THE SYNTHESIS OF 4-O-OLIGOETHYLENE GLYCOL DERIVATIVES OF 1,6-ANHYDRO-β-D-GLUCOPYRANOSE AND CROWN-ETHERS FORMED BY THEIR INTRAMOLECULAR CYCLIZATION*

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Received February 2, 1991
Accepted March 22, 1991

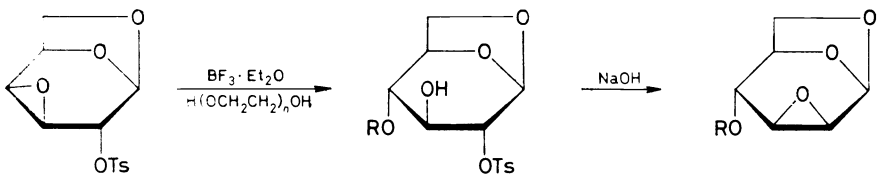
Dedicated to Professor Alois Vystrčil on the occasion of his 70th birthday.

Using acid catalysed reaction of 1,6 : 3,4-dianhydro-2-O-*p*-toluenesulfonyl-β-D-galactopyranose (*I*) with mono-, di-, tri- and tetraethylene glycol, 4-O-oligoethylene glycol derivatives of 1,6-anhydro-2-O-*p*-toluenesulfonyl-β-D-glucopyranose *II*—*V* were obtained which were converted to 4-O-substituted 1,6 : 2,3-dianhydro-β-D-mannopyranoses *VI*—*IX* under the effect of sodium hydroxide. Of them 4-O-(2-hydroxyethyl)- and 4-O-(11-hydroxy-3,6,9-trioxaundecyl) derivatives *VI* and *IX* were intramolecularly cyclized in basic medium under formation of 1,6-anhydro-3,4-O-ethylene-β-D-altropyranose (*X*) or 1,6-anhydro-2,4-O-(3,6,9-trioxaundecane-1,11-diyl)-β-D-glucopyranose (*XV*), respectively. Oxidation of the hydroxyl group in compound *XV* led to corresponding 3-ulose *XIX*, the reduction of which with sodium borohydride gave an isomer of compound *XV*, i.e. compound *XX* of D-*allo*-configuration. The structures of the compounds described in this paper were proved using ^{1}H and ^{13}C NMR spectra. Compounds *XV*, *XIX* and *XX* represent a new structural type of sugar crown-ethers.

A large number of chiral crown-ethers containing a sugar molecule as the chiral component, for example a substituted aldose or a sugar alcohol, has already been described in literature[1]. The polyether part consists most frequently of 15-crown-5 or 18-crown-6. The complexing properties of these compounds are dependent on the geometry of the polyether ring, which is forced to a certain extent both by the configuration of the sugar moiety and by the type of its attachment to the cycle. It was also proved that the presence of a free hydroxyl group in the polyether ring may affect the complexing properties and, moreover, enable the introduction of substituents[2] with various polar or chiral properties. In our experiments aimed at the preparation of a new type of crown ether based on 1,6-anhydro-β-D-*gluco*- or D-*allo*-hexopyranose we have taken these views into consideration.

* Part XXXIX in the series Syntheses with Anhydro Sugars; Part XXXVIII: Collect. Czech. Chem. Commun. *54*, 2753 (1989).

1,6 : 3,4-Dianhydro-2-O-*p*-toluenesulfonyl-β-D-galactopyranose[3] (*I*) was used as starting compound. Its oxiran ring was cleaved under catalysis with boron trifluoride with mono-, di-, tri- and tetraethylene glycol to give O-(oxaalkyl) derivatives of 1,6-anhydro-2-O-*p*-toluenesulfonyl-β-D-glucopyranose *II*–*V* (Scheme 1); the reac-



I $n = 1-4$

II, R = CH_2CH_2OH
III, R = $(CH_2CH_2O)_2H$
IV, R = $(CH_2CH_2O)_3H$
V, R = $(CH_2CH_2O)_4H$

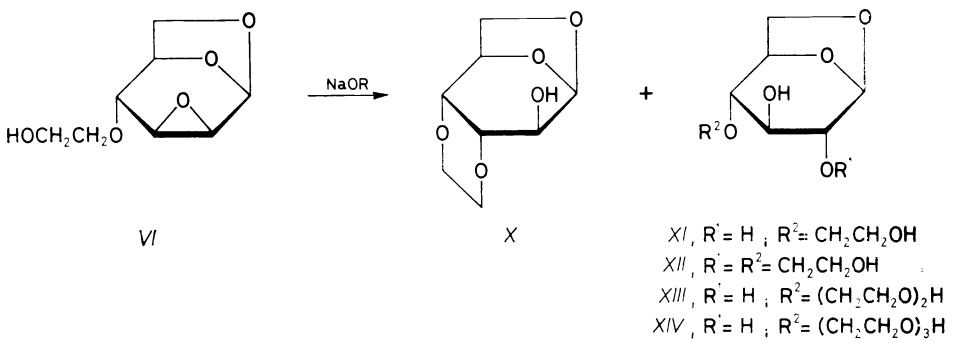
VI, R = CH_2CH_2OH
VII, R = $(CH_2CH_2O)_2H$
VIII, R = $(CH_2CH_2O)_3H$
IX, R = $(CH_2CH_2O)_4H$

SCHEME 1

tion proceeded regioselectively, as with other alcohols[4]. The crude products obtained in this manner were converted (without further purification) on reaction with sodium hydroxide in aqueous dioxane and at room temperature, to corresponding 4-O-substituted derivatives of 1,6 : 2,3-dianhydro-β-D-mannopyranose *VI*–*IX* which we assumed would be suitable for intramolecular cyclization.

We tried to carry out the cyclization of dianhydro derivatives *VI*–*IX* using sodium tert-butoxide in tert-butyl alcohol or with sodium hydride in dioxane, i.e. under the conditions used in other instances[5]. Compounds of oligomeric character were formed from compound *VI* (cf. ref.[6]), the identification of which was not undertaken, and also 1,6-anhydro-3,4-O-ethylene-β-D-altropyranose (*X*) in negligible amount. In contrast to this, when an aqueous sodium hydroxide solution or sodium glycolate were used in the reaction at elevated temperature, compound *X* was formed in about 15% yield (Scheme 2). In both cases the main reaction products were formed by solvolysis of the oxiran ring of compound *VI* and they were identified as 1,6-anhydro-4-O-(2-hydroxyethyl)-β-D-glucopyranose (*XI*) or 1,6-anhydro-2,4-di-O-(2-hydroxyethyl)-β-D-glucopyranose (*XII*).

Attempts at an analogous intramolecular cyclization of dianhydro derivatives *VII* and *VIII*, carried out under various conditions, were unsuccessful, probably in consequence of steric interactions generally unfavourable for the formation of medium size cycles. Only products of hydrolysis could be isolated from the reaction mixture, i.e. compounds *XIII* and *XIV*, the structure of which was proved by NMR spectra (see Tables I and II).



SCHEME 2

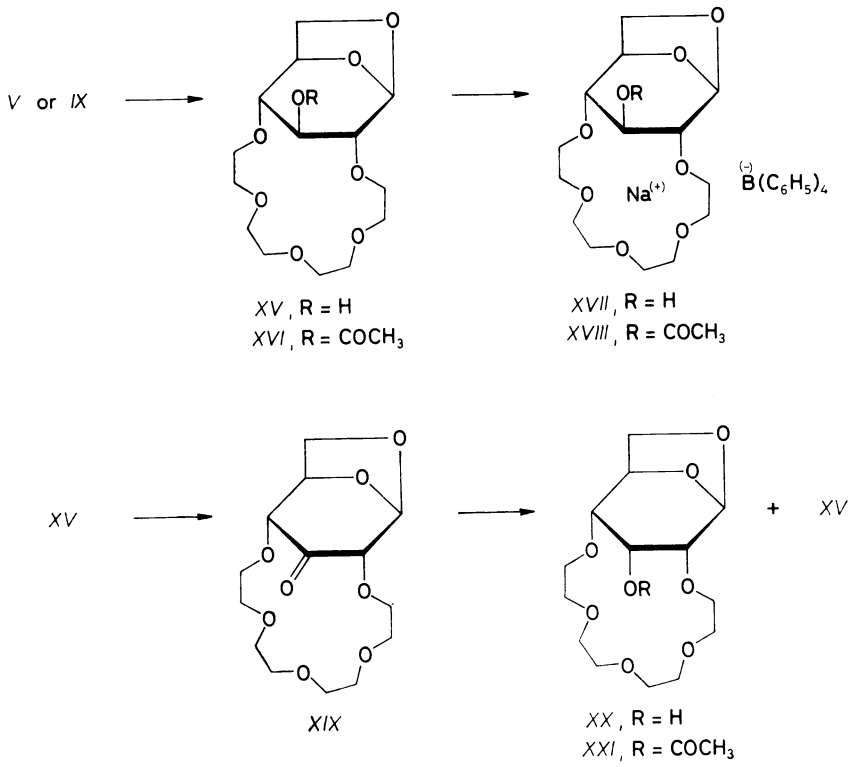
On the other hand the cyclization of dianhydro derivative *IX*, and especially of its precursor – tosyl ester *V*, took place without difficulty when using sodium tert-butoxide leading to crystalline 1,6-anhydro-2,4-O-(3,6,9-trioxaundecane-1,11--diyl)-β-D-glucopyranose (*XV*) in a yield of about 80% (Scheme 3). The crown ether *XV* was converted to 3-O-acetyl derivative *XVI* and crystalline 1 : 1 complexes were prepared from both compounds using sodium tetraphenylborate, i.e. compounds *XVII* and *XVIII*.

The values of the stability constants of the complexes with sodium ions were $4{\cdot}2 \cdot 10^4$ for compound *XV* and $4{\cdot}0 \cdot 10^4$ for compound *XVI* and they are close to the values given in literature for other sugar crown-ethers[1].

The free hydroxyl group in the crown-ether *XV* was oxidized with chromium trioxide in acetic acid and the ketone *XIX* formed was reduced with aqueous sodium borohydride. A mixture of isomers *XV* and *XX* was obtained in an approximately 1 : 3 ratio, as estimated after their acetylation from the ^{1}H NMR spectra of the mixture of corresponding acetates *XVI* and *XXI*. Hence, the reduction of ketone *XIX* did not proceed in favour of the D-*allo* configuration with such a high selectivity as in the case of other 2,4-di-O-substituted 1,6-anhydro-β-D-ribo-hexopyranos-3--uloses[7].

In the majority of cases the structures of the compounds described in this paper were proved by the methods of ^{1}H and ^{13}C NMR spectroscopy (the data are given in Tables I and II). The D-*gluco* configuration of tosyl ester *II* follows from the relatively small and approximately equal values of $J(2, 3) = 3{\cdot}6$ and $J(3, 4) = 3{\cdot}7$ Hz, which also indicate a partial planarization of the $^1C_4$ conformation of the pyranoid ring (cf. ref.[8]). The presence of the hydroxyl group in position 3 was demonstrated by the in situ reaction with trichloroacetyl isocyanate (for the TAI method see refs[9,10]). After TAI acylation the hydrogen H-3 was shifted from δ 3·95 to δ 5·15. We have assumed an analogous structure for tosyl esters *III* – *V* too, because

together with tosyl ester *II* they gave oxiran derivatives *VI*–*IX* of D-manno configuration in alkaline medium. The protons H-2 and H-3 of the oxiran ring in these derivatives display the expected chemical shifts (δ 3·46 and 3·20) and agreeing coupling constant values ($J(1, 2) = 3{\cdot}1$, $J(2, 3) = 3{\cdot}8$ and $J(3, 4) < 1$ Hz).



SCHEME 3

For the tricyclic 1,4-dioxane derivative *X*, formed on intramolecular cyclization of epoxide *VI*, we proposed D-*altro* configuration on the basis of the high negative value of optical rotation, $[\alpha]_D$ −168°. The second possible product of cyclization – a 1,4-dioxepan derivative with an ethylene bridge connecting the carbons C-2 and C-4 – should have a substantially less negative optical rotation value in consequence of the D-*gluco* configuration (see ref.[11]). The NMR parameters and the mass spectra confirm the structure *X*: The coupling constant $J(2, 3) = 8{\cdot}7$ Hz indicates a *trans* (*ax*, *ax*) arrangement of the hydrogens H-2 and H-3 and the value $J(3, 4) = 4{\cdot}2$ Hz a *gauche* (*ax*, *eq*) orientation of hydrogens H-3 and H-4. The presence of the hydroxyl group in position 2 follows from the coupling constant

TABLE I

Proton NMR parameters of compounds *II*–*XXI* in deuteriochloroform

Compound	H-1 (J(1, 2))	H-2 (J(2, 3))	H-3 (J(3, 4))	H-4 (J(4, 5))	H-5 (J(5, 6en); J(5, 6ex))	H-6en; H-6ex (J(6en, 6ex))	Other signals
II	5·28	4·21	3·95	3·33	4·62	3·97; 3·68	3·35 b (OH); 3·61–3·79 m (2 × CH_2O);
	(1·2)	(3·6)	(3·7)	(1·4)	(0·8; 5·5)	(7·5)	2·44 s, 7·36 m, 7·83 m (OTs)
II + TAI	5·29	4·30	5·15	3·52	4·68	4·08; 3·78	3·98 m, 4·43 m (2 × CH_2O); 2·46 s
							7·81 m (OTs); 9·07 s, 8·75 s (2 × NH)
III	5·27	4·21	3·98	3·38	4·59	3·96; [a]	3·50–3·85 m (4 × CH_2O);
	(<1)	(3·5)	(3·5)	(1·4)	(1·0; 5·5)	(7·6)	2·47 s, 7·40 m, 7·88 m (OTs)
III + TAI	5·34	4·34	5·05	3·46	4·70	4·03; [a]	3·61–3·98 m (3 × CH_2O); 2·46 s, 7·37 m,
							7·84 m (OTs); 8·57 s, 8·86 s (2 × NH)
IV	5·26	4·18	[a]	3·32	4·55	3·91; [a]	3·58–3·95 m (6 × CH_2O);
	(1·0)	(3·8)	(4·0)	(1·4)	(1·0; 5·5)	(7·3)	2·44 s, 7·31 m, 7·84 m (OTs)
V	5·22	4·24	[a]	3·39	4·54	3·99; [a]	3·57–4·02 m (8 × CH_2O);
	(≈1·0)	([a])	([a])	(≈1·4)	(1·0); 5·8)	(7·3)	2·44 s, 7·33 m, 7·83 m (OTs)
VI	5·72	3·47	3·20	3·65	4·54	3·72; 3·75	3·80 b (2 × CH_2O)
	(3·1)	(3·8)	(0·7)	(1·1)	(2·1; 6·6)	(7·3)	
VII	5·70	3·46	3·20	3·65	4·56	[a]; [a]	2·47 t (OH, J = 5·7); 3·60–3·87 m
	(3·1)	(3·8)	(≈0)	(1·1)	(2·7; 6·0)	([a])	(4 × CH_2O)
VIII	5·70	3·45	3·22	[a]	4·55	[a]; [a]	3·58–3·87 m (6 × CH_2O)
	(3·1)	(3·7)	(≈0)	(1·1)	(2·8; 5·8)	([a])	
IX	5·71	3·46	3·21	3·66	4·55	[a]; [a]	3·58–3·87 m (8 × CH_2O)
	(3·1)	(3·8)	(≈0)	(1·2)	(2·9; 5·8)	([a])	
X	5·48	4·21	3·67	3·80	4·57	3·73; 3·83	3·55–4·00 m (2 × CH_2O);
	(1·9)	(8·7)	(4·2)	(2·4)	(1·2; 5·4)	(8·0)	2·24 d (OH, J = 7·0)
XI[b]	5·13	3·16	3·41	3·13	4·52	3·81; 3·52	3·46–3·60 m (2 × CH_2O); 4·57 t (J = 5·0);
	(1·0)	(3·7)	(3·8)	(1·3)	(1·2; 5·8)	(7·1)	4·80 d (J = 6·2); 5·04 d (J = 4·4) (3 × OH)

XII	5·48 (<1·0)	3·27 (4·2)	[a] (4·2)	3·35 (1·4)	4·63 (0·9; 5·5)	3·97; 3·75 (7·5)	3·60–3·92 m (4 × CH_2O)
XII + TAI	5·51 (≈1·2)	3·39 (≈1·5)	5·01 (≈1·5)	3·54 (≈1·5)	4·70 (1·0; 5·7)	4·10; 3·81 (7·7)	3·87–4·05 m (2 × CH_2O); 4·33–4·57 m (2 × CH_2O); 8·60 s, 8·84 s, 8·92 s (3 × NH)
XIII	5·45 (0·8)	[a] ([a])	3·51 ([a])	3·42 ([a])	4·62 (0·9; 5·4)	4·13; [a] (7·3)	3·57–3·90 m (4 × CH_2O)
XIV	5·42 ([a])	[a] ([a])	3·49 ([a])	3·37 ([a])	4·60 (0·9; 5·6)	4·08; [a] (7·3)	3·57–3·89 (6 × CH_2O)
XV	5·35 (0·5)	3·24 (5·5)	[a] (5·8)	3·32 (0·9)	4·49 (1·7; 5·4)	[a]; [a] ([a])	3·55–3·99 m (8 × CH_2O); 4·37 d (OH, J = 7·0)
XV + TAI	5·50	3·32	5·06	3·42	4·69	4·14; [a]	3·60–3·99 m (8 × CH_2O); 8·63 s (NH)
XVI	5·46 (≈1·7)	3·16 (≈1·5)	5·03 (≈1·5)	3·23 (≈1·5)	4·63 (1·1; 6·0)	3·98; 3·79 (7·3)	3·59–3·94 m (8 × CH_2O); 2·09 s (OAc)
XVII[b]	5·52 (≈1·8)	3·21 (≈1·5)	3·65 (≈1·5)	3·34 (≈1·5)	4·73 (1·2; [a])	4·06; [a] (7·2)	3·48–3·88 m (8 × CH_2O); 5·46 d (OH, J = 3·8); 6·79 m, 6·93 m, 7·19 m (4 × C_6H_5)
XVII[c]	5·40 (1·8)	3·25 ([a])	[a] ([a])	3·40 ([a])	4·72 (1·2; 6·0)	4·11; [a] (7·3)	3·48–3·92 m (8 × CH_2O); 6·64 m, 6·79, 7·20 m (4 × C_6H_5)
XVII[d]	5·54 (1·8)	3·29 (1·5)	3·83 (1·5)	3·39 (1·5)	4·75 (1·2; 6·0)	4·21; 3·74 (7·3)	3·59–3·93 m (8 × CH_2O); 6·83 m, 6·96 m, 7·20 m (4 × C_6H_5)
XVIII	5·35 (1·6)	3·01 (≈1·5)	4·65 (≈1·5)	3·15 (≈1·5)	4·21 (1·0; 5·8)	3·88; 3·65 (8·0)	3·19–3·72 m (8 × CH_2O); 2·10 s (OAc); 6·85–7·08; m, 7·40 m (4 × C_6H_5)
XIX	5·64 (1·9)	3·49 (—)	— (—)	3·51 (1·8)	4·83 (1·2; 5·4)	3·71; 3·81 (8·1)	3·56–3·80 m (8 × CH_2O)
XX	5·48 (2·5)	3·44 (≈3·3)	3·82[e] (≈3·8)	3·45 (≈2·6)	4·63 (<1; 5·5)	3·64–3·76[e] ([a])	3·57–3·95 m (8 × CH_2O); 5·53 d (OH, J = 3·5)
XXI	5·49 (2·5)	3·62[e] (4·6)	4·92 (4·6)	3·70[e] ([a])	4·69 ([a]; [a])	3·72–3·80[e] ([a])	3·56–3·95 m (8 × CH_2O); 2·20 s (OAc)

[a] The value of the parameter could not be determined; [b] data from CD_3SOCD_3 solution; [c] data from CD_3COCD_3 solution; [d] data from CD_3OD solution; [e] the position of the hidden signal was determined from a 2 D – COSY spectrum.

TABLE II

Carbon-13 chemical shifts of compounds *IV*, *V*, *VII*–*X*, *XII*–*XXI* in deuteriochloroform

Compound	C-1	C-2	C-3	C-4	C-5	C-6	Other carbons
IV	99·88	79·89	69·90	81·55	75·46	66·49	72·81, 71·40, 70·41, 70·17, 69·69, 61·52 (6 × CH_2O); 144·97, 133·28, 129·82, 127·98, 21·59 (OTs)
V	99·43	78·70	69·59	80·67	75·43	65·88	72·69, 72·02, 70·65, 70·49, 70·10, 69·92, 69·82, 61·47 (8 × CH_2O); 144·88, 133·45, 129·81, 127·93, 21·60 (OTs)
VII	97·53	54·35	47·73	71·37	75·22	65·70	72·57, 70·43, 69·74, 61·70 (4 × CH_2O)
VIII	97·48	54·34	47·72	71·55	75·32	65·70	72·52, 70·69(2), 70·24, 69·81, 61·63 (6 × CH_2O)
IX	97·58	54·38	47·77	71·51	75·29	65·72	72·49, 70·72, 70·57, 70·53, 70·43, 70·18, 69·75, 61·60 (8 × CH_2O)
X	101·81	73·75	72·76	67·32	75·81	66·82	65·62, 59·98 (2 × CH_2O)
XII	100·94	80·53[a]	69·46	81·01[a]	74·90	66·47	71·60, 71·30, 61·70, 61·63 (4 × CH_2O)
XIII	102·07	70·31[a]	70·66[a]	78·95	74·74	65·45	72·51, 70·54, 68·81, 61·53 (4 × CH_2O)
XIV	102·33	70·89[a]	71·11[a]	79·79	74·79	65·69	72·70, 70·72, 70·43, 69·99, 68·78, 61·44 (6 × CH_2O)
XV	102·98	83·03[a]	72·79	83·19[a]	76·69	67·39	71·14, 70·96, 70·41(2), 70·36, 69·94, 69·83, 69·78 (8 × CH_2O)
XVI	99·72	75·15	68·46	76·12	73·53	64·44	70·63(2), 70·29, 70·25, 70·09, 70·05(2), 69·36 (8 × CH_2O); 169·34, 20·96 (OAc)
XVII[b]	100·01	78·47	[c]	79·24	73·03	65·17	69·85(3), 69·62, 69·37, 68·95, 68·74, 68·58 (8 × CH_2O); 122·19, 125·94, 137·02, 163·70 (4 × C_6H_5)
XVII[d]	98·72	77·22	68·47	77·98	71·80	64·16	68·91, 68·82, 68·76, 68·57, 68·28, 68·18, 67·96, 67·48 (8 × CH_2O); 163·54 d (*J*(C, B) = 49·3), 135·72, 125·48 d (*J*(C, B) = 2·7), 121·71 (4 × C_6H_5)

TABLE II
(*Continued*)

Compound	C-1	C-2	C-3	C-4	C-5	C-6	Other carbons
XVIII	98·46	74·57	68·60	75·40	71·87	64·68	68·77, 68·60(2), 68·47, 68·28, 67·94, 67·80(2) (8 × CH_2O); 169·50, 20·96 (OAc); 121·75, 125·55, 136·21, 163·55 (4 × C_6H_5)
XVIII[d]	98·38	74·49	68·33	74·95	72·20	64·03	68·92, 68·81(2), 68·65(3), 68·49, 67·93 (8 × CH_2O); 169·18, 20·78 (OAc); 163·54 d (J(C, B) = 49·3), 125·14 d (J(C, B) = 2·7), 135·39, 121·37 (4 × C_6H_5)
XIX	101·43	81·45	200·66	82·71	75·93	65·29	71·03, 70·97, 70·60, 70·39(2), 69·98, 69·83(2) (8 × CH_2O)
XX	99·86	78·35[a]	63·60	78·60[a]	73·56	64·56	71·47, 70·54, 70·20(2), 70·10(2), 69·85(2) (8 × CH_2O)
XXI	99·87	76·08[a]	67·24	76·23[a]	73·58	64·76	71·77, 70·84, 70·49, 70·39, 70·33, 70·17(3) (8 × CH_2O); 169·18, 20·78 (OAc)

[a] The assignment of the signals may be interchanged; [b] data from CD_3COCD_3 solution; [c] the value of the parameter could not be determined; [d] data from CD_3SOCD_3 solution.

of the hydroxyl proton with hydrogen H-2 (found: $J(2, OH) = 7·0$ Hz). In the mass spectrum the molecular peak m/z 188 (1·6%, $C_8H_{12}O_5$) is discernible, but the strongest peak m/z 86 (100%, $C_4H_6O_2$) corresponds to 1,4-dioxene.

The structure of triol *XI* follows from the comparison of its NMR parameters with those of tosyl ester *II*. The coupling constant values of hydrogens, as well as the chemical shifts, are very similar in both compounds (with the exception of H-2 where the change is connected with the absence of the tosyl group). The NMR parameters of triol *XII* correlate well with the parameters of crown-ether *XV* and triol *XI* (Table I and II).

The structure of crown ether *XV* was deduced from an incomplete series of parameters: D-*gluco* configuration is also evidenced by the anomalously large coupling constants $J(2, 3) = 5·5$ Hz and $J(3, 4) = 5·8$ Hz, but only under the assumption that the conformation of the $^1C_4$ pyranoid ring is considerably planarized. The

presence of the hydroxyl group in position 3 and the attachment of the polyether chain in positions 2 and 4 were again demonstrated by in situ TAI-acylation. Acetylation of crown ether *XV* gave acetate *XVI* which afforded an easily interpretable spectrum, all the parameters of which (for example $J(2, 3) = J(3, 4) = 1{\cdot}5$ Hz) correspond to the $^1C_4$ conformation and D-*gluco* configuration. This unexpected change of conformation of compound *XV*, caused by acetylation, is probably due to the steric interaction of the acetyl group with the polyether cycle or the stabilization of the planarized conformation of compound *XV* by a hydrogen bond of the hydroxyl hydrogen in position 3 to some of the oxygen atoms of the polyether cycle. The existence of an intramolecular hydrogen bond in compound *XV* was demonstrated in the IR spectrum on the basis of the ν(OH) band at 3 491 cm^{-1}. A comparison with the value ν(OH) 3 576 cm^{-1} found for 1,6-anhydo-2,4-dideoxy-β-D-threo-hexopyranose[12] in which the hydrogen bond is oriented to the oxygen atom O(6) of the anhydride bond indicates that the hydrogen bond in compound *XV* is formed with the oxygen atoms of the polyether ring and that it is very strong.

The structures of complexes of crown-ether *XV* and its acetate *XVI* with sodium tetraphenylborate – compounds *XVII* and *XVIII* – were confirmed by means of ^{1}H, ^{13}C, ^{11}B and ^{23}Na NMR spectra. The vicinal interactions of hydrogens in both compounds *XVII* and *XVIII* are mutually very similar and in agreement with the values of acetate *XVI*. The generally small values of ^3J(H, H) hydrogens of the pyranose cycle (about 1·5 Hz; see Table I) indicated a partially planarized chair form. The overlap of the signals of hydrogens of eight CH_2O groups of the polyether ring within the narrow region of about δ 3·5 – 3·9 makes it impossible to draw conclusions concerning its conformation.

Detailed information of the spatial arrangement of the complex *XVII* was obtained by X-ray structural analysis[13]. It was found that the pyranoid ring in the crystal is partly planarized, similarly as in 1,6-anhydro-β-D-glucopyranose and that the five-membered dioxolane ring has a geometry close to the envelope conformation, with the atom O(5) out of the plane of the ring (cf. ref.[14]). The polyether ring differs in its geometry from the typical "crown" arrangement which was found, for example, in the complex 15,15-bis(dodecyloxymethyl) 16-crown-5 with sodium thiocyanate[15]. The main deviations were observed in the region of atoms O(9), C(10), C(11) and O(12) (the polyether part is numbered 7 – 17 from the carbon atom connected with O(4)), where disorder became evident, as well – as according to our expectation – in the region which is common to the polyether and the pyranoid ring.

The structure of ketone *XIX* followed from a comparions with the parameters of the NMR spectrum of the starting hydroxy derivative *XV*; the presence of the carbonyl group was demonstrated in the IR spectrum by the band ν(CO) 1 726 cm^{-1} and the characteristic signal at δ 200·66 in the ^{13}C NMR spectrum. Reduction of ketone *XIX* gave D-*allo* derivative *XX* which was identified in the form of acetate *XXI* (in admixture with acetate *XVI*); in the ^{1}H NMR spectrum of compound *XXI*

signals of hydrogens H-1 ($J(1, 2) = 2{\cdot}5$ Hz) and H-3 ($J(3, 2) = J(3, 4) = 4{\cdot}6$ Hz) were found, indicating an $eq-ax-eq$ arrangement of the protons H-2, H-3 and H-4.

EXPERIMENTAL

The melting points were measured on a Boëtius micro melting point apparatus and they are not corrected. Optical rotations were measured on a Bendix–Ericsson ETL 143 A polarimeter, at 20°C. The ^1H and ^{13}C NMR spectra were measured on a FT NMR spectrometer Varian XL-200 (200 or 50·3 MHz, respectively) in $CDCl_3$ (except for compounds *XI*, *XIX* and *XX*, which were measured in CD_3COCD_3, CD_3OD, CD_3SOCD_3). The proton chemical shifts were referenced to tetramethylsilane (TMS) as internal reference; carbon-13 chemical shifts were referenced to the signal of the solvent and recalculated to TMS, using the relations: $\delta(CDCl_3) = 77{\cdot}0$ ppm, $\delta(CD_3COCD_3) = 29{\cdot}8$ ppm and $\delta(CD_3SOCD_3) = 39{\cdot}7$ ppm. The proton signals were structurally assigned by means of chemical shift arguments, splitting patterns and selective homodecoupling experiments. The 2D-COSY spectra of compounds *XIX*, *XX* and *XXI* (on a Varian UNITY-500 MHz instrument) confirmed the proposed assignments and allowed us to determine the positions of some hidden signals (due to overlap with polyether ring protons). TAI-acylations were carried out as usual (the addition of a small excess of TAI to the $CDCl_3$ solution of hydroxy derivative in the NMR tube) and the products were characterized by NMR spectra. The carbon chemical shifts were determined from proton broadband decoupled ^{13}C NMR spectra. For their structural assignments we used the information on the number of directly bonded protons (obtained from the "attached proton test" experiments), chemical shift arguments and the comparison within series of similar compounds.

The course of the reactions was followed using thin-layer chromatography (TLC) on silica gel Merck (Kieselgel G — Stahl). The mobile phases used were: A chloroform–methanol (10 : 1), B isopropyl alcohol–chloroform–ammonia–water–ethanol (20 : 20 : 2 : 2 : 1), C cyclohexane–ethyl acetate–ethanol (3 : 2 : 2), D chloroform–methanol–ammonia (13 : 6 : 1), E chloroform–methanol (20 : 1). The compounds were detected by spraying with 50% sulfuric acid and heating. Samples for analyses were dried over phosphorus pentoxide under reduced pressure (10—20 Pa) for 8 h at 50—60°C. Chromatography of the reaction mixtures was carried out on silica gel columns (Silpearl, Lachema) using a fifty-fold amount of sorbent of the weight of the reaction mixture. The solvents were evaporated at about 50°C. The formation of complexes of crowns with sodium ion was followed potentiometrically in 99% aqueous methanol, alkalized with tetramethylammonium hydroxide (0·01 mol l^{-1}). The values of the stability constants of complexes (K_s) were determined by titration of the corresponding compound with 0·01M solution of sodium chloride, using an ion-selective electrode (Radiometer G 512 Na), and for the calculation of the stability constants a MINIQUAD program[16] was used. The mass spectra were measured on a JEOL MS 0100 instrument, the accurate m/z for the assignment of elemental compositions were obtained by the method of peak adaptation, using PSK as internal reference. The sample was introduced by direct inlet. The spectra were recorded within the 30—90°C temperature range. The metastable transitions were followed by increasing the acceleration tension at constant fields of the analysers, by the defocussing method.

1,6-Anhydro-4-O-(2-hydroxyethyl)-2-O-*p*-toluenesulfonyl-β-D-glucopyranose (*II*)

A mixture of tosyl epoxide *I* (10 g, 33·5 mmol), ethylene glycol (25 g), 1,2-dimethoxyethane (25 ml) and boron trifluoride etherate (1 ml) was heated on a boiling water bath for 2 h, when the starting compound *I* with R_F 0·89 disappeared in favour of the product with R_F 0·41 (*II*)

(control by TLC in mobile phase A). Two by-products were formed in small amounts, with R_F 0·51 and 0·54. The reaction mixture was concentrated to a minimum volume on an oil bath in a vacuum (oil pump). The reaction product was crystallized from a mixture of ether and ethanol. Yield 4·8 g (13·3 mmol), i.e. 40%. M.p. 121—124°C; $[\alpha]_D$ −43° (*c* 0·9, chloroform). For $C_{15}H_{20}O_8S$ (360·4) calculated: 49·99% C, 5·59% H, 8·90% S; found: 49·96% C, 5·45% H, 8·86% S.

1,6-Anhydro-4-O-(5-hydroxy-3-oxapentyl)-2-O-*p*-toluenesulfonyl-β-D-glucopyranose (*III*)

A mixture of tosyl epoxide *I* (5 g, 16·8 mmol), diethylene glycol (10 ml), chloroform (20 ml) and boron trifluoride etherate (4 ml) was refluxed for 4 h, until the disappearance of the starting compound of R_F 0·89 (TLC, mobile phase A). Product *III* (R_F 0·45) was formed, accompanied by traces of by-products with R_F 0·50 and 0·65. Chloroform was distilled off from the reaction mixture, water was added (100 ml) and the product extracted with four 30 ml portions of chloroform. The combined chloroform extracts were dried over magnesium sulfate and evaporated. The residue was crystallized from a mixture of toluene and acetone (15 : 1). Yield, 5·6 g (82%) of compound *III*, m.p. 110—112°C; $[\alpha]_D$ −42° (*c* 1·1, chloroform). For $C_{17}H_{24}O_9S$ (404·4) calculated: 50·49% C, 5·98% H, 7·93% S; found: 50·68% C, 5·86% H, 8·00% S.

1,6-Anhydro-4-O-(8-hydroxy-3,6-dioxaoctyl)-2-O-*p*-toluenesulfonyl-β-D-glucopyranose (*IV*)

A mixture of tosyl epoxide *I* (4·97 g, 16·7 mmol), triethylene glycol (10 ml), boron trifluoride etherate (0·2 ml) and chloroform (20 ml) was refluxed for 8 h. After this time the starting compound (R_F 0·89, TLC, mobile phase A) disappeared and the main product *IV* (R_F 0·43) and traces of two by-products with R_F 0·52 and 0·60 were formed. The reaction mixture was evaporated almost to dryness on a vacuum rotatory evaporator and the residue was dissolved in water (300 ml). The by-products were extracted with toluene (2 × 20 ml) and the main product with chloroform (3 × 100 ml). After drying the chloroform solution over magnesium sulfate it was evaporated under reduced pressure. Product *IV* was obtained in the form of a syrup. Yield, 6·82 g (91%), $[\alpha]_D$ −34° (*c* 0·9, chloroform). For $C_{19}H_{28}O_{10}S$ (448·4) calculated: 50·88% C, 6·29% H, 7·15% S' found: 49·18% C, 6·34% H, 6·75% S;

1,6-Anhydro-4-O-(11-hydroxy-3,6,9-trioxaundecyl)-2-O-*p*-
-toluenesulfonyl-β-D-glucopyranose (*V*)

A mixture of tosyl epoxide *I* (5·00 g, 16·8 mmol), tetraethylene glycol (10 ml), boron trifluoride etherate (0·2 ml) and chloroform (20 ml) was refluxed for 8 h and then worked up as in the case of compound *IV* (see the preceding experiment). Yield, 6·78 g (82%) of product *V* in the form of a syrup, $[\alpha]_D$ − 32° (*c* 1·3, chloroform). For $C_{21}H_{32}O_{11}S$ (492·4) calculated: 51·21% C, 6·55% H, 6·51% S; found: 50·87% C, 6·44% H, 6·10% S.

General Procedure for the Preparation of 1,6 : 2,3-Dianhydro Derivatives *VI*—*IX*

A 2M solution of NaOH in water (5·5 ml) was added to a solution of tosylate *II*—*V* (10 mmol) in dioxane (20 ml) and water (5 ml) and allowed to stand at room temperature for 2 h. The mixture was neutralized with 3M hydrochloric acid and the solution was evaporated to dryness. The residue was extracted with chloroform, the extract dried over sodium sulfate and the solvent evaporated to give the product. The reaction course was followed using TLC in mobile phase E. Tosyl esters had R_F 0·35, epoxides R_F 0·30.

1,6 : 2,3-D*ianhydro*-4-O-(2-*hydroxyethyl*)-β-D-*mannopyranose* (VI). Yield, 903 mg (48%), m.p. 93–95°C (ethanol, ether), $[\alpha]_D$ −22° (*c* 0·9, chloroform). For $C_8H_{12}O_5$ (188·2) calculated; 51·06% C, 6·43% H; found: 51·29% C, 6·27% H.

1,6 : 2,3-*Dianhydro*-4-O-(5-*hydroxy*-3-O-*oxapentyl*)-β-D-*mannopyranose* (*VII*). Yield, 2·159 g (93%), syrup, $[\alpha]_D$ −29° (*c* 0·8, chloroform). For $C_{10}H_{16}O_6$ (232·2) calculated: 51·72% C, 6·94% H: found: 51·90% C, 6·99% H.

1,6 : 2,3-*Dianhydro*-4-O-(8-*hydroxy*-3,6-*dioxaoctyl*)-β-D-*mannopyranose* (VIII). Yield 2·376 g (86%) syrup, $[\alpha]_D$ −24° (*c* 1·6, chloroform). For $C_{12}H_{20}O_7$ (276·3) calculated: 52·17% C, 7·30% H; found: 51·53% C, 7·18% H.

1,6 : 2,3-*Dianhydro*-4-O-(11-*hydroxy*-3,6,9-*trioxaundecyl*)-β-D-*mannopyranose* (IX). Yield, 3·008 g (94%), syrup, $[\alpha]_D$ −20° (*c* 2·2, chloroform). For $C_{14}H_{24}O_8$ (320·0) calculated: 52·49% C, 7·55% H; found: 52·37% C, 7·55% H.

1,6-Anhydro-3,4-O-ethylene-β-D-altropyranose (*X*) and 1,6-
-Anhydro-4-O-(2-hydroxyethyl)-β-D-glucopyranose (*XI*)

A solution of epoxide *V* (2·00 g, 10·6 mmol) and KOH (2·5 g, 45 mmol) in water (50 ml) was heated in a sealed glass tube at 105°C for 8 h. The reaction mixture was then neutralized with cation exchanger Dowex 50 W in H^+ cycle, evaporated to dryness and separated chromatographically on a silica gel column using mixture A as mobile phase.

Compound X: Yield, 324 mg (16%), m.p. 134–136°C, R_F 0·45 (TLC, mobile phase A), $[\alpha]_D$ −168° (*c* 0·4, chloroform). For $C_8H_{12}O_5$ (188·2) calculated: 51·06% C, 6·43% H; found: 51·43% C, 6·63% H.

Compound XI: Yield, 1·418 g (65%), m.p. 126–128°C, R_F 0·10 in (A), $[\alpha]_D$ −60° (*c* 0·9, water). For $C_8H_{14}O_6$ (206·2) calculated: 46·60% C, 6·84% H; found: 46·48% C, 7·22% H.

1,6-Anhydro-2,4-bis-O-(2-hydroxyethyl)-β-D-glucopyranose (*XII*) and Compound *X*

A solution of compound *VI* (1·36 g, 7·2 mmol) (R_F 0·54, TLC, mobile phase C) in a 2% solution of sodium in ethylene glycol (25 ml) was heated at 120°C for 3 h. The reaction mixture was neutralized with 3M hydrochloric acid and ethylene glycol was distilled off under reduced pressure. Ethanol was added, the separated sodium chloride was filtered off and the mixture was concentrated and separated by chromatography on a silica gel column, using phaseA for elution. Yield, 207 mg (15%) of compound *X*, R_F 0·43 in system C. Yield of compound *XII* was 1·10 g (61%), in the form of a syrup, R_F 0·12 (TLC, mobile phase C), $[\alpha]_D$ −10° (*c* 1·0, water). For $C_{10}H_{18}O_7$ (250·2) calculated: 48·00% C, 7·25% H; found: 47·35% C, 7·25% H.

1,6-Anhydro-2,4-O-(3,6,9-trioxaundecane-1,11-diyl)-β-D-
-glucopyranose (*XV*) and its Complex with $NaB(C_6H_5)_4$ (*XVII*)

A) A 0·1M solution of sodium tert-butylate in tert-butyl alcohol (120 ml) was added to a stirred solution of tosylate *V* (4·83 g, 9·8 mmol) in tert-butyl alcohol (70 ml) and the mixture was heated at 40°C for 10 h. The mixture was neutralized with 3M hydrochloric acid, evaporated to dryness and the residue dissolved in water (50 ml). The unreacted intermediary product *IX* was extracted with chloroform (3 × 75 ml) and the aqueous solution was filtered through a column of anion exchanger IRA 410 (Cl^- form) (100 ml). Evaporation of the solution obtained to dryness gave a complex of the required product with sodium chloride. The pure product *XV*

was obtained by extraction of the complex with chloroform (50 ml), filtration through silica gel and evaporation of the solvent. Yield, 2·54 g (81%), m.p. 82—83°C; $[\alpha]_D$ −33° (*c* 0·9, chloroform). For $C_{14}H_{24}O_8$ (320·3) calculated: 52·49% C, 7·55% H; found: 52·51% C, 7·36% H. K_s = 42 000 (methanol, Na^+).

B) A suspension of sodium hydride (1·0 g, 41·7 mmol) in dioxane (20 ml) was added to a stirred solution of epoxide *IX* (6·91 g, 21·6 mmol) in dioxane (500 ml) and the reaction mixture was heated under stirring at 40°C for 2 h (followed by TLC, mobile phase D). Practically all the starting compound (R_F 0·90) disappeared after this time and the product *XV* (R_F 0·35) was formed. The reaction mixture was diluted with water (100 ml), neutralized with 3M HCl, concentrated to dryness and the by-product (together with a smaller amount of compound *XV*) was extracted at room temperature with chloroform (2 × 50 ml). The insoluble residue was dissolved in a mixture of acetone and water (99 : 1) and filtered through silica gel. Evaporation of the solvents gave a chromatographically pure crystalline complex of crown-ether *XV* with sodium chloride. Pure crown-ether *XV* was obtained by boiling the complex with chloroform, filtration through silica gel and evaporation of the solvent. Yield, 3·32 g (48%).

C) Crown-ether *XV* may be separated from the reaction mixture obtained as under *A*) or *B*) by precipitation from an aqueous solution with sodium tetraphenylborate. 10% solutions of both components in water are suitable for the precipitation. The complex was filtered off, washed with water, dissolved in a 20-fold amount of a mixture of acetone and water (3 : 2) and filtered slowly through a column of the anion exchanger IRA-410 (in Cl-form, using a 200-fold amount by weight of the complex). The solution was evaporated, the residue dissolved in water, filtered, evaporated, dissolved in chloroform, filtered and evaporated again, to afford crown ether *XV*, which was freed of the traces of salts by vacuum distillation (250°C, 40 Pa).

3-O-Acetyl-1,6-anhydro-2,4-O-(3,6,9-trioxaundecane-1,11-diyl)-
-β-D-glucopyranose (*XVI*) and its Complex with $NaB(C_6H_5)_4$ (*XVIII*)

A) Epoxide *IX* (4·6 g, 14·4 mmol) was allowed to react as in the case of compound *XV* (procedure *B*). The reaction mixture was neutralized with 3M hydrochloric acid, evaporated to dryness, pyridine (40 ml) and acetic anhydride (20 ml) were added and the mixture allowed to stand overnight. The reaction mixture was concentrated to a minimum volume. After addition of water (50 ml) and sodium acetate (1 g) the by-products were extracted with chloroform (control by TLC in the mobile phase D); the aqueous phase was evaporated to dryness and the required acetate *XVI* (R_F 0·65) was separated from sodium acetate by extraction with chloroform. Yield, 3·10 g (59%), $[\alpha]_D$ −38° (*c* 0·8, chloroform). K_s 40 000 (methanol, Na^+). For $C_{16}H_{26}O_9$ (362·4) calculated: 53·03% C, 7·23% H; found: 53·80% C, 7·24% H.

B) Acetate *XVI* can also be purified via the complex with sodium tetraphenylborate, which may be prepared analogously to that of compound *XV*. From the complex the acetate may be set free by distillation under reduced pressure (260°C, 15 Pa).

1,6-Anhydro-2,4-O-(3,6,9-trioxaundecane-1,11-diyl)-β-D-ribohexopyranos-3-ulose (*XIX*)

A) A solution of chromium trioxide (155 mg, 1·5 mmol) in water (0·5 ml) was added dropwise to a solution of crown-ether *XV* (210 mg, 0·65 mmol) in a mixture of acetic acid and sulfuric acid (50 : 1, 2 ml) and allowed to stand for 24 h at room temperature. The mixture was diluted with water (5 ml) and extracted with chloroform (7 × 5 ml). The combined chloroform extracts were dried and purified by filtration through a small column of silica gel. After evaporation of the solvent, crystalline ketone *XIX* was obtained which was crystallized from ether. Yield, 110 mg (53%), m.p. 119—122°C; $[\alpha]_D$ −33° (*c* 0·8, chloroform). For $C_{14}H_{22}O_8$ (318·3) calculated: 52·82% C, 6·97% H; found: 52·61% C, 6·84% H.

B) A mixture of crown-ether *XV* (663 mg, 2·07 mmol), dimethyl sulfoxide (7 ml) and acetic anhydride (2·3 ml) was heated at 80°C for 2 h. The reaction mixture was concentrated to a minimum volume in a vacuum, then coevaporated several times with toluene and crystallized from a toluene–light petroleum mixture. Yield 490 mg (74%).

1,6-Anhydro-2,4-O(3,6,9-trioxanundecane-1,11-diyl)-β-D-allo-
-pyranose (*XX*) and 3-O-Acetyl Derivative *XXI*

A solution of ketone *XIX* (270 mg, 0·85 mmol) in water (1 ml) was added dropwise to a solution of $NaBH_4$ (70 mg, 1·85 mmol) in water (5 ml) and the reaction mixture was allowed to stand at room temperature overnight. It was then neutralized with hydrochloric acid, evaporated to dryness and the product extracted with chloroform. Evaporation of chloroform gave a crystalline mixture of compounds *XV* and *XX*. Acetylation of this mixture with acetic anhydride in pyridine gave a mixture of acetates *XXI* and *XVI*. In both cases an NMR analysis showed that the ratio of compounds *XV* and *XX*, or *XVI* and *XXI* in the mixture was 1 : 3.

We thank Dr J. Koudelka for the measurement of the stability constants of complexes and the analytical department (Head Dr V. Pechanec) for elemental analyses. The mass spectra were measured and interpreted by Dr V. Hanuš and Dr M. Smrčina of the J. Heyrovský Institute of Physical Chemistry and Electrochemistry, Czechoslovak Academy of Sciences in Prague.

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Translated by Ž. Procházka.