METHYL ETHERS OF METHYL 2-DEOXY-α- AND β-D-*threo*-PENTOPYRANOSIDE

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Methyl 2-deoxy-α- and β-D-*threo*-pentopyranosides (*Ia*, *IIa*) were prepared. Various conditions for partial methylation of the β-anomer *IIa* were tried out, leading to methyl 2-deoxy-3-O-methyl-β-D-*threo*-pentopyranoside (*IIc*), methyl 2-deoxy-4-O-methyl-β-D-*threo*-pentopyranoside (*IId*) and methyl 2-deoxy-3,4-di-O-methyl-β-D-*threo*-pentopyranoside (*IIe*). The structures of the products were determined by means of ^{1}H NMR.

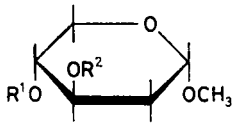
In preceding communications[1-6] we investigated the preparation of methyl ethers of sugars by partial methylation under various conditions and tested the reactivity of individual OH groups in the sugar molecule during this reaction. It became evident[7] that partial methylation is a suitable method for the preparation of individual methyl ethers of sugars, even though it requires a difficult separation of complex reaction mixtures; in many cases it is better than the multistep syntheses of these substances where various protecting groups are made use of.

The aim of this study was to confirm the possibility of using partial methylation for the preparation of methyl ethers of 2-deoxy-D-xylose.

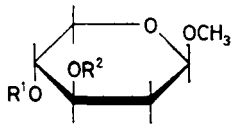
The preparation of the starting methyl 2-deoxy-α- and -β-D-*threo*-pentopyranoside (*Ia*, *IIa*) described in literature[8] starts with diacetyl-D-xylal which on addition of bromine and the substitution of the bromine atom on $C_{(1)}$ by the methoxy group and subsequent reduction affords a mixture of anomeric deoxypentosides *Ib*, *IIb* (see also ref.[9]). The latter compounds were separated chromatographically and deacetylated under formation of pure anomers *Ia* and *IIa*. We used for their preparation methoxymercuration[10] of D-xylal, followed by reduction of the mixture of the mercuro-derivatives formed with sodium borohydride. Chromatography of the mixture of the anomers gave a part of the β-anomer *IIa* in pure form, while the α-anomer *Ia* was obtained after acetylation of the remaining fraction by further chromatography and deacetylation, similarly as described in ref.[8]; the physical constants of compounds *Ia* and *Ib* differ slightly from those in literature[8,9].

The configuration of the α-anomer *Ia* is confirmed by the coupling constant

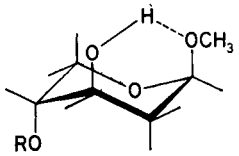
values $J_{1,2e} = 1{\cdot}5$, $J_{1,2a} = 3{\cdot}5$, $J_{2e,3} = 5$, $J_{2a,3} = 11$ Hz. The value of the last mentioned constant shows that *Ia* is almost exclusively in $^4C_1$(D) conformation, with the hydroxyl groups in equatorial positions. In contrast to this in the case of β-anomer *IIa* none of the coupling constants ($J_{1,2a} = J_{1,2e} = J_{2e,3} = 3$ Hz, $J_{2a,3} = 4$ Hz) indicates an antiperiplanar arrangement of the vicinal hydrogen atoms; hence, compound *IIa* must exist predominantly in $^1C_4$(D) conformation, with all the bulky groups in axial positions. The reason for such a distinct shift of the conformational equilibrium on change of configuration at $C_{(1)}$ may consist – in addition to the anomeric effect – in the possibility of the existence of intramolecular hydrogen bond $O_{(3)}H\cdots O_{(1)}$ in $^1C_4$(D) conformation (see formula *III*). This corresponds to the results of the conformational studies[11,12] of partially acetylated methyl α- and β-D-xylopyranosides, where just the β-anomers with a free $O_{(3)}H$ group have the greatest tendency to adopt the $^1C_4$(D) conformation.



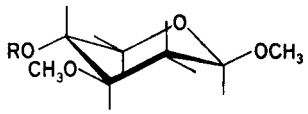
Ia, $R^1 = R^2 = H$
Ib, $R^1 = R^2 = COCH_3$
Ic, $R^1 = H$; $R^2 = CH_3$
Id, $R^1 = CH_3$; $R^2 = H$
Ie, $R^1 = R^2 = CH_3$



IIa, $R^1 = R^2 = H$
IIb, $R^1 = R^2 = COCH_3$
IIc, $R^1 = H$; $R^2 = CH_3$
IId, $R^1 = CH_3$; $R^2 = H$
IIe, $R^1 = R^2 = CH_3$
IIf, $R^1 = CH_3$; $R^2 = COC_6H_5$
IIg, $R^1 = COC_6H_5$; $R^2 = CH_3$



III, R = H, CH_3



IV, R = H, CH_3

In our effort to find the optimum conditions for the preparation of monomethyl derivatives *IIc*, *IId*, we carried out preliminary methylations of compound *IIa* with methyl iodide and silver oxide in the presence of various solvents. We followed the course of the reaction by gas chromatography. The results are expressed similarly as in our preceding papers[1–7,13,14] in the form of the ratios of rate constants of the reaction to the first and the second steps, and they are presented in Table I. In the majority of cases 4-O-methyl derivative *IId* predominated over 3-O-methyl derivative

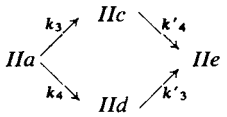
IIc during the whole reaction ($k_4/k_3 > 1$, $k'_4/k'_3 > 1$). From the preparative viewpoint methylation with methyl iodide and silver oxide in ether was found best, when interrupted at the stage of the maximum concentration of compounds *IIc* or *IId*. The mixture of the products formed was separated by chromatography on silica gel and in addition to the starting compound *IIa* three methylated products were obtained, pure according to TLC and gas chromatography. Their structure and conformations were determined in the following manner:

The substance with the shortest retention time and the highest R_F value, formed during the methylation as the last one, and with the ^{1}H NMR signal corresponding to three methoxy groups, was assigned the structure of dimethyl ether *IIe*. $J_{1,2a} = 7$ Hz corresponds to the $^4C_1$(D) conformation.

According to elemental analyses and the ^{1}H NMR spectra both the remaining substances are isomeric monomethyl derivatives *IIc* and *IId*. Their structures were assigned by conversion to corresponding benzoyl derivatives *IIg*, *IIf*, of which one, methyl 4-O-benzoyl-2-deoxy-3-O-methyl-β-D-*threo*-pentopyranoside (*IIg*), was described in literature[15]. The ^{1}H NMR data of the substances described[15] and prepared by us (*IIg*) were identical and permitted the location of the benzoyl group into posi-

TABLE I

Course of methylation of *IIa* under various conditions



IIa mg	Ag_2O mg	CH_3I ml	Solvent[a] ml	k_4/k_3	k_3/k'_3	k_4/k'_4
5·7	100	0·4	0·4 AC	1·1	1·4	0·9
6·4	100	0·4	0·4 ME	1·0	0·9	0·6
3·7	100	0·4	0·4 AN	1·1	2·1	1·6
4·0	100	0·8	—	1·2	3·4	3·5
5·4	104	0·4	0·4 DMF	1·7	0·9	0·9
6·3	105	0·4	0·05 DMF	1·2	1·7	1·7
6·3	99	0·4	0·025 DMF	1·2	1·9	1·5
6·5	98	0·4	0·0125 DMF	0·8	3·6	1·0
6·0	100	0·4	0·4 E	1·5	1·2	1·0

[a] AC acetone, ME methanol, AN acetonitrile, DMF dimethylformamide, E diethyl ether.

tion 4 unambigously. However, their physical constants were different*. Compound *IIc* from which it was prepared must have a hydroxyl group in this position and therefore it must have the structure of methyl 2-deoxy-3-O-methyl-β-D-*threo*-pentopyranoside. Similarly the spectrum of derivative *IIf* also displayed a corresponding downfield shift of the proton signal of H-3, neighbouring with the benzoyl group; compound *IId* has the structure of methyl 2-deoxy-4-O-methyl-β-D-*threo*-pentopyranoside. 4-O-Methyl derivative *IId* has the chemical shifts and the coupling constants of protons H-1, H-2a and H-2e almost identical with the starting diol *IIa*, while the spectrum *IIc* is similar to that of dimethyl derivative *IIe*. Compounds *IIa* and *IId* are thus predominantly in $^1C_4$(D) conformation (formula *III*), compounds *IIc* and *IIe* in $^4C_1$(D) conformation (formula *IV*), which corresponds to the above consideration concerning the effect of the intramolecular hydrogen bond $O_{(3)}H...O_{(1)}$ on the position of the conformational equilibrium. The different conformation of the two isomers *IIc* and *IId* also explains the large difference in their R_F values and the ensuing relatively easy preparative chromatographic separation of the two substances. The higher R_F value of 4-O-methyl derivative *IId* is also in agreement with the empirical rule that the isomer with a six-membered intramolecular hydrogen bridge is eluted more rapidly.

From the preparative methylation of the α-anomer *Ia* we obtained in addition to the unreacted starting substance *Ia* and dimethyl ether *Ie* merely mixtures of both monomethyl ethers *Ic* and *Id*, with a very similar chromatographic behaviour, which could not be separated. The difficulties in the separation may be due to the fact that *Ic* and *Id* will exist in solution (the same as *Ia* and *Ie*) in the same conformation $^4C_1$(D), different from the situation of the β-anomers *IIc* and *IId*.

EXPERIMENTAL

The melting points were determined on a Kofler block and they are not corrected. Optical rotation was measured on an Opton photoelectric polarimeter, in chloroform at $c = 1 \pm 0{\cdot}1$ concentration, unless stated otherwise. The solutions were evaporated in a vacuum on a rotational evaporator, at 40°C of bath temperature.

Preparative chromatography was carried out on silica gel 100—160 μm, thin-layer chromatography was used for the observation of the reaction course and checking the purity of the products, and they were carried out on silica gel G according to Stahl (Merck). The size of the plates was 25 × 75 mm and the layer thickness 0·2—0·3 mm. For the development the following systems were employed: chloroform with 1—5% of methanol and light petroleum–ethyl acetate 4 : 1 and 2 : 1. The substances were detected by spraying with a 2% cerium (IV) sulfate solution in 10%

* After consultation with K. Bock and C. Pedersen it became evident that in the experimental part of their paper[15] on p. 79 there is a printing error which caused an exchange of the constants for *erythro* and *threo* isomers labelled β-4 and β-5. On line 10 β-5 should be written instead of β-4 and on line 13, on the contrary, β-4 instead of β-5; after this correction the physical constants of the *threo*-isomer β-5 also agree with the physical constants of our product *IIg*.

sulfuric acid and heating. Gas chromatography was carried out on a Varian-Aerograph 2 100 instrument with flame ionisation detection and a Hewlett–Packard 3 380 A integrator. (Column 1 800 × 2 mm, packed with 0·5% TRIDOX, 0·7% DEGS, 0·12% PDEA on Varaport 30. The temperature was programmed to 4°C/min in the 110—150°C interval, 1 μl of the reaction mixture was injected at 180°C, helium flow 20 ml/min). The ^{1}H NMR spectra were measured in deuteriochloroform on a Varian XL — 100 — 15 instrument with tetramethylsilane as internal reference (δ-scale, coupling constants in Hz).

Methyl 2-Deoxy-α- and β-D-*threo*-Pentopyranosides (*Ia*, *IIa*)

Mercuric acetate (41 g) in 250 ml of methanol was added under stirring to a solution of 12 g of D-xylal in 700 ml of methanol at −15°C and the mixture was stirred for 30 min and then allowed to stand at room temperature for 1 h. The insoluble material was filtered off and the filtrate concentrated. Yield, 45 g of a chromatographically pure mixture of isomers (m.p. 145 to 148°C from methanol) which was dissolved in 700 ml of methanol. 1M-NaOH (187 ml) and 2·2 g of sodium borohydride in 42 ml of 1M-NaOH were added under stirring and the mixture was stirred for another 90 min at 60°C. After cooling and filtration the filtrate was neutralized by bubbling through carbon dioxide, and then evaporated. The residue was extracted with four 100 ml portions of acetone, the combined acetone fractions were filtered and evaporated, to yield 12·1 g (79%) of a syrupy mixture of anomers *Ia* and *IIa*. Chromatography with chloroform–3% methanol gave 4·1 g of β-anomer *IIa*, which was crystallized from a mixture of ethyl acetate and light petroleum to yield 3·8 g of pure product, m.p. 83—84°C, $[\alpha]_D^{15}$ −167°, in agreement with literature[8]. ^{1}H NMR spectrum: 4·66 (1 H, t, $J_{1,2a} = J_{1,2e} = 3$, H-1), 4·10 (1 H, dd, $J_{5a,5e} = 12$, $J_{4,5} = 2$, H-5e), 3·4—3·9 (3 H, m, H-3, H-4, H-5a), 3·42 (3 H, s, CH_3O), 2·24 (1 H, m, $J_{1,2e} = 3$, $J_{2a,2e} = 14$, $J_{2e,3} = 3$, H-2e), 1·74 (1 H, m, $J_{1,2a} = 3$, $J_{2a,2e} = 14$, $J_{2a,3} = 4$, H-2a).

Further, 6·6 g of a mixture of anomers were obtained, which was acetylated with acetic anhydride in pyridine. The mixture of acetyl derivatives *Ib*, *IIb* obtained was separated chromatographically in the system light petroleum–ethyl acetate 5 : 1. Yield, 4·1 g of acetyl derivative *Ib*, m.p. 27°C, $[\alpha]_D^{20}$ +85·6°, described as a syrup with $[\alpha]_D^{20}$ +85·7° (ref.[8]) and +86·5° (ref.[9]), and 3·2 g of acetyl derivative *IIb*, syrup, $[\alpha]_D^{20}$ −101° in agreement with the literature[8,9].

Deacetylation of *Ib* with a catalytic amount of sodium methoxide in methanol gave 2·4 g of methyl 2-deoxy-α-D-*threo*-pentopyranoside (*Ia*), m.p. 55—56°C (ethyl acetate–light petroleum) which is described in literature[8] as a low melting solid. ^{1}H NMR spectrum: 4·73 (1 H, dd, $J_{1,2a} = 3·5$, $J_{1,2e} = 1·5$, H-1), 3·33 (3 H, s, OCH_3), 2·31 (1 J, m, $J_{1,2e} = 1·5$, $J_{2a,2e} = 13$, $J_{2e,3} = 5$, H-2e), 1·63 (1 H, m, $J_{1,2a} = 3·5$, $J_{2a,2e} = 13$, $J_{2a,3} = 11$, H-2a), $[\alpha]_D^{20}$ +125°.

From the acetyl derivative *IIb* another 1·8 g of methyl 2-deoxy-β-D-*threo*-pentopyranoside (*IIa*) were obtained. Totally, 15% of α-anomer *Ia* and 36% of β-anomer *IIa* were isolated.

Methylation of Methyl 2-Deoxy-β-D-*threo*-pentopyranoside (*IIa*)

A mixture of 756 mg of pyranoside *IIa*, 5 g of silver oxide, 30 ml of ether, and 15 ml of methyl iodide was stirred at room temperature for 65 min and filtered. The filtrate was evaporated and the residue chromatographed in chloroform–1% methanol system, to give: 88 mg (9·8%) of dimethyl derivative *IIe*, syrup, $[\alpha]_D^{15}$ −121°. ^{1}H NMR spectrum: 4·70 (1 H, dd, $J_{1,2a} = 3·5$, $J_{1,2e} = 2·5$, H-1), 3·75 (1 H, dd, $J_{5a,5e} = 11·5$, $J_{5e,4} = 4·5$, H-5e), 3·47, 3·43, 3·33 (3 × 3 H, 3 s, 3 CH_3O), 2·17 (1 H, m, $J_{1,2e} = 2·5$, $J_{2e,3} = 4·5$, $J_{2a,2e} = 13$, H-2e), 1·54 (1 H, m, $J_{1,2a} = 3·5$, $J_{2a,3} = 10$, $J_{2a,2e} = 13$, H-2a), further 267 mg (32%) of 4-O-methyl derivative *IId*, syrup, $[\alpha]_D^{15}$ −128°. ^{1}H NMR spectrum: 4·68 (1 H, t, $J_{1,2a} = 3$, $J_{1,2e} = 3$, H-1), 4·05 (1 H, dd, $J_{5a,5e} =$

= 12, $J_{4,5e}$ = 2·5, H-5e), 3·44, 3·40 (2 × 3 H, 2 s, 2 CH_3O), 3·1–3·9 (3 H, m, H-3, H-4, H-5a), 2·20 (1 H, m, $J_{2a,2e}$ = 14, $J_{1,2e}$ = 3, $J_{2e,3}$ = 3, H-2e), 1·75 (1 H, m, $J_{2a,2e}$ = 14, $J_{1,2a}$ = 3, $J_{2a,3}$ = 5, H-2a). For $C_7H_{14}O_4$ (162·2) calculated: 51·83% C, 8·70% H; found: 51·81% C, 8·66% H.

Further, 157 mg (19%) of 3-O-methyl derivative *IIc* were obtained, $[\alpha]_D^{15}$ −115°. ^{1}H NMR spectrum: 4·40 (1 H, dd, $J_{1,2a}$ = 8, $J_{1,2e}$ = 3, H-1), 4·06 (1 H, dd, $J_{5a,5e}$ = 11, $J_{4,5e}$ = 4, H-5e), 3·46, 3·41 (2 × 3 H, 2 s, 2 CH_3O), 3·1–3·8 (3 H, m, H-3, H-4, H-5a), 2·28 (1 H, m, $J_{2a,2e}$ = 13, $J_{1,2e}$ = 3, $J_{2e,3}$ = 4·5, H-2e), 1·49 (1 H, m, $J_{2a,2e}$ = 13, $J_{1,2a}$ = 8, $J_{2a,3}$ = 9·5, H-2a). For $C_7H_{14}O_4$ (162·2) calculated: 51·83% C, 8·70% H; found: 51·60% C, 8·75% H. Finally 235 mg (31%) of the regenerated starting pyranoside *IIa* were also isolated.

Methyl 3-O-Benzoyl-2-deoxy-4-O-methyl-β-D-*threo*-pentopyranoside (*IIf*)

IIf was prepared on reaction of *IId* with benzoyl chloride in pyridine as a syrup, $[\alpha]_D^{15}$ −116°. ^{1}H NMR spectrum: 5·23 (1 H, n, $J_{2e,3}$ = 4·5, $J_{2a,3}$ = 7·5, $J_{3,4}$ = 7·5, H-3), 4·58 (1 H, dd, $J_{1,2e}$ = 3, $J_{1,2a}$ = 5·5, H-1), 4·18 (1 H, m, H-5e), 3·3–3·6 (2 H, m, H-4, H-5a), 3·52, 3·49 (2 × 3 H, 2 s, 2 CH_3O), 2·38 (1 H, m, $J_{1,2e}$ = 3, $J_{2e,3}$ = 4·5, $J_{2a,2e}$ = 13·5, H-2e), 1·81 (1 H, m, $J_{1,2a}$ = 5·5, $J_{2a,3}$ = 7·5, $J_{2a,2e}$ = 13·5, H-2a). For $C_{14}H_{18}O_5$ (266·3) calculated: 63·14% C, 6·81% H; found: 63·44% C, 6·83% H.

Methyl 4-O-Benzoyl-2-deoxy-3-O-methyl-β-D-*threo*-pentopyranoside (*IIg*)

IIg was obtained by benzoylation of *IIc*; m.p. 53–54°C, $[\alpha]_D^{15}$ −151°. For $C_{14}H_{18}O_5$ (266·3) calculated: 63·14% C, 6·81% H; found: 62·85% C, 7·07% H. The constants and the ^{1}H NMR spectrum are in agreement with literature, see footnote on p. 1674.

Methylation of Methyl 2-Deoxy-α-D-*threo*-pentopyranoside (*Ia*)

Methylation of α-anomer *Ia* and the isolation of the products was carried out in the same manner as in the case of β-anomer *IIa*. From 412 mg of pyranoside *Ia* 98 mg (24%) of the starting compound *Ia* were obtained, further 231 mg (51%) of a mixture of both monomethyl isomers *Ic*, *Id*, and 78 mg (16%) of methyl 2-deoxy-3,4-di-O-methyl-α-D-*threo*-pentopyranoside (*Ie*), a syrup. $[\alpha]_D^{15}$ +78°.

Effect of the Solvent Added on the Methylation Course of Methyl 2-Deoxy-β-D-*threo*-pentopyranoside

Pyranoside *IIa* (5 mg) was weighed in a test tube and 100 mg of silver oxide and 0·4 ml of methyl iodide with the corresponding solvent (for data see Table I) were added to it. The mixture was shaken and allowed to stand at room temperature. Every 20 min a sample of the supernatant was withdrawn and analysed by gas chromatography. The mixture was shaken again. The results of the measurements were processed according to refs[13,14] and the ratios of rate constants obtained are given in Table I.

Elemental analyses and spectral measurements were carried out in the department of organic analysis of the Prague Institute of Chemical Technology (head Dr L. Helešic) and the department of NMR *spectroscopy (head Dr P. Trška); we thank the collaborators of these departments for their help. Our thanks are also due to Mr V. Ineman for collaboration in the analytical determinations by gas chromatography.*

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