MACROHETEROCYCLES.

49.* SIMPLE SYNTHESIS OF CRYPTANDS BASED ON INTRACOMPLEX MACROCYCLIZATION

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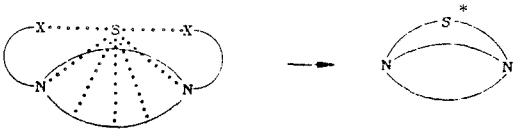
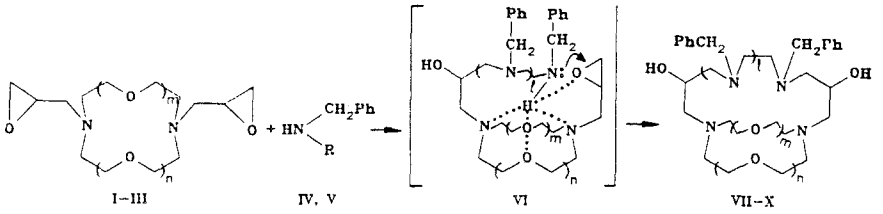
An effective method for synthesizing cryptands by reaction of bis(methyleneepoxy)diazacrown ethers with benzylamine and N,N'-dibenzylethylenediamine is reported. The good yields of cryptands are explained by formation of an intermediate in which the placement of reaction centers is favorable for intramolecular closure due to binding of the macrocycle to substrate.

Crown ethers with reactive functional groups in the side chain can selectively bind substrate and effect its chemical transformation. Such crown ethers act as typical catalysts since their functional groups are regenerated due to subsequent reactions [2, p. 167]. An irreversible intracomplex reaction of crown ether with substrate should lead to chemical transformation of the ligand itself. It would be interesting to use this principle for effective synthesis of cryptands by the scheme below (S* is the chemically transformed substrate).



We studied the reaction of bis(methyleneepoxide)-diazacrown ethers I-III with amines IV and V as a model. These amines are known to form stable complexes with crown ethers [2, p. 337] and to react readily with epoxides.



I-III IV, V VI VII-X

I $m=n=1$; II $m=1$, $n=2$; III $m=n=2$; IV R=H; V $R=CH_2CH_2NHCH_2Ph$; VII $m=n=1$, $l=0$; VIII $m=1$, $n=2$, $l=0$; IX $m=n=2$; $l=0$; X $m=n=2$, $l=1$

Cryptands VII-X were isolated as mixtures of diastereomers. The alternate formation of cyclic or linear products is controlled by the contribution of intra- or intermolecular addition of the second epoxide to the amine. Thus, good yields of cryptands VII-X are rather unexpected since the reaction was not conducted under high dilution conditions (concentration of starting reagents $5 \cdot 10^{-2}$ mole/liter) and cations were absent from the reaction mixture so that their matrix effect could not facilitate macrocyclization.

In our opinion, the high yield of cryptands is due to formation of intermediates VI in which the spatial placement of reaction centers is favorable for closure due to binding of substrate to the macrocycle. The high yield of cryptand IX (91%) on reaction of bis(methyleneepoxide)diaza-18-crown-6 (III) with benzylamine at a mole ratio of 1:2 confirms this hypothesis.

*For Communication 48, see [1].

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EXPERIMENTAL

PMR spectra were recorded on a Bruker AM-250 spectrometer in $CDCl_3$ with an internal standard of HMDS. Mass spectra were recorded on an MX-1331 instrument. TLC were developed on glass plates with a deposited layer of neutral aluminum oxide L 5/40 (Czech. SSR) in $CHCl_3$–C_6H_6–MeOH–i-PrOH, 8:3:0.2:0.2 (for VII-IX) and $CHCl_3$–C_6H_{14}–i-PrOH, 8:3:0.1 (for X). Neutral aluminum oxide L 40/250 (Czech. SSR) was used for column chromatography.

Elemental analyses for C, H, and N corresponded to those calculated.

1,7-Di(2,3-epoxy-1-propyl)-4,10-dioxa-1,7-diazacyclododecane (I, $C_{14}H_{26}N_2O_4$). A mixture of 7 g (40 mmoles) diaza-12-crown-4 and 37.2 g (402 mmoles) epichlorohydrin was stirred for 5 h at 20°C. A solution of 3.7 g NaOH in 4 ml water was added to the reaction mixture and stirring was continued for 30 min. The reaction mixture was diluted with 5 ml water and extracted with ether (2 × 50 ml). The ether extracts were discarded. The remainder was extracted with benzene (5 × 200 ml). Compound I was obtained as a colorless oil after removal of benzene. Yield 10.3 g (90%). M^+ 286. PMR spectrum: 2.45 (4H, m, OCH_2 epoxide), 2.79 (12H, m, NCH_2), 3.08 (2H, m, CHO), 3.58 ppm (8H, m, OCH_2).

1,7-Di(2,3-epoxy-1-propyl)-4,10,13-trioxa-1,7-diazacyclopentadecane (II, $C_{16}H_{30}N_2O_5$) was prepared analogously. Yield 58% (light-yellow oil). M^+ 330. PMR spectrum: 2.45 (4H, m, OCH_2 epoxide), 2.82 (12H, m, NCH_2), 3.05 (2H, m, CHO), 3.59 ppm (12H, m, OCH_2).

1,10-Di(2,3-epoxy-1-propyl)-4,7,13,16-tetraoxa-1,10-diazacyclooctadecane (III, $C_{18}H_{34}N_2O_6$) was prepared analogously. Yield 72%, mp 89-90°C (from n-C_6H_{14}). M^+ 374. PMR spectrum: 2.44 (4H, m, OCH_2 epoxide), 2.82 (12H, m, NCH_2), 3.02 (2H, m, CHO), 3.58 ppm (16H, m, OCH_2).

3,10-Dihydroxy-5-benzyl-12,17-dioxa-1,5,9-triazabicyclo[7.5.5]nonadecane (VII, $C_{21}H_{35}N_3O_4$). A solution of 0.5 g (1.75 mmoles) I and 0.21 g (1.93 mmoles) benzylamine IV in 30 ml dry alcohol was boiled for 8 h. After removing the ethanol, the residue was chromatographed on a column. Compound VII was obtained as a colorless oil. Yield 0.6 g (83%). M^+ 393. PMR spectrum: 2.40 (4H, m, $PhCH_2\mathbf{NCH_2}$), 2.65 (12H, m, NCH_2), 3.50 (14H, m, OCH_2, CHOH, $Ph\mathbf{CH_2}N$), 7.22 ppm (5H, m, arom.).

12,16-Dihydroxy-14-benzyl-4,7,20-trioxa-1,10,14-triazabicyclo[8.7.5]docosane (VIII, $C_{23}H_{39}N_3O_5$) was prepared analogously as a light-yellow oil. Yield 62%. M^+ 437. PMR spectrum: 2.45 (4H, m, $PhCH_2\mathbf{CH_2}$), 2.61 (12H, m, NCH_2), 3.48 (16H, m, OCH_2, CHOH), 3.58 (2H, s, Ph $_2$N), 7.20 ppm (5h, m, arom.).

20,24-Dihydroxy-22-benzyl-4,7,13,16-tetraoxa-1,10,22-triazabicyclo[8.8.7]pentacosane IX, $C_{25}H_{43}N_3O_6$) was prepared analogously. Yield 85% (light-yellow oil). M^+ 481. PMR spectrum: 2.63 (4H, m, $PhCH_2\mathbf{NCH_2}$), 2.74 (12H, m, NCH_2), 3.48 (8H, t, $O\mathbf{CH_2}CH_2N$; J = 5.0 Hz), 3.56 (4H, m, CHOH), 3.59 (8H, s, OCH_2CH_2O), 3.69 (2H, s, $Ph\mathbf{CH_2}N$), 7.21 ppm (5H, m, arom.).

2,3-Dihydroxy-4,7-dibenzyl-14,17,22,25-tetraoxa-1,4,7,11-tetraazabicyclo[9.8.8]-heptacosane (X, $C_{34}H_{54}N_4O_4$) was prepared analogously from 1 g (2.7 mmoles) III and 0.65 g (2.7 mmoles) dibenzylethylenediamine V. Yield 1.0 g (61%), colorless oil. M^+ 582. PMR spectrum: 2.40 (8H, m, $PhCH_2\mathbf{NCH_2}$), 2.68 (12H, m, NCH_2), 3.48 (8H, m, OCH_2), 3.56 (8H, s, OCH_2CH_2O), 3.62 (4H, s, $Ph\mathbf{CH_2}N$), 3.85 (4H, m, CHOH), 7.19 ppm (10H, m, arom.).

LITERATURE CITED

1. N. G. Luk'yanenko, S. S. Basok, L. K. Filonova, and N. V. Kulikov, Zh. Org. Khim. (in press).
2. R. M. Izatt (ed.), Synthesis of Macrocycles, Wiley, New York (1987).