substituted pentapyranoses and tetrapyranoses.

PMR spectroscopy is one of the most important methods of establishing the structures of chemical compounds. An important point in its use is the interpretation of the PMR spectra. In many cases, the interpretation of the spectra is fairly complex. Several variants of the technique of double resonance, isotopic exchange, shift and broadening reagents, solvent changes, etc., are used to solve this problem.

A more complicated approach is the transformation by chemical methods of the compound obtained followed by the separation of the reaction products and the study of their NMR spectra. However, the use of chemical reactions taking place selectively with quantitative yields permits not only the isolation of the reaction products but also a substantial simplification of the investigation.

The aim of the present work was to demonstrate the possibility of using the periodate oxidation reaction in combination with PMR spectroscopy for determining the structures of several classes of natural compounds. The periodate oxidation reaction is widely used in nucleoside and carbohydrate chemistry [1-3]. Periodic acid and its salts cleave a diol group to a dialdehyde group, and a triol system to a dialdehyde derivative and formic acid, which may lead a priori to a substantial simplification of the PMR spectra: the elimination of the spin-spin coupling constant (SSCC) between the protons in the diol and triol groups and also a downfield shift of the signals of the protons of the aldehyde groups. Favorable points in the use of this reaction for the interpretation of PMR spectra are the facts that it can be carried out directly in the ampul for the recording of the PMR spectra, it takes place quantitatively and comparatively rapidly, and it is not accompanied by C–H exchange in the groups when the reaction is performed in D_2O.

Earlier, in a study of the PMR spectra of dialdehyde derivatives obtained by the oxidation of nucleosides, it was observed that in comparison with the spectra of the initial nucleosides they were not simplified but on the contrary, became considerably more complicated [4]. This observation is explained by the fact that, in water, dialdehyde derivatives exist in the form of hydrates which may also form internal semiacetals and polymeric products [4]. The spectra of dialdehyde derivatives of the 5'-phosphate esters of nucleosides have the same complex character [5, 6].

However, in a number of cases we succeeded in observing a substantial simplification of the PMR spectra after the performance of periodate oxidation. The procedure for performing the reaction is simple: to a solution of a nucleoside or monosaccharide in D_2O (concentration ~$5 \cdot 10^{-2}$ M), after the PMR spectrum has been recorded, is added 1.2-1.3 equivalents of $NaIO_4$

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