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One- or Two-Step Syntheses of 2-(2-Alkoxyethyl)-1,3-dioxacyclanes

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2-(2-Alkoxyethyl)-1,3-dioxanes (**1**) were prepared by a *p*-toluenesulfonic acid-catalyzed, one-step reaction of propenal with a mixture of aliphatic alcohol and trimethylene glycol in good yields. The transacetalization reaction of 1,1,3-trialkoxypropanes (**3**) with ethylene glycol or propylene-(1,2)glycol afforded good yields of pure 2-(2-alkoxyethyl)-1,3-dioxolanes (**5** or **6**), respectively. This reaction proceeds through an intermediate 1,3-dialkoxy-1-(2-hydroxyalkoxy)-propane.

(Keywords: 2-(2-Alkoxyethyl)-1,3-dioxane; 2-(2-Alkoxyethyl)-1,3-dioxolane; 2-(2-Alkoxyethyl)-4-methyl-1,3-dioxolane; 1,3-Dialkoxy-1-(2-hydroxyalkoxy)-propane; Transacetalization reaction)

Ein- oder Zweistufensynthese von 2-(2-Alkoxyethyl)-1,3-dioxacyclanen

In der durch *p*-Toluolsulfonsäure — katalysierten, direkten Reaktion von Propenal mit einem Gemisch von aliphatischem Alkohol und Trimethylenglykol wurden die entsprechenden 2-(2-Alkoxyethyl)-1,3-dioxane (**1**) in guten Ausbeuten erhalten. Die Umacetalisierung von 1,1,3-Trialkoxypropanen (**3**) mit Ethylenglykol oder 1,2-Propylenglykol lieferte 2-(2-Alkoxyethyl)-1,3-dioxolane (**5** oder **6**) in guten Ausbeuten. Die Umacetalisierungsreaktion von 1,1,3-Trialkoxypropanen verläuft über 1,3-Dialkoxy-1-(2-hydroxyalkoxy)-propane als Zwischenprodukte.

Introduction

In previous papers[2—5] we have reported that 2-alkyl-substituted derivatives of 1,3-dioxolane and 1,3-dioxane readily adsorb at the water solution/air interface. Syntheses of these products, however, required a homologous series of aliphatic aldehydes[2,6] or ketones[3,5]. In the present study we propose convenient methods for syntheses of 2-substituted, five- and six-membered 1,3-dioxacyclanes based on one carbonyl starting

material, namely propenal, appropriate aliphatic alcohols, and 1,2- or 1,3-diols.

It has been shown in previous papers[7–9] that the addition of alcohols to two reactive centers of α,β-unsaturated aldehydes is possible. The direct one-step reaction of propenal with a mixture of alcohol and diol affording high yields of 2-(2-alkoxyethyl)-1,3-dioxolanes and 2-(2-alkoxyethyl)-1,3-dioxanes would be a very simple method for the preparation.

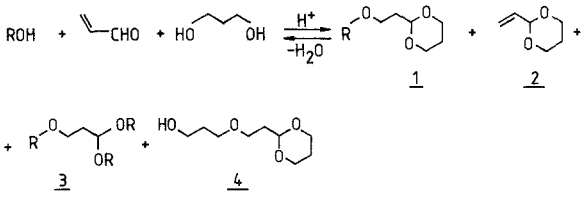
It could have been expected that in using the mixture of alcohols many consecutive and competitive reactions would proceed. The composition of reaction products should be dependent first of all on the diol used, molar ratio of substrates, temperature and reaction time.

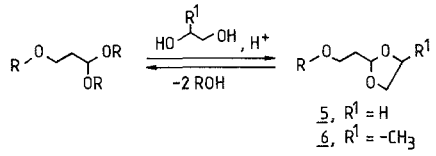
Results and Discussion

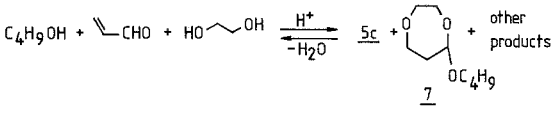
The direct one-step reaction of propenal with a mixture of alcohol and diol yielding 2-(2-alkoxyethyl)-1,3-dioxacyclanes can be realized in the case of 1,3-diols. The reaction of propenal with a mixture of aliphatic alcohol and trimethylene glycol gives high yields of 2-(2-alkoxyethyl)-1,3-dioxanes (**1**). 2-Vinyl-1,3-dioxane (**2**), appropriate 1,1,3-trialkoxypropane (**3**) and 2-[2-(3-hydroxypropoxy)ethyl]-1,3-dioxane (**4**) are formed as by-products, which are easy to separate from **1**. The amounts of **2**, **3**, and **4** in the reaction mixture can be minimized by choosing the proper reaction time (**2** being an intermediate product), and the molar ratio of substrates. The yields of **1** in the reaction mixtures (determined by GLC) are 75–80%. The practical yields of pure compounds (Table 1), however, are dependent on the b. p. differences between corresponding **1** and **3**.

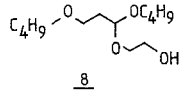
The direct reaction of propenal with a mixture of aliphatic alcohol and 1,2-diol is more complicated: If an 1,2-diol is added to propenal a seven-membered cyclic internal hemiacetal is formed[10], which in the reaction with an alcohol produces 5-alkoxy-1,4-dioxepane derivatives. Thus, in the reaction product of propenal with a mixture of *n*-butyl alcohol and ethylene glycol there are several compounds[11] besides the main product 2-(2-butoxyethyl)-1,3-dioxolane (**5c**). 5-Butoxy-1,4-dioxepane (**7**), isomeric to **5c**, is the one most difficult to separate from **5c**.

Similarly, the reaction product of 2-butenal with ethylene glycol contains about 20% of 5-(2-hydroxyethoxy)-7-methyl-1,4-dioxepane[12] besides 2-[2-(2-hydroxyethoxy)propyl]-1,3-dioxolane. Furthermore, the transacetalization reaction of 2-[2-(2-hydroxyethoxy)ethyl]-1,3-dioxolane with aliphatic alcohol carried out at room temperature leads to a mixture of 1,1-dialkoxy-3-(2-hydroxyethoxy)-propane and 5-alkoxy-1,4-dioxepane[11,13]. The addition of such weakly nucleophilic agents as alcohols to α,β-unsaturated aldehydes is reversible under some conditions[14]. It makes the reaction products of 2-alkyl-1,3-dioxolanes









1, 3, 5, 6	a	b	c	d	e
R	C_2H_5	n-C_3H_7	n-C_4H_9	n-C_5H_{11}	n-C_6H_{13}

with vinylalkyl ethers [mixtures of corresponding 2-(2-alkoxyalkyl)-1,3-dioxolanes and 5-alkoxy-7-alkyl-1,4-dioxepanes[15, 16]] difficult to separate. Recently it has been reported[17], that rather unexpectedly 1,4-dioxepane derivatives were not formed in the reaction of 2-[2-(2-hydroxyalkoxy)ethyl]-1,3-dioxolanes with aliphatic alcohols at elevated temperature (an exchange of substituent at the ether bond of molecules has also occured), and 2-(2-alkoxyethyl)-1,3-dioxolanes were obtained in 12.5–49.5% yields.

For these reasons, we propose to perform the synthesis of pure 2-(2-alkoxyethyl)-1,3-dioxolanes **5** and **6** in two steps: First, synthesizing 1,1,3-trialkoxypropanes (**3**) by known methods[7, 18–20] and then subjecting them to the transacetalization reaction with ethylene glycol or propylene-(1,2)-glycol. The ether bond cleavage does not occur under the mild conditions of the transacetalization reaction, and compounds **5** and **6** are obtained in high yields.

Table 1. *2-(2-Alkoxyethyl)-1,3-dioxacyclanes* **1**, **5**, *and* **6**

Compound No.	Yield[a] [mol-%]	B.P./Torr[b] [°C]	n_D^{20}	d_4^{20}	Molecular formula[c,d]		Molar refraction	
							calc.	found
1a	53	84/13	1.4340	0.9941	$C_8H_{16}O_3$	(160.2)	42.12	41.97
1b	63	95/12	1.4360	0.9807	$C_9H_{18}O_3$	(174.2)	46.73	46.46
1c	72	117/12	1.4372	0.9637	$C_{10}H_{20}O_3$	(188.3)	51.35	51.20
1d	70	122/11	1.4401	0.9535	$C_{11}H_{22}O_3$	(202.3)	55.97	55.93
1e	73	140/11	1.4435	0.9456	$C_{12}H_{24}O_3$	(216.3)	60.59	60.70
5a[e]	59	69/12	1.4260	1.0027	$C_7H_{14}O_3$	(146.2)	37.50	37.36
5b[e]	68	83/12	1.4281	0.9852	$C_8H_{16}O_3$	(160.2)	42.12	41.85
5c	80	95/11	1.4311	0.9666	$C_9H_{18}O_3$	(174.2)	46.73	46.66
5d	80	114/14	1.4339	0.9571	$C_{10}H_{20}O_3$	(188.3)	51.35	51.22
5e	75	128/12	1.4370	0.9473	$C_{11}H_{22}O_3$	(202.3)	55.97	55.95
6a[e,f]	57	72/13	1.4220	0.9675	$C_8H_{16}O_3$	(160.2)	42.12	42.08
6b[e,f]	62	85/12	1.4250	0.9545	$C_9H_{18}O_3$	(174.2)	46.73	46.68
6c[f]	78	98/11	1.4276	0.9405	$C_{10}H_{20}O_3$	(188.3)	51.35	51.46
6d[f]	80	117/12	1.4315	0.9387	$C_{11}H_{22}O_3$	(202.3)	55.97	55.84
6e[f]	78	134/14	1.4338	0.9288	$C_{12}H_{24}O_3$	(216.3)	60.59	60.63

[a] Yield of pure ($\geqslant 98\%$) isolated product.
[b] Not corrected.
[c] Satisfactory microanalyses obtained: $C \pm 0.3$, $H \pm 0.2$.
[d] Molecular weights, determined by the oxime method[21], consistent with calculated values: $M_w \pm 2.5$.
[e] Complete spectral analyses, IR, MS, and ^{1}H-NMR, have been presented in Ref.[17].
[f] Mixture of diastereomers.

Additionally, it may be deduced from the example of the reaction of **5c** with ethylene glycol that the transacetalization reaction of 1,1,3-trialkoxypropanes with 1,2-diols proceeds through an intermediate stage of relatively stable 1,3-dialkoxy-1-(2-hydroxyalkoxy)-propanes: 1,3-dibutoxy-1-(2-hydroxyethoxy)-propane (**8**) was isolated and characterized.

Experimental

1,1,3-Trialkoxypropanes **3** were obtained by known methods[7,18–20] from propenal and appropriate normal aliphatic alcohols. The chemical structures of **3** were confirmed by chemical[21] and spectral analyses. ^{1}H-NMR spectra were recorded on a Tesla BS 497 100 MHz instrument for 10% solutions in $CDCl_3$. Chemical shifts are reported as ppm (δ) downfield from internal *TMS* standard.

2-(2-Butoxyethyl)-1,3-dioxane **1c** *(General Procedure)*

28 g (0.5 mol) of propenal, 122 g (1.65 mol) of *n*-butanol, 57 g (0.75 mol) of trimethylene glycol and 1.5 g of *p*-toluenesulfonic acid monohydrate were heated in 400 ml of chloroform for about 10 h, removing liberated water azeotropically. The reaction mixture was cooled to room temperature and neutralized with an excess of anhydrous K_2CO_3. The neutralization products were filtered off and the filtrate was freed of chloroform. The residue was subjected to fractional distillation providing the following fractions: small amount ($\leqq$ 2 mol-%) of 2-vinyl-1,3-dioxane (**2**); b. p. 106 °C/207 torr, n_D^{20} 1.4444, d_4^{20} 0.9995 (Ref.[22], b. p. 136–139 °C, n_D^{20} 1.4441); heterogeneous azeotrope of 2-(2-butoxyethyl)-1,3-dioxane (**1c**) with trimethylene glycol; b. p. 112 °C/12 torr; 10.4 g (8 mol-%) of 1,1,3-tributoksypropane **3c**; b. p. 89 °C/0.2 torr, n_D^{20} 1.4258 (Ref.[19], n_D^{20} 1.4258) and 6.7 g (7 mol-%) of 2-[2-(3-hydroxypropoxy)ethyl]-1,3-dioxane (**4**); b. p. 104 °C/0.15 torr, n_D^{20} 1.4600, d_4^{20} 1.0861 (Ref.[7], b. p. 153 °C/10 torr, n_D^{20} 1.4598). The fraction of azeotrope **1c** with trimethylene glycol was extracted with 150 ml of hexane. The glycol layer was separated and shaken additionally with 3 × 10 ml of hexane. The residue—after evaporation of hexane—was distilled to give 67.8 g (72 mol-%) of 2-(2-butoxyethyl)-1,3-dioxane (**1c**); b. p. 117 °C/12 torr, n_D^{20} 1.4372, d_4^{20} 0.9637. The molecular weight of **1c**, determined by the oxime method[21], was 187 ± 2.5 (the calculated value for $C_{10}H_{20}O_3$ is 188.3).

^{1}H-NMR of **1c** ($CDCl_3$/*TMS*): δ = 0.86 (t, 3 H, J = 7 Hz, CH_3); δ = 1.17–1.72 (m, 4 H, $CH_3CH_2CH_2CH_2$), 3.39 (t, 2 H, J = 6.5 Hz, $C_3H_7CH_2$), 3.49 (t, 2 H, J = 6.5 Hz, $CH_{2(\beta)}$), 1.84 (m, 2 H, J = 5 Hz and 6.5 Hz, $CH_{2(\alpha)}$), 4.66 (t, 1 H, J = 5 Hz, acetal methine proton CH), 3.61–4.17 (m, 4 H, axial and equatorial protons at C-4,6 carbon atoms of the 1.3-dioxane ring), 1.99–2.29 (m, 2 H, axial and equatorial proton at C-5 carbon atom of the 1,3-dioxane ring).

2-(2-Butoxyethyl)-1,3-dioxolane **5c** *and 2-(2-butoxyethyl)-4-methyl-1,3-dioxolane* **6c** *(General Procedure)*

130 g (0.5 mol) of 1,1,3-tributoxypropane **3c**, 93 g (1.5 mol) of ethylene glycol and several crystals of *p*-toluenesulfonic acid monohydrate were maintained in 200 ml of 1,4-dioxane at room temperature. The course of the reaction was controlled chromatographically (GLC). After the equilibrium was reached (2–3 days, about 90% of conversion) the reaction mixture was neutralized with an

excess of anhydrous K_2CO_3. The neutralization products were filtered and 1,4-dioxane was distilled off. The residue was subjected to distillation giving **5c** and ethylene glycol as a heterogeneous azeotrope, b. p. 92 °C/11 torr. The azeotropic fraction was shaken with 150 ml of hexane. The glycol layer was shaken additionally with 3 × 10 ml of hexane. The residue—after evaporation of hexane—was distilled to give **5c**: yield 69.7 g (80 mol-%); b. p. 95 °C/11 torr, n_D^{20} 1.4311, d_4^{20} 0.9686. The molecular weight of **5c** (determined by the oxime method) was 176 ± 2 (the calculated value for $C_9H_{18}O_3$ is 174.2).

^{1}H-NMR of **5c** ($CDCl_3$/*TMS*): δ = 0.90 (t, 3 H, J = 7 Hz, CH_3), 1.19–1.70 (m, 4 H, $CH_3CH_2CH_2CH_2$), 3.40 (t, 2 H, J = 6.5 Hz, $C_3H_7CH_2$), 3.54 (t, 2 H, J = 6.5 Hz, $CH_{2(\beta)}$), 1.91 (m, 2 H, J = 5 Hz and 6.5 Hz, $CH_{2(\alpha)}$), 4.96 (t, 1 H, J = 5 Hz, acetal methine proton CH), 3.88 (m, A_2B_2, 4 H, OCH_2CH_2O).

The same procedure was applied to obtain the *cis*- and *trans*-isomer mixture of 2-(2-butoxyethyl)-4-methyl-1,3-dioxolane (**6c**): yield 78 mol-%; b. p. 98 °C/11 torr, n_D^{20} 1.4276, d_4^{20} 0.9405. The molecular weight of **6c** was 189 ± 3 (the calculated value for $C_{10}H_{20}O_3$ is 188.3).

^{1}H-NMR of **6c** ($CDCl_3$/*TMS*): δ = 1.27 [d, 2.3 H, J = 6 Hz, CH_3 (C-4) *cis* isomer], 1.23 [d, 0.7 H, J = 6 Hz, CH_3 (C-4) *trans* isomer], 0.91 (t, 3 H, J = 7 Hz, CH_3), 1.36–1.68 (m, 4 H, $CH_3CH_2CH_2CH_2$), 3.40 (t, J = 6.8 Hz, $C_3H_7CH_2$ *cis* isomer), 3.39 (t, J = 7 Hz, $C_3H_7CH_2$ trans isomer), 3.54 (t, J = 6.8 Hz, $CH_{2(\beta)}$ *cis*), 3.53 (t, J = 7 Hz, $CH_{2(\beta)}$ *trans*), 1.93 (m, J = 5 Hz and 6.8 Hz, $CH_{2(\alpha)}$ *cis*), 1.88 (m, J = 5 Hz and 7 Hz, $CH_{2(\alpha)}$ *trans*), 5.00 [t, ~0.8 H, J = 5 Hz, CH (C-2) *cis*], 5.12 [t, ~0.2 H, J = 5 Hz, CH(C-2) *trans*], 3.85–4.23 [m, 3 H, CH—CH_2(C-4,5)].

1,3-Dibutoxy-1-(2-hydroxyethoxy)-propane **8**

0.15 g of *p*-toluenesulfonic acid monohydrate was added at room temperature to the 1,4-dioxane solution (50 ml) of **3c** (10 g, 38 mmol) and ethylene glycol (7 g, 115 mmol). The course of the transacetalization reaction was controlled chromatographically (GLC). The reaction was stopped with an excess of anhydrous K_2CO_3 at the moment of the maximum concentration of **8** in the reaction mixture (1 h, about 40 mol-% of **8**). The neutralization products were filtered off and the solvent evaporated. The residue was subjected to distillation to give **8**: yield 2.8 g (30 mol-%); b. p. 98 °C/0.2 torr, n_D^{20} 1.4379, d_4^{20} 0.9484. The molecular weight of **8** was 250 ± 4 (the calculated value for $C_{13}H_{28}O_4$ is 248.4).

^{1}H-NMR of **8** ($CDCl_3$/*TMS*): δ = 0.96 (t, 6 H, J = 7 Hz, 2 CH_3), 1.15–1.70 (m, 8 H, 2 $CH_3CH_2CH_2CH_2$), 3.33–3.63 (m, 6 H, 3 OCH_2), 3.67 (s, 4 H, OCH_2CH_2O), 3.05 (s, 1 H, OH), 4.68 (t, 1 H, J = 6 Hz, CH).

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