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MACROHETEROCYCLES.

31.* BINUCLEAR CROWN ETHERS BASED ON 1,1,2,2-TETRAHYDROXYMETHANYLETHANE

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UDC 547.898.07

Methods for the synthesis and production of a number of new binuclear crown ethers based on 1,1,2,2-tetrahydroxymethylethane and its derivatives were developed.

The selectivity of the complexing of crown ethers with metal cations frequently increases substantially as a result of the formation of complexes of the "sandwich type" with a 2:1 crown ether—cation composition [2]. From this point of view a great deal of attention has been directed to binuclear crown ethers, which are structurally prepared for the formation of such complexes and in many cases display greater cationic selectivity as compared with their monocyclic analogs [3-5].

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*See [1] for Communication 30.

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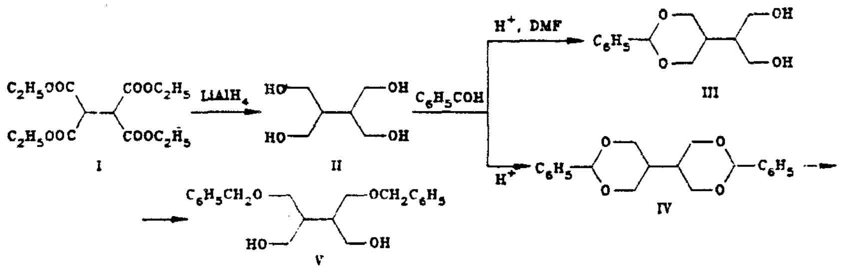
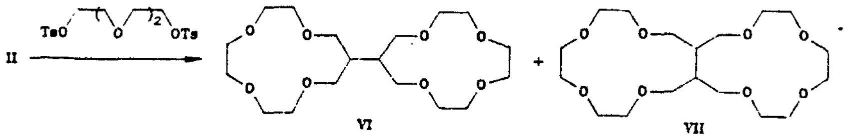
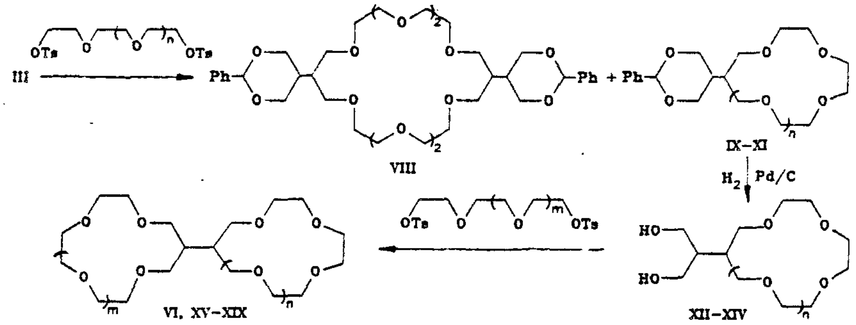
We have previously described the synthesis of the first representatives of chiral binuclear crown ethers, which were obtained on the basis of D(+)-tartaric acid [6]. The present communication is devoted to the synthesis of new binuclear crown ethers on the basis of 1,1,2,2-tetrahydroxymethylethane. A convenient starting subject for the synthesis of binuclear crown ethers is bismalonic ester I, which was obtained in high yield by dimerization of malonic ester [7]. The reduction of ester I with lithium aluminum hydride leads to tetrol II [8], by the condensation of which with benzaldehyde, bisacetal IV was obtained. Attempts to obtain monoacetal III by the reaction of tetrol II with one equivalent of benzaldehyde under the generally used conditions, including those described for the selective protection of two hydroxy groups of pentaerythritol [9], were unsuccessful — the principal reaction product in all cases was bisacetal IV. Acetal III was obtained in satisfactory yield when the reaction was carried out in DMF at 30°C for 5 h. An increase in the temperature or the reaction time leads to a decrease in the yield of the desired product. Diol V was obtained by the action of diborane on bisacetal IV. Compounds III and V were subsequently used as the base compounds in the synthesis of the binuclear crown ethers.



The reaction of tetrol II with triethylene glycol ditosylate in tert-butanol—dioxane in the presence of sodium tert-butoxide leads to a difficult-to-separate mixture of crown ethers VI and VII in a ratio of 2:1.



In this connection a more promising method is the synthesis of binuclear crown ethers by the successive formation of two polyether rings of the same or different size.



IX, XII n=1; X, XIII n=2; XI, XIV n=3; XV n=m=2; XVI n=m=3; XVII n=1, m=2; XVIII n=1, m=3; XIX n=2, m=3

The condensation of monoacetal III with polyethylene glycol ditosylates in dioxane in the presence of sodium hydride leads to crown ethers IX-XI in 30-40% yields. In the reaction of triethylene glycol ditosylate, in addition to crown ether IX, its cyclic dimer VIII was isolated from the reaction mixture in 14% yield. Removal of the acetal group in crown ethers IX-XI by acidic hydrolysis leads to the desired products XII-XIV in no higher than 65% yields. Different results were obtained in removal of the acetal group by catalytic hydrogenolysis (H_2, Pd/C). The reaction of crown ethers XII-XIV with polyethylene glycol ditosylates in dioxane in the presence of sodium hydride leads to binuclear crown ethers VI and XV-XIX.

A general approach to the specific synthesis of binuclear crown ethers with an ethano bridge consists in the condensation of diol V with triethylene glycol ditosylate, which leads

TABLE 1. Characteristics of I-XXII

Compound	T_{mp}, °C	PMR spectrum (in $CDCl_3$), ppm	Found, %		Empirical formula	Calc., %		M	Yield, %
			C	H		C	H		
1	2	3	4	5	6	7	8	9	10
I	76	1,25 (12H, t, CH_3); 4,01 (2H, s, CH); 4,20 (8H, q, CH_2)	52,8	7,0	$C_{14}H_{22}O_8$	52,9	7,0	318	95
II	110	1,83 (2H, m, CH); 3,60 (8H, d, CH_2)*	47,9	9,4	$C_6H_{14}O_4$	47,9	9,4	150	50
III	132	1,43 (1H, m, CH); 2.29 (1H, m, CH); 3,47—4,57 (10H, m, CH_2O, OH); 5,46 (1H, s, C_6H_5CH); 7,41 (5H, m, C_6H_5)	65,6	7,6	$C_{13}H_{18}O_4$	65,5	7,6	238	75
IV	240	2,80 (2H, m, CH); 3,46—4,66 (8H, m, CH_2O); 5,46 (2H, br., C_6H_5CH); 7,40 (10H, m, C_6H_5)	73,5	6,7	$C_{20}H_{22}O_4$	73,6	6,8	326	93
V		1,80 (2H, m, CH); 3.23—4,70 (8H, m, CH_2O); 4,30 (4H, s, $C_6H_5CH_2$); 7,20 (5H, m, C_6H_5)	73,6	7,9	$C_{20}H_{26}O_4$	73,7	7,9	330	98
VI	117	1,86 (2H, m, CH); 3,21—3,76 (32H, m, CH_2O)	57,1	9,1	$C_{18}H_{34}O_8$	57,1	9,0	378	27
VII		2,03 (2H, m, CH): 3,30—3,70 (32H, m, CH_2O)	57,1	9,0	$C_{18}H_{34}O_8$	57,1	9,0	378	26
VIII		2,08 (4H, m, CH): 3,00—4,37 (40H, m., CH_2O); 5,30 (2H, m, C_6H_5CH); 7,03—7,40 (10H, m, C_6H_5)	64,5	7,9	$C_{38}H_{56}O_{12}$	64,7	8,0	704	14
IX	63—64	1,51 (1H, m, CH); 2,25 (1H, m, CH); 2,83—4,45; (20H, m, CH_2O); 5,35 (1H, s, C_6H_5CH); 7,01—7,50 (5H, m, C_6H_5)	64,6	7,9	$C_{19}H_{28}O_6$	64,7	8,0	352	39
X		1.51 (1H, m, CH); 2,33 (1H, m, CH); 2,75—4,25; (24H, m, CH_2O); 5,33 (1H, s, C_6H_5CH); 7,08—7,50 (5H, m, C_6H_5)	63,4	8,0	$C_{21}H_{32}O_7$	63,6	8,1	396	35
XI		1,50 (1H, m, CH); 2,21 (1H, m, CH); 2,70—4,38 (28H, m, CH_2O); 5.30 (1H, s, C_6H_5CH); 7,01—7,45 (5H, m, C_6H_5)	62,5	8,1	$C_{23}H_{36}O_8$	62,7	8,2	440	31
XII		1,98 (2H, m, CH); 3,35—3,85 (22H, m, CH_2O, OH)	54,4	9,1	$C_{12}H_{24}O_6$	54,5	9,1	264	92
XIII		1.95 (2H, m, CH); 3,25—3,91 (26H, m, CH_2O, OH)	54,3	9,1	$C_{14}H_{28}O_7$	54,5	9,1	308	92
XIV		1.88 (2H, m, CH); 2,90—3,90 (30H, m, CH_2O, OH)	54,3	9,1	$C_{16}H_{32}O_8$	54,5	9,1	352	90
XV		2.14 (2H, m, CH); 2,83—3,95 (40H, m, CH_2O)	56,4	9,1	$C_{22}H_{42}O_{10}$	56,6	9,1	466	31
XVI		1.96 (2H, m, CH); 3,28—3,74 (48H, m, CH_2O)	56,0	9,1	$C_{26}H_{50}O_{12}$	56,3	9,1	564	29
XVII		2.01 (2H, m, CH); 3,16—3,75 (36H, m, CH_2O)	56,6	9,1	$C_{20}H_{38}O_9$	56,8	9,1	422	32
XVIII		1,81 (2H, m, CH); 3,16—3,83 (40H, m, CH_2O)	56,5	9,1	$C_{22}H_{42}O_{10}$	56,6	9,1	466	27
XIX		2.25 (2H, m, CH); 3,00—4,00 (44H, m, CH_2O)	54,7	8,7	$C_{24}H_{46}O_{11}$	54,7	8,8	510	29
XX		1,83—2,41 (4H, m, CH); 3,13—3,86 (40H, m, CH_2O); 4,25—4.55 (8H, m, $C_6H_5CH_2$); 7,00—7,41 (20H, m, C_6H_5)	70,0	8,1	$C_{52}H_{72}O_{12}$	70,2	8,2	889	12
XXI		2,16 (2H, m, CH); 3,16—3,78 (20H, m, CH_2O); 4,35 (4H, s, $C_6H_5CH_2$); 7,00—7,35 (10H, m, C_6H_5)	70,2	8,1	$C_{26}H_{36}O_6$	70,2	8,2	444	40
XXII		1,79 (2H, m, CH); 2,23 (2H, br., OH); 3,01—3,60 (20H, m, CH_2O)	54,4	9,0	$C_{12}H_{24}O_6$	54,5	9,1	264	93

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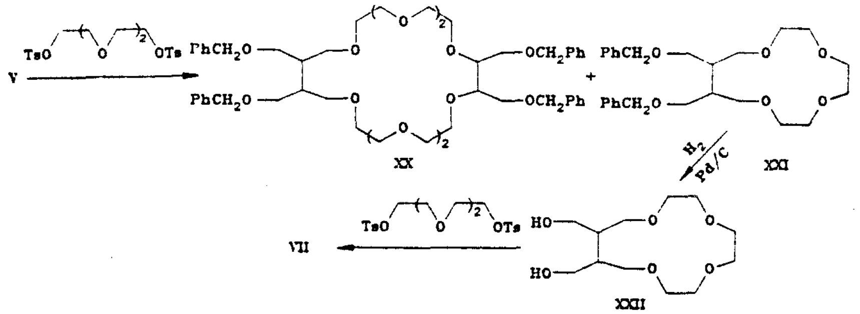
*Solution in CD_3OD

to crown ethers XX and XXI in 12% and 40% yields, respectively. Removal of the benzyl groups in crown ether XXI and subsequent condensation of the resulting crown ether XXII with triethylene glycol ditosylate gives binuclear crown ether VII.



The compositions and structures of all of the compounds obtained were confirmed by the results of elementary analysis, by PMR and mass-spectrometric data, and, in some cases, by alternative synthesis. Their properties are described in Table 1. Compounds III, IV, VII-XI, XX, and XXI were isolated in the form of mixtures of stereoisomers.

The approaches to the synthesis of binuclear crown ethers that we have developed are, in our opinion, efficient and generally make it possible to obtain binuclear crown ethers with various anchor groups.

EXPERIMENTAL

The PMR spectra were obtained with Tesla BS-467 (60 MHz) and Tesla BS-497 (100 MHz) spectrometers with hexamethyldisiloxane (HMDS) as the internal standard. The mass spectra were recorded with a Varian MAT-112 spectrometer. Gas—liquid chromatography (GLC) was carried out with a Chrom-5 chromatograph; the liquid phase was SP-2100 (5%) on Chromaton N-Super, the column was 1.5 m by 4 mm, and detection was accomplished by means of flame ionization. Thin-layer chromatography (TLC) was carried out in a thin layer of neutral aluminum oxide or on Silufol UV-254 plates.

Ethanetetracarboxylic Acid Tetraethyl Ester (I). A 160-g (1 mole) sample of freshly distilled malonic ester was added to a cooled solution of sodium ethoxide, obtained from 23 g (1 mole) of sodium in 300 ml of dry ethanol, after which the reaction mixture was stirred for 30 min, and a solution of 127 g (0.5 mole) of iodine in dry diethyl ether was added slowly dropwise with cooling (5-10°C). After 1 h, 300 ml of water was added, and the aqueous layer was extracted with ether (two 150-ml portions). The ether layer was washed with a dilute solution of sodium thiosulfate and dried with sodium sulfate. The solvent was removed by distillation to a final volume of 0.5 of the original volume. Product I crystallized out from the residue upon cooling. The yield was 302 g.

1,1,2,2-Tetrahydroxymethylethane (II). A solution of 95.4 g (0.3 mole) of tetraester I in 400 ml of dry ether was added slowly dropwise with cooling and vigorous stirring to a suspension of 57 g (1.5 mole) of lithium aluminum hydride in 500 ml of dry diethyl ether. The reaction mixture was refluxed for 2 h and stirred at 20°C for 24 h. It was then cooled to 0°C, and 54 ml of water in 100 ml of ethanol was added slowly dropwise with vigorous stirring. The mixture was then neutralized (to pH 7) with 2 N sulfuric acid solution and filtered. The precipitate was refluxed in water (two 700-ml portions), and the aqueous extracts were evaporated to half their original volume under reduced pressure. The concentrate was heated (50-60°C) with stirring with 3 g of activated charcoal for 30 min and filtered, and the filtrate was evaporated to dryness with a rotary evaporator. The resulting solid residue was refluxed in methanol (four 100-ml portions), and the combined methanol extracts were concentrated to 150 ml. Tetrol II crystallized out after cooling and was recrystallized from methanol. The yield was 22.5 g.

2-Phenyl-5-(1,3-dihydroxyisopropyl)-1,3-dioxane (III). A 15-g (0.1 mole) sample of tetrol was dissolved at 60°C in 100 ml of dry DMF, the solution was cooled to 25°C, 0.5 ml of concentrated HCl was added, and 15.9 g (0.15 mole) of freshly distilled benzaldehyde was added slowly dropwise. The reaction mixture was stirred at 30°C for another 5 h, and ammonium hydroxide was added until the mixture had pH 8-9. The solvent was removed by distillation at reduced pressure, and the residue was washed with ether (two 50-ml portions) to remove the excess benzaldehyde and then refluxed for 15 min in 100 ml of a 1.5% aqueous solution of sodium carbonate. The undissolved crystalline substance was removed by filtration and recrystallized from chloroform to give diacetal IV in 12% yield. Monoacetal III, which precipitated when the aqueous filtrate was cooled, was removed by filtration and dissolved in chloroform. An additional amount of the product was leached out by extraction from the aqueous solution with chloroform (three 70-ml portions). The combined extracts were dried with sodium sulfate and concentrated to 100 ml. The concentrate was cooled and filtered to isolate monoacetal III. The yield was 11.3 g.

1,1'-Bis(4-phenyl-3,5-dioxane) (IV). Five to seven drops of concentrated HCl were added cautiously with vigorous stirring at 50°C to a mixture of 15 g (0.1 mole) of II and 26 g (0.25 mole) of freshly distilled benzaldehyde (the mixture frothed and crystallized instantly). The reaction mass was cooled, ether (two 50-ml portions) were added, 50 ml of hot 1.5% aqueous sodium carbonate solution was added, and the precipitate was recrystallized from chloroform. The yield was 30.3 g.

2,3-Dibenzyloxymethylbutane-1,4-diol (V). A suspension of 7.98 g (0.21 mole) of lithium aluminum hydride in 50 ml of dry THF was added slowly dropwise with cooling to a solution of 20.9 g (0.64 mole) of boron trifluoride etherate, after which 13.04 g (0.04 mole) of IV was added to the mixture. The reaction mixture was then stirred for 15 min at −5°C, for 30 min at 20°C, and for 20 h at 40°C. It was then cooled to 0°C, and the excess reducing agent was decomposed with the calculated amount of water. More water was then added until the precipitate had dissolved completely, and the mixture was extracted with ether (five 100-ml portions). The combined ether extracts were washed with an aqueous solution of sodium carbonate until the washings had pH 7 and dried with sodium sulfate. The ether was removed by distillation, 30 ml of methanol was added to the reaction product to remove the boric acid residues, and the mixture was evaporated with a rotary evaporator. The latter operation was performed twice. The oily residue (12.9 g) was virtually pure V.

1,1'-Bis(3,6,9,12-tetraoxacyclotridecane) (VI) and Bicyclo[12.12.0]-3,6,9,12,16,19,22,-25-octaoxacyclohexacosane (VII). A 3.4-g (0.023 mole) sample of II was added to a solution of 11.04 g (0.115 mole) of sodium tert-butoxide in 200 ml of dry tert-butyl alcohol, and the mixture was stirred at 80°C in a nitrogen atmosphere for 1 h. A solution of 21.06 g (0.046 mole) of triethylene glycol ditosylate in 70 ml of dry dioxane was then added slowly dropwise, and the mixture was refluxed with stirring for 10 h. It was then poured into 200 ml of water, and the aqueous mixture was extracted with chloroform (three 100-ml portions). The combined extracts were dried with magnesium sulfate, and the solvent was removed by distillation. The reaction products were isolated by column chromatography on neutral aluminum oxide by elution with hexane—isopropyl alcohol (10:0.3). The yields of VI and VIII were 2.52 g and 1.22 g, respectively.

3-(4-Phenyl-3,5-dioxacyclohexyl)-1,5,8,11-tetraoxacyclotridecane (IX), 3,16-Bis(4-phenyl-3,5-dioxacyclohexyl)-1,5,8,11,14,18,21,24-octaoxacyclohexacosane (VIII), 3-(4-Phenyl-3,5-dioxacyclohexyl)-1,5,8,11,14-pentaoxacyclohexadecane (X), and 3-(4-Phenyl-3,5-dioxacyclohexyl)-1,5,8,11,14,16-hexaoxacyclononadecane (XI). A solution of 0.025 mole of III in 50 ml of dry dioxane was added to a suspension of 2.4 g (0.1 mole) of sodium hydride in 150 ml of dry dioxane, and the mixture was stirred at 70°C for 1 h in a nitrogen atmosphere. A solution of 0.025 mole of the ditosylate of the corresponding polyethylene glycol in 200 ml of dry dioxane was added slowly dropwise to the resulting mixture, and the new mixture was stirred at 80°C for 12 h. The excess sodium hydride was decomposed with water, the solvent was removed by distillation at reduced pressure, and the residue was dissolved in 100 ml of water. The aqueous solution was extracted with chloroform (three 70-ml portions), and the combined extracts were dried with magnesium sulfate. The solvent was removed by distillation, and the products were isolated by column chromatography on neutral aluminum oxide by elution with hexane—isopropyl alcohol (10:0.15 for VIII-X, and 10:0.2 for XI).

3,4-Dibenzyloxymethyl-1,6,9,12-tetraoxacyclotridecane (XXI) and 3,4,17,18-Tetrabenzyloxymethyl-1,6,9,12,15,20,23,26-octaoxacyclooctacosane (XX). These compounds were similarly obtained by condensation of V with triethylene glycol ditosylate. The products were purified by column chromatography on neutral aluminum oxide by elution with hexane—isopropyl alcohol (10:0.15).

3-(1,3-Dihydroxyisopropyl)-1,5,8,11-tetraoxacyclotridecane (XII). Hydrogen was passed through a suspension of 0.02 mole of IX and 1 g of 10% Pd/C in 100 ml of methanol for 5 h at 20°C.

and normal pressure. The catalyst was removed by filtration, and the solvent was removed by distillation to give the virtually pure compound.

3-(1,3-Dihydroxyisopropyl)-1,5,8,11,14-pentaoxacyclohexadecane (XIII), 3-(1,3-Dihydroxyisopropyl)-1,5,8,11,14,17-hexaoxacyclononadecane (XIV), and 3,4-Dihydroxymethyl-1,6,9,12-tetraoxacyclotridecane (XXII). These compounds were similarly obtained.

1,1'-Bis(3,6,9,12-tetraoxacyclotridecane) (VI), 3-(3,6,9,12-Tetraoxacyclotridecyl)-1,5,8,11,14-pentaoxacyclohexadecane (XVII), and 3-(3,6,9,12-Tetraoxacyclotridecyl)-1,5,8,11,14,17-hexaoxacyclononadecane (XVIII). A solution of 1.98 g (7.5 mmole) of XII in 50 ml of dry dioxane was added to a suspension of 0.72 g (30 mmole) of sodium hydride in 70 ml of dry dioxane, and the mixture was stirred at 70°C for 1 h in a nitrogen atmosphere. A solution of 7.5 mmole of the ditosylate of the corresponding polyethylene glycol in 100 ml of dry dioxane was added slowly dropwise to the resulting mixture, and the new mixture was stirred for 16 h at 80°C. The excess sodium hydride was decomposed with water, the solvent was removed by distillation at reduced pressure, and the residue was dissolved in 50 ml of water. The aqueous solution was extracted with chloroform (three 70-ml portions), and the combined extracts were dried with magnesium sulfate. The solvent was removed by distillation, and the substances were isolated by column chromatography on neutral aluminum oxide by elution with hexane—isopropyl alcohol (10:0.6).

1,1'-Bis(3,6,9,12,15-pentaoxacyclohexadecane) (XV) and 3-(3,6,9,12,15-Pentaoxacyclohexadecyl)-1,5,8,11,14,17-hexaoxacyclononadecane (XIX). These compounds were similarly obtained by condensation of XIII with the ditosylate of the corresponding polyethylene glycol.

1,1'-Bis(3,6,9,12,18-hexaoxacyclononadecane) (XVI). This compound was obtained by the reaction of XIV with pentaethylene glycol ditosylate.

Bicyclo[12.12.0]-3,6,9,12,16,19,22,25-octaoxacyclohexacosane (VII). This compound was obtained by condensation of XXII with triethylene glycol ditosylate.

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