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34.* SYNTHESIS AND ENANTIOMERIC SELECTIVITY OF CHIRAL AZACROWN

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Chiral azacrown ethers were obtained by the condensation of (4S,5S)-4,5-ditosyloxymethyl-2,2-dimethyl-1,3-dioxolane with 6-benzyl-3,9-dioxa-6-azaundecane-1,11-diol. Their debenzylation and deacetalization were realized. The enantiomeric selectivity in the complex formation between the obtained crown ethers and the hydrochlorides of L- and D-valine methyl esters was determined by a potentiometric method. The chiral azacrown ethers exhibit higher enantioselectivity than their oxygen analogs.

The ability of chiral crown ethers to form diastereomeric complexes with the enantiomers of amines and amino acids and to realize their transport through synthetic and biological membranes and also from one phase to another opens up wide prospects for the use of these compounds as enantiodifferentiating agents, catalysts of asymmetric synthesis, and models of biological systems [2, 3]. Chiral azacrown ethers have been studied little. It is interesting that the substitution of one or several oxygen atoms in the ring of crown ethers by nitrogen atoms has a significant effect on their complexing capacity [4], and in the case of the chiral compounds it must clearly also be reflected in their enantiodifferentiating characteristics.

A suitable chiral precursor for crown ethers is (4S,5S)-4,5-dihydroxymethyl-2,2-dimethyl-1,3-dioxolane (Ia), which was obtained by the acetalization and subsequent reduction of diethyl L(+)-tartrate [5]. The reaction of the dioxolane (Ia) with p-toluenesulfonyl chloride gave the ditosyloxy derivative (Ib). The diol (II) was obtained by the alkylation of benzylamine with diethylene glycol chlorohydrin. The condensation of the ditosyloxy derivative (Ib) with the diol (II) in dioxane in the presence of sodium hydride led to a mixture of the chiral azacrown ethers (III, IV, V), which were isolated in the individual state by chromatography on a column of aluminum oxide. The crown ethers (III) and (IV) are the products from the normal reaction of ditosyloxy derivatives with glycols by (1 + 1) and (2 + 2) mechanisms respectively. The formation of the azacrown ether (V) can be represented as the result from the alkylation of the diol (II) with two molecules of the ditosyloxy derivative (Ib) and hydrolysis or elimination (under the influence of traces of moisture or sodium hydroxide impurities in the sodium hydride) of one of the tosyloxy groups in the intermediately formed ditosyloxy derivative and subsequent intramolecular cyclization. Similar transformations were observed during the condensation of ditosyloxy derivatives with glycols [6].

The catalytic hydrogenolysis of the crown ether (III) leads with a high yield to the crown ether (VI), while acid hydrolysis of the dioxolane ring in the crown ethers (III) and (VI) gives the crown ethers (VII) and (VIII). For a comparative assessment of the effect of the nature of the heteroatom on the enantioselective characteristics of the crown ethers we synthesized our previously described [7] crown ethers IX, X, XI.

Compounds II-VIII were obtained in the form of colorless oils. Their compositions and structures were confirmed by the data from elemental analysis, PMR spectroscopy, and mass spectrometry. In the PMR spectra of the azacrown ethers (III-VIII) the signals for the protons of the NCH_2 groups appear in the form of a triplet in the region of 2.33-2.98 ppm. The signals for the protons of the CH_2O groups of the polyether ring are superimposed on the sig-

*See [1] for Communication 33.

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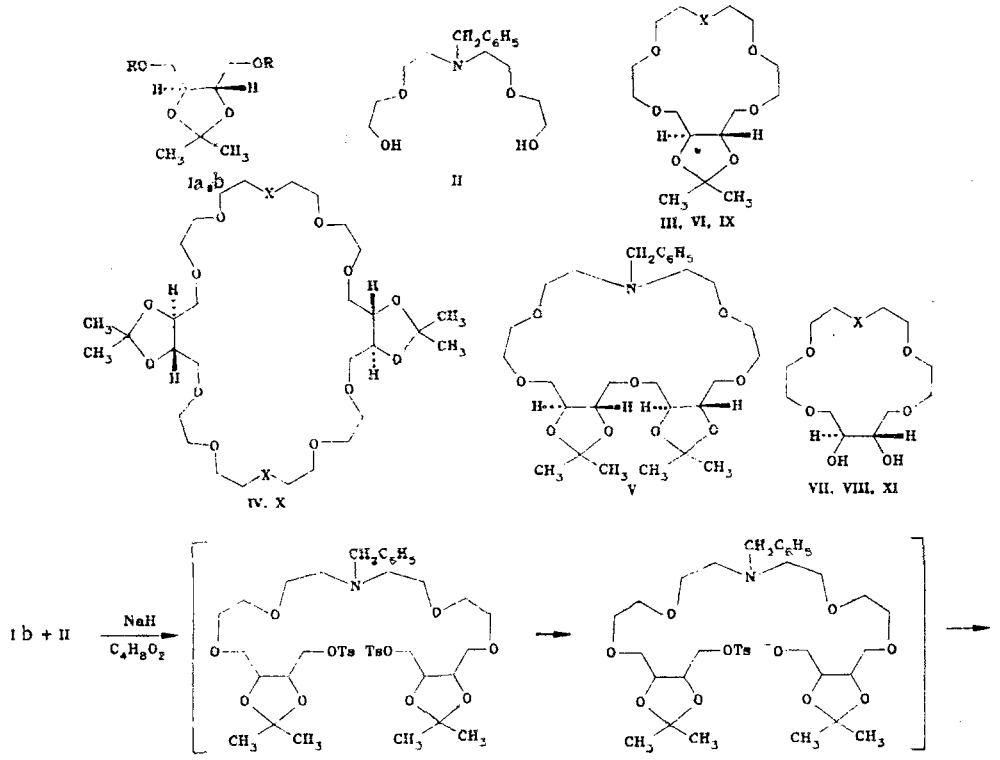

Ia R=H; b R=Ts; III, IV, VII X=$CH_2C_6H_5$; VI, VIII X=NH; IX, X, XI X=O

nals for the protons at the asymmetric centers and are observed in the form of a complex multiplet in the region of 3.12-3.75 ppm. The spectra of the azocrown ethers III-VIII contain signals for all the other existing groups, and this confirms their structure (Table 1).

An interesting and useful feature of the chiral crown ethers is the enantioselectivity in the formation of complexes with optically active substrates. The enantiomeric selectivity in the complex formation between the crown ethers (III-VII, XI) and the hydrochlorides of L- and D-valine methyl esters was determined by a potentiometric method in the cell:

$$\text{Ag,AgCl}\,|\ \text{reference solution}\ ||\ \text{membrane}\ ||\ \text{measured solution}\ |\ \text{AgCl, Ag.}$$

The enantioselectivity coefficients K_{LD} were calculated by means of the equation [8]:

$$\lg K_{LD} = E_L - E_D = \Delta E_{LD}/S,$$

where E_L and E_D are the electrode potentials at identical concentrations of the hydrochlorides of the L- and D-valine methyl esters and S is the slope of the calibration curve. The coefficients K_{LD} characterizing the preference for the reaction of the crown ethers with one of the enantiomers of the substrate are given in Table 2.

All the investigated azacrown ethers III-VII react preferentially with the hydrochlorides of L-valine methyl ester. Attention is drawn to the relatively good enantiomeric selectivity of the 17-membered crown ethers (III, VI, VII), which opens up the possibility for the creation of enantioselective electrodes on their basis. Increase of the ring size and destruction of its symmetry lead to a decrease in the enantioselectivity of compounds (IV, V). The somewhat greater enantioselectivity of the crown ether (VI) compared with its benzylated analog (III) is evidently due to the possibility of additional stabilization of the complexes of the crown ether (VI) through hydrogen bonds. All the investigated crown ethers exhibit greater enantioselectivity than their full oxygen analogs (IX-XI), and this makes it possible to consider the chiral azacrown ethers to be a promising type of enantioselective ligand.

EXPERIMENTAL

The PMR spectra were recorded on a Tesla BS-467 (60 MHz) in CCl_4 with HMDS as internal standard. Mass spectrometry was conducted on a Varian MAT-112 spectrometer with direct in-

TABLE 1. Characteristics of the Synthesized Compounds

Compound	$[\alpha]_D^{20}$, deg (c, %)*	PMR spectrum, δ, ppm	M+	Found, %			Molecular formula	Calculated, %			Yield, %
				C	H	N		C	H	N	
Ib	−12,4 (1,5)	1,30 [6H, s, $(CH_3)_2$]; 2,55 [6H, s, $(CH_3Ph)_2$]; 3,95—4,15 [6H, m, $(OCH_2)_2$+$(OCH)_2$]; 7,22—7,88 [8H, q, $(C_6H_4)_2$]	470	53,7	5,6	—	$C_{21}H_{26}O_8S_2$	53,6	5,5	—	80
II	—	2,50—2,68 [4H, t, $(NCH_2)_2$]; 3,35—3,62 [12H, m, $(OCH_2)_6$]; 3,68 (2H, s, CH_2Ph); 4,12—4,48 [2H, $(OH)_2$, br]; 7,28 (5H, s, C_6H_5)	283	63,2	9,1	4,9	$C_{15}H_{25}NO_4$	63,6	8,9	4,9	69
III	8,6 (1.5)	1,17 [6H, s, $(CH_3)_2$]; 2,40—2,70 [4H, t, $(NCH_2)_2$]; 3,12—3,57 [18H, m, $(OCH_2)_8$+$(OCH)_2$]; 3,73 (2H, s, CH_2Ph); 7,07 (5H, s, C_6H_5)	409	64,7	8,6	3,3	$C_{22}H_{35}NO_6$	64,5	8,6	3,4	30
IV	−2,6 (3,3)	1,17 [12H, s, $(CH_3)_4$]; 2,50—2,80 [8H, t, $(NCH_2)_4$]; 3,25—3,52 [36H, m, $(OCH_2)_{16}$+$(OCH)_4$]; 3,68 [4H, s, $(CH_2Ph)_2$]; 7,13 [10H, s, $(C_6H_5)_2$]	818	64,9	8,6	3,6	$C_{44}H_{70}N_2O_{12}$	64,5	8,6	3,4	9
V	−6,0 (0,8)	1,25 [12H, s, $(CH_3)_4$]; 2,75—2,98 [4H, t, $(NCH_2)_2$]; 3,40—3,68 [24H, m, $(OCH_2)_{10}$+$(OCH)_4$]; 3,88 (2H, s, CH_2Ph); 7,20 (5H, s, C_6H_5)	553	63,0	8,4	2,6	$C_{29}H_{47}NO_9$	62,9	8,5	2,5	22
VI	5,6 (1,2)	1,32 [6H, s, $(CH_3)_2$]; 2,33—2,40 (1H, t, NH); 2,74—3,00 [4H, t, $(NCH_2)_2$]; 3,44—3,71 [18H, m, $(OCH_2)_8$+$(OCH)_2$]	319	56,4	9,2	4,3	$C_{15}H_{29}NO_6$	56,4	9,1	4,4	83
VII	6,1 (0,9)	2,33—2,67 [4H, t, $(NCH_2)_2$]; 2,80—2,96 [2H, $(OH)_2$, br]; 3,17—3,58 [18H, m, $(OCH_2)_8$+$(OCH)_2$]; 3,73 (2H, s CH_2Ph); 7,07 (5H, s, C_6H_5)	369	62,0	8,6	3,8	$C_{19}H_{31}NO_6$	61,8	8,4	3,8	93
VIII	9,1 (0,3)	2,22—2,30 (1H, t, NH); 2,60—2,83 [4H, t, $(NCH_2)_2$]; 3,11—3,28 [2H, $(OH)_2$, br]; 3,43—3,75 [18H, m, $(OCH_2)_8$+ +$(OCH)_2$]	279	51,6	9,2	5,1	$C_{12}H_{25}NO_5$	51,6	9,0	5,0	86

*The angle of rotation of compound (I) was determined in chloroform, and those of compounds (II-VIII) were determined in ethanol.

TABLE 2. The Enantioselectivity Coefficients of the Crown Ethers III-VII, IX-XI

Compound	$K_{L/D}$	Compound	$K_{L/D}$
(*S*, *S*)-III	1,65	(*S*, *S*)-VII	1,46
(*S*, *S*)-IV	1,19	(*S*, *S*)-IX	1,22
(*S*, *S*)-V	1,18	(*S*, *S*)-X	1,00
(*S*, *S*)-VI	1,72	(*S*, *S*)-XI	1,08

jection into the ion source at 70 eV. The specific angles of optical rotation were measured on a Polamat A spectropolarimeter in absolute ethanol. The preparative GLC was conducted on a Pye-Unicam-204 chromatograph with a flame-ionization detector (2.1 m × 8 mm glass column, 5% SE-30 on Chromaton N-AW, helium). Analytical GLC was conducted on a Chrom-5 instrument with a flame-ionization detector (3m × 3 mm column, 5% SP-2100 on Chromaton N-Super). Preparative liquid chromatography was conducted on glass columns with neutral aluminum hydroxide (L40/250) in a 100:1 mixture of hexane and isopropanol.

(4S,5S)-4,5-Ditosyloxymethyl-2,2-dimethyl-1,3-dioxolane (Ib). To a cooled solution (0-10°C) of 10.04 g (62 mmoles) of (4S,5S)-4,5-dihydroxymethyl-2,2-dimethyl-1,3-dioxolane (I) ($|\alpha|_D^{20}$ = 5.1°; c 5.0; $CHCl_3$) [5] and 14.14 g (140 mmoles) of triethylamine in 6 ml of dioxane we added dropwise with stirring a solution of 23.62 g (124 mmoles) of p-toluenesulfonyl chloride in 50 ml of dioxane. The reaction mixture was stirred for 3 h, and the precipitate was filtered off. The filtrate was concentrated to half the volume and added to a mixture of 50 g of ice and 75 ml of water. The crystals were filtered off and recrystallized from methanol; mp 91-92°C. The yield was 23.31 g (80%).

6-Benzyl-3,9-dioxa-6-azaundecane-1,11-diol (II). A mixture of 43.52 g (350 mmoles) of 5-chloro-3-oxapentan-1-ol (Fluka), 18.72 g (175 mmoles) of benzylamine, and 37.10 g (350 mmoles) of ground anhydrous sodium carbonate was stirred at 150°C for 3 h, cooled, and poured into 100 ml of water. The reaction products were extracted with ether (5 × 100 ml). The extracts were dried with anhydrous sodium sulfate, the ether was distilled, and the residue was purified by vacuum distillation at 170-172°C (0.05 mm Hg); n_D^{20} 1.5184. The yield was 34.17 g (69%).

(1S,2S)-1,2-O-Isopropylidene-10-benzyl-4,7,13,16-tetraoxa-10-azacycloheptadecane (III), (1S,2S,18S,19S)-1,2,18,19-O-Diisopropylidene-10,27-dibenzyl-4,7,13,16,21,24,30,33-octaoxa-10,27-diazacyclotetratriacontane (IV), and (1S,2S,6S,7S)-1,2,6,7-O-Diisopropylidene-15-benzyl-4,9,12,18,21-pentaoxa-15-azacyclodocosane (V). To a suspension of 4.32 g (180 mmoles) of sodium hydride in 250 ml of dry dioxane, while stirring, we added dropwise in an atmosphere of argon 5.10 g (18 mmoles) of the diol (II) in 350 ml of dry dioxane. The mixture was stirred at 50-60°C for 1 h, and a solution of 8.46 g (18 mmoles) of the ditosyloxy derivative (Ib) in 350 ml of dry dioxane was added dropwise at the same temperature. The mixture was stirred at 60-80°C for 6-7 h. The excess of sodium hydride was decomposed with 100 ml of iced water. The product was extracted with chloroform (5 × 100 ml) and dried with magnesium sulfate, and the solvent was distilled. The products were isolated by column chromatography on neutral aluminum oxide with a 100:1 mixture of hexane and isopropanol as eluent.

Compound (III): R_f 0.50, yield 2.21 g (30%). Compound (IV): R_f 0.17, yield 1.33 g (9%). Compound (V): R_f 0.41, yield 2.19 g (22%).

(1S,2S)-1,2-O-Isopropylidene-4,7,13,16-tetraoxa-10-azacycloheptadecane (VI). We placed 100 ml of palladium black in a flat-bottomed flask and added 40 ml of methanol. The catalyst was activated by passing a stream of hydrogen for 2 h. A 490 mg portion (1.2 mmole) of compound (III) was added, and a stream of hydrogen was passed for 8 h. The precipitate was filtered off and washed with methanol. The solvent was distilled, and the product was isolated by preparative GLC; t_R = 192 sec (T_{col} = 290°C). The yield was 320 mg (83%).

(1S,2S)-1,2-dihydroxy-10-benzyl-4,7,13,16-tetraoxa-10-azacycloheptadecane (VII) and (1S,2S)-1,2-Dihydroxy-4,7,13,16-tetraoxa-10-azacycloheptadecane (VIII). From a solution of 1720 mg (4.2 mmoles) of the crown ether (III) or 1340 mg (4.2 mmoles) of (VI) in a mixture of 0.6 ml of 0.5 N hydrochloric acid and 4.5 ml of methanol we slowly distilled a mixture of acetone and methanol with a fractionating column over 5 h. The residue was dissolved

in 100 ml of chloroform. The product was washed with 1 ml of a saturated aqueous solution of sodium hydrocarbonate and dried with magnesium sulfate. After distillation of the solvents the products were isolated by preparative GLC. Compound (VII): t_R 228 sec, yield 1.440 mg (93%). Compound (VIII): t_R 144 sec, yield 1010 mg (86%).

The enantiomeric selectivity of the crown ethers (III-VII, IX-XI) was determined in 10 mM aqueous solutions of the hydrochlorides of L- and D-valine methyl esters. As reference solution we used a 10 mM solution of the hydrochloride of L,D-valine methyl ester. In all cases the membrane was a 1% solution of the crown ether in chloroform. The membrane was separated from the investigated solution by a cellophane film with a thickness of 20 μ. The electrode potential was measured by means of a Radelkis OP-208/1 digital pH-meter at 25 ± 1°C.

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