

## A CONVENIENT SYNTHESIS OF CROWN AND AZACROWN ETHERS WITH PENDANT OXIRANE GROUP\*

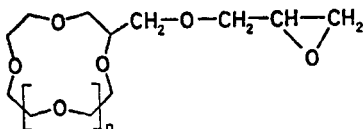
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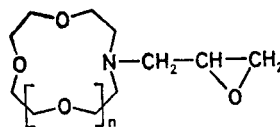
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Synthesis of 4,5-epoxy-2-oxa-1-pentylcrown (*I*) and N-(2,3-epoxy-1-propyl)azacrown ethers (*II*) from accessible materials is described.

Functionalized macrocyclic polyethers and their heteroatom analogues (crown ethers or crowns) are subject of a considerable interest. Pendant electron-donating groups, *e.g.*, can participate in ion binding and modulate thus selectivity and/or stability of ion-crown complexes<sup>1-4</sup>. Reactive pendant groups allow at the same time further transformations of crowns including polymerization and anchoring on polymeric matrices<sup>5-9</sup>.



*I a-e, n=1-5*



*II a-c, n=1-3*

In this paper we report synthesis of novel crown and azacrown compounds *Ia-e* and *IIa-c*, respectively\*\*, distinguished by a pendant oxirane group. As it will be shown in subsequent papers<sup>10</sup>, the epoxy derivatives may serve as versatile synthons in multidentate ligand chemistry.

### EXPERIMENTAL

Analytical samples were dried at 90°C/6.5 Pa for 24 h. <sup>1</sup>H NMR spectra were taken on a Tesla B467 (60 MHz) and/or on a Tesla BS497 (100 MHz) instrument employing tetramethylsilane

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\*\* For the sake of brevity, the generally accepted trivial nomenclature is used in this paper; for IUPAC nomenclature of newly described compounds see footnotes in Tables II and III.

as internal reference. Mass spectra were measured on a AEI MS902 spectrometer with a double focussation. Thin-layer chromatography (TLC) was performed on Kieselgel GF<sub>254</sub> (Merck) using CHCl<sub>3</sub>-CH<sub>3</sub>OH (95 : 5; in preparation of epoxy crowns *I*) or CHCl<sub>3</sub>-CH<sub>3</sub>OH-aq. NH<sub>4</sub>OH (88 : 10 : 2; in preparation of epoxy azacrowns *II*) as the elution system and the substances were detected by spraying with the Dragendorff's reagent. Preparative flash chromatography of epoxy crown ethers *Id,e* was carried out on silica gel (Merck H for TLC) using CH<sub>2</sub>Cl<sub>2</sub>-CH<sub>3</sub>OH (95 : 5) as the elution system. Gas chromatography was performed on a Pye Unicam 102 instrument with flame ionization detection (column 150 × 0.4 cm packed with 3% OV-17 on Chromosorb, the temperature was programmed to 4°C/min in the 180–280°C interval. Molecular distillation was carried out on a Spezial-Glas (Mainz) apparatus at 5 × 10<sup>-3</sup> Pa.

**Materials:** 1-(Alkoxyethyl)oligoethylene glycols *IIIa–b* (R = benzyl or allyl), oligoethylene glycol ditosylates *IVa–c*, benzyloxymethyl-12-crown-4 (*Va*, *n* = 1, R = benzyl) and azacrown ethers *Ila–c* were prepared following the known procedures<sup>11–14</sup>.

#### Benzyloxymethyl Crown Ethers *Vb–e* (R = benzyl)

To a stirred suspension of a powdered alkali hydroxide (3 mol) in dioxane (1 500 ml) was at 80°C added dropwise (10 h) a mixture of an appropriate 1-(benzyloxymethyl)oligoethylene glycol *IIIa,b* (0.75 mol) and the complementary oligoethylene glycol ditosylate *IVa–c* (0.75 mol) dissolved in dioxane (1 500 ml). After stirring for another 8 h at the same temperature, the deposited salts were filtered off at ambient temperature and washed with dichloromethane. The solvents were taken down on a rotatory evaporator, less volatile by-products were distilled off on an oil

TABLE I

Cyclisation of 1-(alkoxymethyl)oligoethylene glycols *III* with oligoethylene glycol ditosylates *IV* promoted by alkali hydroxides (MOH)

Product	Starting Compound	MOH	Yield, %	B.p., °C/Pa
<i>Vb</i> (R = benzyl)	<i>IIIa</i> (R = benzyl) <i>IVa</i>	NaOH	56	140/0.01 <sup>a</sup>
<i>Vb</i> (R = allyl)	<i>IIIa</i> (R = allyl) <i>IVa</i>	NaOH	54	115/0.01 <sup>a</sup>
<i>Vc</i> (R = benzyl)	<i>IIIa</i> (R = benzyl) <i>IVb</i>	KOH	52	160/0.01 <sup>a</sup>
<i>Vc</i> (R = allyl)	<i>IIIa</i> (R = allyl) <i>IVb</i>	KOH	51	130/0.1 <sup>b</sup>
<i>Vd</i> (R = benzyl)	<i>IIIb</i> (R = benzyl) <i>IVb</i>	KOH	60	195/0.005 <sup>a</sup>
<i>Ve</i> (R = benzyl)	<i>IIIb</i> (R = benzyl) <i>IVc</i>	KOH	45	220/0.005 <sup>a</sup>

<sup>a</sup> Molecular distillation; <sup>b</sup> Kugelrohr apparatus.

pump (160–180°C) and the residue was subjected to molecular distillation ( $5 \cdot 10^{-3}$  Pa). The products obtained in better than 96.5% purity were identical with authentic samples from literature<sup>15–24</sup>. Yields and specifications of individual reaction runs are summarized in Table I.

**Debenzylation:** Hydrogenolysis on Pd/C catalyst at 25°C and at elevated hydrogen pressure (1 MPa) in presence of trace amounts of *p*-toluenesulphonic acid afforded the corresponding hydroxymethyl crowns *Vb–e* (R = H) in practically quantitative yields.

#### Allyloxymethyl Crown Ethers *Vb, c* (R = allyl)

Prepared from a powdered alkali hydroxide (1 mol), 1-(allyloxymethyl)triethylene glycol (0.25 mol), and di- or triethylene glycol ditosylate (0.25 mol) in dioxane (1 500 ml) under the same conditions as described above for the corresponding benzyloxymethyl derivatives. The products isolated by molecular distillation in about 55% yields and better than 97% purity (GLC) were identical with authentic samples from literature.

#### 4,5-Epoxy-2-oxa-1-pentyl Crown Ethers *Ia–e*

**A)** (Chloromethyl)oxirane (15 ml; 0.2 mol) was treated with a 50% aqueous solution of sodium hydroxide (30 g; 0.375 mol) and with an appropriate hydroxymethyl crown *Va–e* (0.02 mol) dissolved in benzene (50 ml). The heterogeneous mixture was shaken at ambient temperature for 30 h. The aqueous layer was separated and washed with dichloromethane ( $4 \times 50$  ml). The combined organic layers were dried ( $\text{MgSO}_4$ ), the solvents were taken down on aspirator and the residue was either distilled *in vacuo* (Kugelrohr apparatus) or subjected to a flash chromatography on silica gel. Data are given in Table II.

**B)** Allyloxymethyl crown *Vb, c* (R = allyl; 0.02 mol) was dissolved in chloroform (40 ml) and treated with *meta*-chloroperbenzoic acid (85%; 5.2 g) in the presence of sodium hydrogen carbonate (2 g). After stirring (18 h) at ambient temperature the epoxidation was found (TLC) to be practically completed. The mixture was filtered over a layer of silica and the filtrate was successively washed with 10% aqueous sodium sulfite, saturated aqueous sodium hydrogen carbonate and with water, and dried with  $\text{MgSO}_4$ . After a usual work-up the crude product was distilled on the Kugelrohr apparatus. The products obtained in about 60–70% yields were identical with the corresponding ones obtained by the procedure **A**.

#### N-(2,3-Epoxy-1-propyl)azacrown Ethers *Ila–c*

An unsubstituted azacrown ether *VIa–c* (10 mmol) was dissolved in an excess of (chloromethyl)oxirane (9.5 ml; 120 mmol) and in presence of catalytic<sup>25</sup> amounts of water (0.4 ml) heated at 40°C for 1.5 h. After cooling down a 50% aqueous solution of sodium hydroxide (2 g) was added and the mixture was stirred at room temperature for 1 h. The aqueous layer was separated, washed with dichloromethane ( $4 \times 30$  ml), the combined organic layers were dried ( $\text{MgSO}_4$ ) and the unreacted (chloromethyl)oxirane was distilled off. The yields of the distilled products (Kugelrohr apparatus), boiling points, elemental analyses, and spectral data are summarized in Table III.

#### Alkoxyethyl Crowns *V*

Although synthesis of the alkoxyethyl crown *V* was given a considerable attention in the past decade, none of the procedures described appears to be satisfactorily

TABLE II  
4,5-Epoxy-2-oxa-1-pentyl crown ethers I

Compound <sup>a</sup>	Yield, % B.p., °C/Pa	Formula (mol. weight)	Calculated/found		Mass spectrum, <i>m/z</i> (%) <sup>c</sup>
			% C	% H	
<i>Ia</i>	65 117/1.3	C <sub>12</sub> H <sub>22</sub> O <sub>6</sub> (262.3)	53.12 <sup>b</sup>	8.54 <sup>b</sup>	M <sup>+</sup> = 262(<1); 45(100); 87(95); 175(62); 57(45); 59(42); 188(7) 8.25
			53.01	8.25	
<i>Ib</i>	81 142/1.3	C <sub>14</sub> H <sub>26</sub> O <sub>7</sub> (306.35)	54.90	8.56	M <sup>+</sup> = 306(1.5); 87(100); 45(92); 219(40); 131(29); 249(4) 8.65
			54.92	8.65	
<i>Ic</i>	70 162/1.3	C <sub>16</sub> H <sub>30</sub> O <sub>8</sub> (350.4)	53.46 <sup>b</sup>	8.69 <sup>b</sup>	M <sup>+</sup> = 350(1); 45(100); 87(95); 59(43); 74(40); 133(27); 175(20); 263(15)
			53.83	8.68	
<i>Id</i>	63 182/1.3	C <sub>18</sub> H <sub>34</sub> O <sub>9</sub> (394.45)	53.32 <sup>b</sup>	8.70 <sup>b</sup>	M <sup>+</sup> = 394(1.5); 45(100); 87(77); 57(34); 59(34); 133(17); 307(11); 175(5)
			53.37	8.48	
<i>Ie</i>	64	C <sub>20</sub> H <sub>38</sub> O <sub>10</sub> (438.2)	54.79	8.73	M <sup>+</sup> = 438(1.5); 45(100); 87(70); 59(30); 73(29); 57(29); 133(25); 351(8); 177(6); 175(6)
			54.43	8.46	

<sup>a</sup> IUPAC nomenclature of *Ia*: 2-(4,5-epoxy-2-oxa-1-pentyl)-1,4,7,10-tetraoxacyclododecane, *Ib*: 2-(4,5-epoxy-2-oxa-1-pentyl)-1,4,7,10,13-pentaoxacyclododecane, *Ic*: 2-(4,5-epoxy-2-oxa-1-pentyl)-1,4,7,10,13,16-hexaoxacyclododecane, *Id*: 2-(4,5-epoxy-2-oxa-1-pentyl)-1,4,7,10,13,16,19-heptaoxacyclododecane, *Ie*: 2-(4,5-epoxy-2-oxa-1-pentyl)-1,4,7,10,13,16,19,22-octaaxacyclododecane. <sup>b</sup> Calculated for hemihydrate. <sup>c</sup> <sup>1</sup>H NMR (C<sup>2</sup>HCl<sub>3</sub>): 2.62–2.74 m, 2 H (H-5); 3.11–3.18 m, 2 H (H-3); 3.60–3.70 m, from 18 H for *Ia* to 34 H for *Ie* (2 × CH and remaining CH<sub>2</sub>).

TABLE III  
2,3-Epoxy-1-propyl azacrown ethers II

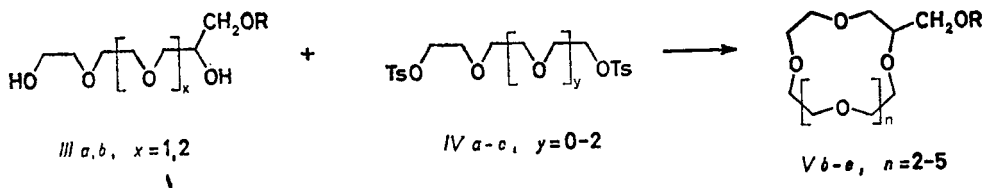
Compound <sup>a</sup>	Yield, % B.p., °C/Pa	Formula (mol. weight)	Calculated/found			Mass spectrum, <i>m/z</i> (%) <sup>c</sup>
			% C	% H	% N	
<i>Ila</i>	78	C <sub>11</sub> H <sub>21</sub> NO <sub>4</sub> (231.3)	57.12	9.15	6.06	M <sup>+</sup> = 231(26); 100(100); 86(75); 188(54); 144(43); 130(40);
	88/1.3		56.56	8.94	5.89	20(37); 128(30); 156(30)
<i>Iib</i>	75	C <sub>13</sub> H <sub>23</sub> NO <sub>5</sub> (275.3)	54.91 <sup>b</sup>	9.22 <sup>b</sup>	4.93 <sup>b</sup>	M <sup>+</sup> = 275(4); 232(100); 100(48); 114(45); 86(40); 144(34);
	112/1.3		55.62	8.88	4.76	202(15); 188(11)
<i>Iic</i>	79	C <sub>15</sub> H <sub>29</sub> NO <sub>6</sub> (319.4)	54.86 <sup>b</sup>	9.21 <sup>b</sup>	4.26 <sup>b</sup>	M <sup>+</sup> = 319(2); 100(100); 232(76); 86(65); 144(33); 130(30);
	123/1.3		55.28	8.92	3.93	114(26); 276(24); 200(12)

<sup>a</sup> IUPAC nomenclature of *Ila*: N-(2,3-epoxy-1-propyl)-1,4,7-trioxa-10-azacyclododecane; *Iib*: N-(2,3-epoxy-1-propyl)-1,4,7,10-tetraoxa-13-azacyclopentadecane; *Iic*: N-(2,3-epoxy-1-propyl)-1,4,7,10,13-pentaoxa-16-azacyclooctadecane. <sup>b</sup> Calculated for hemihydrate. <sup>c</sup> <sup>1</sup>H NMR (C<sup>2</sup>HCl<sub>3</sub>): 2.30–3.25 m, 9 H (H-2, H-3, and CH<sub>2</sub> adjacent to N); 3.65 m, from 12 H for *Ila* to 20 H for *Iic* (remaining CH<sub>2</sub>).

applicable for a wider range of homologues. Cyclisation reaction of 1-O-alkylglycerols with oligoethylene glycol ditosylates or with the corresponding dihalides has been employed for synthesis of the crowns *V* at numerous instances<sup>15-21</sup>. However, a serious drawback is a poor accessibility of higher oligoethylene glycols rendering thus the procedure inconvenient for preparation of the larger macrorings (*e.g.* *Vd* and *Ve*). The same drawback is involved also in the elegant cyclisation of oligoethylene glycol monotosylates by Okahara *et al.*<sup>12,22</sup>.

Bartsch *et al.*<sup>23,24</sup>, in an apparent effort to alleviate the problem of accessibility for the larger rings, examined ring closure reaction of 4-(benzyloxymethyl)-3,6-dioxo-1,8-octanediol with tetra- and pentaethylene glycol ditosylates, however, with only a moderate success. Disappointingly low yields of the 21- and 24-membered benzyloxymethyl crown ethers *Vd* (27%) and *Ve* (14%), respectively, were obtained in spite of the expensive caesium hydroxide employed as the template in the reaction. Much better results were obtained<sup>11</sup> in a similar synthesis of the 18-membered homologue *Vc* from 1-(benzyloxymethyl)-3,6,9-trioxa-1,11-undecanediol and 3-oxa-1,5-pentanediol ditosylate. However, potassium hydride employed as the templating base disqualifies the procedure from application on any larger scale.

Considering, on such grounds, 1-(alkoxymethyl)oligoethylene glycols *III* in combination with oligoethylene glycol ditosylates *IV* as the most promising building blocks for a generally applicable synthesis of the alkoxymethyl crowns *V* (Scheme 1),



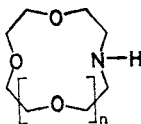
SCHEME 1

we reexamined the above methodology<sup>11</sup> and replaced the troublesome potassium hydride simply with a powdered potassium or sodium hydroxide. Satisfactory yields of the products were obtained over the entire homologous series (Table I). It is noteworthy, in particular, that the yields of the higher homologues *Vd* and *Ve* were superior to those obtained by Bartsch *et al.*<sup>23,24</sup> with the caesium template.

#### 4,5-Epoxy-2-oxa-1-pentyl Crowns I and N-(2,3-Epoxy-1-propyl) Azacrowns II

Allyloxymethyl as well as benzyloxymethyl crowns *V* (R = allyl and benzyl, respectively) allow an easy transformation into the corresponding 4,5-epoxy-2-oxa-1-pentyl crowns *I*. Treatment of the allyloxymethyl derivatives *Vb, c* (R = allyl) with *meta*-

-chloroperbenzoic acid in chloroform afforded directly the corresponding epoxy crowns *Ib, c*. In an alternative, and a more widely explored approach, the benzyloxy-methyl derivatives *Va-e* ( $R = \text{benzyl}$ ) were debenzylated hydrogenolytically and the resulting hydroxymethyl crowns *Va-e* ( $R = \text{H}$ ) were subjected to a two-phase reaction with (chloromethyl)oxirane in presence of aqueous alkali hydroxide. Notable, the reaction does not require an external phase-transfer catalysis; both the reactant as well as the product are involved as efficient catalytic species.



*VI a-c*,  $n=1-3$

In a similar fashion, a treatment of easily accessible<sup>13,14</sup> monoazacrowns *VI* with (chloromethyl)oxirane allows synthesis of the azacrown derivatives with N-pendant 2,3-epoxypropyl group (*II*). An excess of the (chloromethyl)oxirane reagent has been used to prevent the concurring oxirane ring opening in *II* with *VI*.

The recent important discoveries<sup>26,27</sup> allowing a large-scale access to chiral equivalents of (chloromethyl)oxirane provide a strong impetus for exploring synthetic potential of the aforementioned reactions.

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