PARTIAL METHYLATION
OF METHYL 4,6-DIDEOXY-α-D-*arabino*-HEXOPYRANOSIDE*

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The reaction of methyl 4,6-dideoxy-α-D-*arabino*-hexopyranoside with methyl iodide and solid sodium hydroxide in acetonitrile at 20°C gives rise to a mixture the composition of which is determined by the ratios of rate constants $k_2/k_3 = 2.89$, $k'_2/k'_3 = 6.62$, $k'_2/k_2 = 1.18$ and $k'_3/k_3 = 0.52$. The possible sterical and polar effects, affecting the reactivity of both hydroxyl groups, are discussed.

In a previous paper[1] we studied the relative rate of substitution of the OH groups on $C_{(2)}$ and $C_{(3)}$ in methyl 4,6-dideoxy-α-D-*xylo*-hexopyranoside and methyl 4,6-dideoxy-α-L-*lyxo*-hexopyranoside during their alkylation with methyl iodide in acetonitrile, in the presence of sodium hydroxide. In order to check the conclusions expressed there we considered it useful to obtain information of the reaction course in further configurational isomers. In this paper we describe the results of the study of the above mentioned reaction with methyl 4,6-dideoxy-α-D-*arabino*-hexopyranoside.

EXPERIMENTAL

Starting and Reference Substances

Methyl 4,6-dideoxy-α-D-*arabino*-hexopyranoside (*I*) and methyl 4,6-dideoxy-3-O-methyl-α-D--*arabino*-hexopyranoside (*III*) were prepared from methyl 2,3-anhydro-4,6-dideoxy-α-D-*lyxo*--hexopyranoside on reaction with sodium hydroxide or sodium methoxide[2]. Methyl 4,6-dideoxy--2-O-methyl-α-D-*arabino*-hexopyranoside (*II*) was prepared from methyl 2,3-anhydro-4,6-dideoxy--α-D-*ribo*-hexopyranoside on reaction with sodium methoxide[2]. The structure of compounds *I—III* has been confirmed[2] by ^{1}H-NMR, IR and mass spectra. Methyl 4,6-dideoxy-2,3-di-O--methyl-α-D-*arabino*-hexopyranoside (*IV*) was obtained from glycoside *I* on methylation. It is an oil boiling at 75°C/1·3 kPa, $[\alpha]_D^{20}$ +86·2 ± 1·5° (c 1·1, chloroform). For $C_9H_{18}O_4$ (190·2) calculated: 56·82% C, 9·53% H; found: 56·73% C, 9·64% H; ^{1}H-NMR (CDCl₃, 37°C, Varian XL-100-15, tetramethylsilane as internal reference, δ-scale): $H_{(1)}$: 4·58 ppm, $J_{1,2} \sim$ 2 Hz; $H_{(2)}$:

3·07 ppm, $J_{2,1} \sim 2$ Hz, $J_{2,3} \sim 3·5$ Hz; $H_{(3)}$: 3·43 ppm (multiplet); $2 H_{(4)}$: 1·56—1·71 ppm (multiplet); $H_{(5)}$: 4·03 ppm, $J_{5,4a} \sim 7·5$ Hz, $J_{5,4e} \sim 5$ Hz, $J_{5,6} \sim 6·5$ Hz; $3 H_{(6)}$: 1·13 ppm, $J_{6,5} \sim 6·5$ Hz.

Method

Partial methylation of glycoside *I* was carried out in acetonitrile using an excess of methyl iodide and a defined amount of sodium hydroxide. In a typical experiment 71 mg (1·78 mmol) of powdered sodium hydroxide were added at 20°C to a stirred solution of 162 mg (1 mmol) of glycoside *I* in 25 ml of acetonitrile and 4 ml of methyl iodide. At regular time intervals samples for analysis were withdrawn and analysed by gas chromatography. Gas chromatography was carried out on a Varian Aerograph 2100 with a 0·2 × 180 cm column packed with 5% Versamide on Chromosorb T (40—60 mesh) at 180°C, flow rate 20 ml He/min, injection 0·5 µl at 190°C, detection with FID (200°C). An automatic evaluation of the substances investigated and the record of the analyses in molar percents was obtained by means of a Hewlett–Packard 3380 A integrator after previous calibration of the detector responses with standard mixtures. The results of the experiment are given in Table I. From a series of analogous experiments a statistically significant set of values has been obtained (total 230) which was made use of for the calculation of relative rate constants according to the method in ref.[7]. For an independent determination of the ratio of rate constants in the second step of substitution the methylation of a mixture of 22·8 mg (131 µmol) of monomethyl ether *II* and 26·3 mg (151 µmol) of monomethyl ether *III* in 10 ml acetonitrile and 1·5 ml of methyl iodide in the presence of 7·2 mg (180 µmol) of sodium hydroxide was followed. The results of the experiment are given in Table II.

TABLE I

Course of Methylation of Methyl Glycoside *I*

Tabulated values correspond to the experiment described in the Experimental Part.

Time min	Composition of the reaction mixture mol. %				Time min	Composition of the reaction mixture mol. %			
	I	*II*	*III*	*IV*		*I*	*II*	*III*	*IV*
5	96·22	1·99	1·81	—	153	16·28	50·64	9·60	23·46
16	87·45	9·14	3·29	0·93	167	14·65	50·98	9·37	25·01
28	76·59	17·09	5·71	0·57	183	14·40	50·78	9·20	25·63
39	70·02	21·74	7·09	1·15	197	12·52	51·13	8·72	27·61
72	45·42	37·85	11·44	5·30	211	10·02	52·05	8·50	29·43
85	39·53	40·85	11·80	7·80	230	11·16	51·02	8·17	29·63
103	31·28	44·53	11·49	12·68	272	10·00	50·75	7·71	31·56
115	25·14	47·39	11·24	16·25	*a*	0·59	35·66	1·37	62·37
128	19·94	49·88	10·61	19·56					

a 24 h.

RESULTS AND DISCUSSION

Chemical changes that are the subject of this study are represented in Scheme 1, in which k_2, k_3, k_2' and k_3' are the rate constants of the methylation of hydroxyl groups $C_{(2)}$-OH or $C_{(3)}$-OH in the 1st or the 2nd reaction stage. The percentual representation of compounds I, II, III and IV, given in Table I, affords a satisfactory idea of the composition of the reaction mixture in various stages of substitution, but they do not give accurate information on the reactivity of the particular OH groups. Such information can be
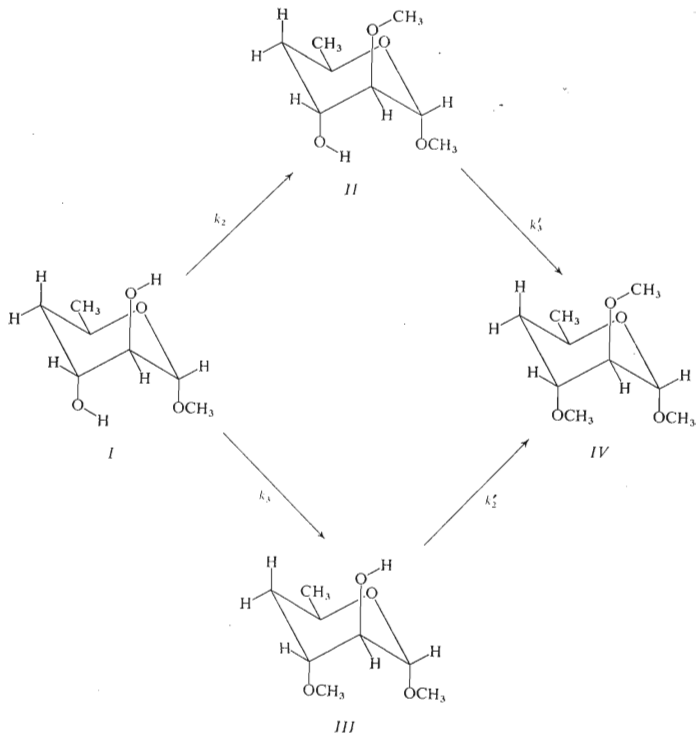
SCHEME 1

obtained by calculating relative rate constants, *i.e.* the ratios k_2/k_3, k_2'/k_3' etc. The method of calculation for the above mentioned system of one parallel and two subsequent reactions was described[3] and made use of in various acylation[3-5] and alkylation[1,6] reactions. According to them, it is necessary to know the ratio of rate constants $k = k_2'/k_3'$ in addition to the percentual composition of the reaction mixture in a certain stage of substitution. This ratio can be obtained from the result of the reaction to which a known mixture of two monosubstituted derivatives is submitted in the presence of a limited amount of alkylating agent. In Table II the results of the analyses at various periods of this reaction are given along with the calculated value for k, corresponding to the composition of the analysed mixture. The average value of the constant sought is $k_2'/k_3' = 6.16$. On the basis of its value and the knowledge of the composition of the reaction mixture at a certain reaction stage, for example 10.0% *I*, 50.75% *II*, 7.71% *III* and 31.56% *IV*, other ratios of the rate constants were also computed in the described manner[3]: $k_2/k_3 = 3.06$, $k_2/k_3' = 5.4$, $k_2'/k_3 = 3.35$, $k_2'/k_2 = 1.13$, $k_3'/k_3 = 0.55$.

We have also checked the modified method[7] of calculation which enables the obtaining of the required ratios of rate constants without an additional experiment with monosubstituted derivatives, *i.e.* on the basis of data given in Table I and further data (totally 230) obtained in analogous experiments only. Curves were constructed representing the dependence of the percentual content in monosubstituted derivatives

TABLE II

Course of the Methylation of the Mixture of Monomethyl Ethers *II* and *III* and the Values of k_2'/k_3'

Tabulated values correspond to the experiment described in the Experimental.

Analysis	Composition of the reaction mixture, %			
	II	*III*	*IV*	k_2'/k_3'[a]
1[b]	46.45	53.57	—	—
2	45.88	49.87	4.25	5.80
3	45.81	49.27	4.92	6.03
4	45.73	48.47	5.80	6.41
5	45.56	47.37	7.08	6.15
6	45.43	46.87	7.70	6.02
7	45.24	45.58	9.18	6.12
8	45.17	45.17	9.65	6.10
9	44.93	42.87	12.21	6.68

[a] Computed from the ratio $k_2/k_3 = (\log c_{II_0} - \log c_{III})/(\log c_{II_0} - \log c_{II})$; [b] starting mixture.

II and III on the content of the starting diol I. The slopes of the conversion curves at points c_{II} and $c_{III} = 0\%$ give the same ratio as the rate constants k_2/k_3. The knowledge of this ratio enables the calculation of the constant $p = k_2/(k_2 + k_3)$, necessary for the finding of the values q and k by solving equations[3] (1) and (2):

$$c_{II} = \frac{p}{(q-1)} \left(c_I - c_{I_0}^{(1-q)} \cdot c_I^q \right), \qquad (1)$$

$$c_{III} = \frac{1-p}{kq-1} \left(c_I - c_{I_0}^{(1-kq)} \cdot c_I^{kq} \right), \qquad (2)$$

where c_I, c_{II} and c_{III} are mol.% of compounds I, II, III, $c_{I_0} = 100$, $q = k_3'/(k_2 + k_3)$, $k = k_2'/k_3'$.

From the determined values of parameters k, p and q the ratio of all rate constants in Scheme 1 can be obtained. Using experimental data, a part of which is given in Table I, the following values were calculated for these ratios by the above mentioned procedure[7]: $k_2/k_3 = 2\cdot89$, $k_2'/k_3' = 6\cdot62$, $k_2/k_3' = 5\cdot6$, $k_2'/k_3 = 3\cdot42$, $k_2'/k_2 = 1\cdot18$, $k_3'/k_3 = 0\cdot52$. These values are in good agreement with the values obtained by the first procedure. Another control of correctness of the determined values of relative rate constants consists in the reverse calculation of the theoretical values of II and III for the selected values of I (in mol.%). The result agrees within the limits of experimental errors with the corresponding experimental results.

The following conclusions follow for the investigated reaction from the values found of relative rate constants: 1. In the starting glycoside I the hydroxyl group on $C_{(2)}$ reacts approximately three times faster than the hydroxyl group on $C_{(3)}$ ($k_2/k_3 = 2\cdot89$). 2. Monomethyl derivative III reacts in the position 2 about six times faster than monomethyl derivative II. This change in relative reactivity of the OH groups on $C_{(2)}$ and $C_{(3)}$ in comparison with the reactivity of these groups in the starting diol I is not caused by the increase in reaction rate in 3-O-methyl derivative ($k_2'/k_2 = 1\cdot18$), but rather by the retardation of the reaction in 2-O-methyl derivative II ($k_3'/k_3 = 0\cdot52$).

The explanation of the values found of relative rate constants was sought in our previous papers[1,6] in polar and steric effects that come into play on individual hydroxyl groups of all substances investigated in a different way. As one of the possible polar effects the change in the localization of electrons, elicited by the formation of intramolecular hydrogen bonds was considered, leading to an increase in nucleophilicity of the oxygen of the bound hydroxyl group. The possibility of forming "double bridges", or their abolition in consequence of methylation of one of the participating hydroxyl groups can also affect the nucleophilicity of the oxygen atom considered. This explained the different reactivity of a certain hydroxyl group during

the comparison of a free diol and a monomethyl ether. On the basis of steric factors a lower reactivity of hydroxyl groups in an axial position (in comparison with the OH groups in an equatorial position) was assumed, and further also the retarding effect of the vicinal methoxyl substituent (in comparison with the unsubstituted OH group). The combination of the above mentioned factors enabled a satisfactory explanation of the values of relative rate constants in methyl 4,6-dideoxy-α-D-*xylo*-hexo-pyranoside[1], methyl 4,6-dideoxy-α-L-*lyxo*-hexopyranoside[1] and methyl 2,6-dideoxy--α-D-*ribo*-hexopyranoside[6], but it is definitely not suitable for the explanation of these constants in methyl 4,6-dideoxy-α-D-*arabino*-hexopyranoside (*I*) and its monomethyl derivative. The conformation $^4C_1(D)$ (if considered unchanged even at the moment of reaction) excludes the possibility in diol *I* of the formation of a "double bridge", and in all substances investigated, *I−III*, the possibility of a mutual steric influence of the substituents on $C_{(2)}$ and $C_{(3)}$. It explains the formation of the strong six-membered intramolecular hydrogen bond $C_{(3)}$—O—H···$O_{(1)}$ and the weaker five-membered $C_{(2)}$—O—H···$O_{(r)}$ (ref.[2]) hydrogen bond. The intensity and the population of these bonds was not reflected, however, in the expected manner in the reactivity of the hydroxyl groups of compounds *I, II* and *III*. It seems that the values observed of the relative rate constants can be explained in these glycosides merely by the inductive effect of the semiacetal group, or by the difference of the inductive effect of the OH and the OCH_3 groups in the position 2 which could affect the reactivity of the OH group on $C_{(2)}$ in compounds *I* and *III*, or the OH group on $C_{(3)}$ in compound *II*. If this hypothesis were valid it should also be considered for the explanation of kinetic data in diastereoisomeric glycosides of D-*xylo* and L-*lyxo* configuration. It is evident that for the expression of a more general theory on the factors affecting the reactivity of the secondary hydroxyl groups on the sugar residue, the results of a larger number of model compounds should be known.

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