POLYFUNCTIONAL MACROHETEROCYCLES

5.* REDUCTION OF ENDOCYCLIC AMIDE AND EXOCYCLIC ESTER OR NITRILE GROUPS OF SOME NITROGEN AND SULFUR CROWN ETHERS

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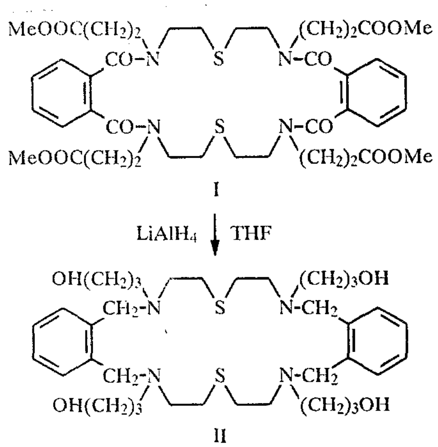
A study was carried out on the $LiAlH_4$ reduction of endocyclic amide and exocyclic ester and nitrile groups of several nitrogen and sulfur crown ethers, which were converted into CH_2NR_2, CH_2OH, and CH_2NH_2 groups, respectively. A macrocycle was synthesized containing endocyclic amide groups and the reduction of this compound, leading to the corresponding CH_2NR_2 derivative, was studied.

The synthesis of new polyfunctional macroheterocycles holds interest in regard to the possibility of the use of such compounds in supramolecular chemistry as endo and exo receptors binding cations, anions, and neutral molecules [2-4].

We have previously studied crown ethers containing endocyclic donor nitrogen and sulfur atoms and exocyclic phenethyl, methoxycarbonylethyl, [1,2-bis(methoxycarbonyl)]ethyl, [1,2-bis(ethoxycarbonyl)]ethyl, and cyanoethyl groups [5-10]. The oxidation of several nitrogen and sulfur macroheterocycles was investigated [9, 10]. These crown ethers form complexes with transition metal ions and neutral organic molecules [11-13]. Complexes of nitrogen and sulfur macrocycles with cupric ions (II) possess spectral and oxidative—reduction properties identical to the active sites of "blue" proteins. Hence, they may be used as models for the study of metalloenzymes [14].

In order to synthesize new types of macroheterocycles containing carbofunctional fragments $(CH_2)_nOH$, $(CH_2)_nNH_2$, and $(CH_2)_nNR_2$, we studied the $LiAlH_4$ reduction of previously reported thiaaza crown ethers containing endocyclic amide and exocyclic ester and nitrile groups.



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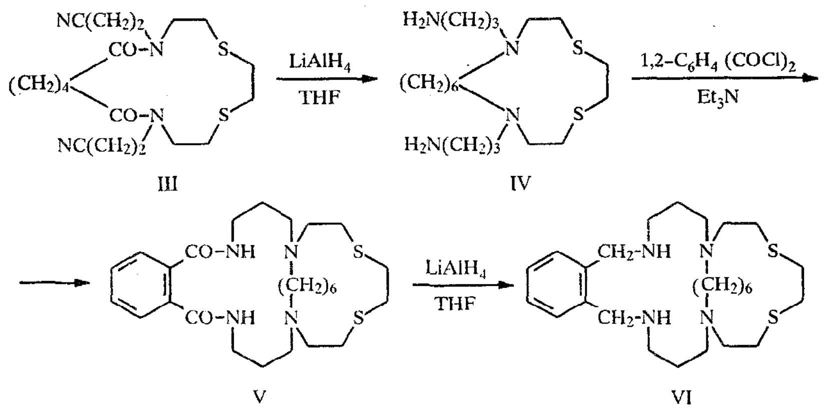
*For Communication 4, see ref. [1].

Irkutsk Institute of Organic Chemistry, Siberian Branch, Russian Academy of Sciences, Irkutsk 664033. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 9, pp. 1286-1288, September, 1992. Original article submitted February 4, 1991.

The amide and ester groups of crown ether I were reduced by excess $LiAlH_4$ in THF at reflux over 3 h. The yield of macroheterocycle II was 80%. The IR spectrum of crown ether II indicated reduction of both the ester and amide groups. This spectrum lacks bands for the amide and ester groups at 1620 and 1720 cm^{-1}, respectively, found for I, but shows a broad band with maximum at 3300 cm^{-1}, characteristic for an associated hydroxyl group.

The reduction of macroheterocycle III containing amide and nitrile groups was carried out analogously.



This reaction was carried out in THF at reflux over 3 h. The yield of crown ether IV was 82%. The preparation of macroheterocycle V was carried out by the cyclocondensation of macroheterocycle IV with the diacid chloride derivative of phthalic acid in benzene under high dilution conditions. The yield of macrobicycle V was 72%. The reduction of the amide groups by $LiAlH_4$ leads to cryptand VI in 80% yield.

Products II and IV-VI are thick oils or crystalline compounds, which have good solubility in benzene, methanol, chloroform, DMF, and DMSO.

The IR spectrum of crown ether IV lacks the bands for the amide and nitrile groups at 1640 and 2260 cm^{-1}, respectively, but has bands at 3340 and 3280 cm^{-1} characteristic for the stretching vibrations of primary amine groups. The IR spectra of macrobicycles V and VI have only one band in the vicinity of 3300 cm^{-1} belonging to a secondary amine group. The band at 1640 cm^{-1} is assigned to the amide group (amide-I band) of macrocycle V.

EXPERIMENTAL

The IR spectra were taken in KBr pellets or vaseline oil on a UR-20 spectrometer. The PMR spectra were taken on a Tesla BS 487C spectrometer at 80 MHz in $CDCl_3$ with HMDS as the internal standard. The molecular mass was determined by the isopiestic method.

4,9,15,20-Tetrakis(3-hydroxypropyl)-6,7,17,18-dibenzo-1,2-dithia-4,9,15,20-tetraazacyclodocosa-6,17-diene (II, $C_{36}H_{60}N_4O_4S_2$). A sample of 8.44 g (0.01 mole) macroheterocycle (I) in 30 ml dry THF was added slowly to a suspension of 3.8 g (0.1 mole) $LiAlH_4$ in 60 ml dry THF and the mixture was stirred at 55°C for 3 h. After cooling, the excess $LiAlH_4$ was decomposed by the addition of water and, then, 15% hydrochloric acid, and extracted with chloroform. The extract was dried over $MgSO_4$ and filtered. The product was precipitated by the addition of petroleum ether. PMR spectrum: 1.38 (8H, m, CH_2), 2.70 (8H, m, SCH_2), 3.20 (24H, m, NH_2), 3.60 (8H, m, OCH_2), 4.60 (4H, s, OH), 7.30 ppm (8H, m, C_6H_4). Found: C, 63.54; H, 8.71; N, 8.02; S, 9.18%; M 630. Calculated: C, 63.90; H, 8.87; N, 8.28; S, 9.46%; M 676. The yield of II was 5.41 g (80%). This product is an oil.

7,14-Bis(3-aminopropyl)-1,4-dithia-7,14-diazacyclohexadecane (IV, $C_{18}H_{40}N_4S_2$) was obtained as an oil analogously from 3.96 g (0.01 mole) macroheterocycle III and 3.8 g (0.01 mole) $LiAlH_4$. Found: C, 57.15; H, 10.38; N, 14.71; S, 16.81%; M 357. Calculated: C, 57.44; H, 10.64; N, 14.89; S, 17.02%; M 376. The yield of IV was 3.08 g (82%).

13,14-Benzo-12,15-dioxo-1,4-dithia-7,11,16,20-tetraazabicyclo[8,12,6]octacos-13-ene (V, $C_{26}H_{42}N_4O_2S_2$). A solution of 3.76 g (0.01 mole) macrocycle IV in 300 ml dry benzene and 2.03 g (0.01 mole) diacid chloride derivative of phthalic acid in 300 ml dry benzene were added simultaneously over 6 h at 20°C and rapid stirring into 1 liter dry benzene containing 2.02 g (0.02 mole) triethylamine. The precipitate formed was filtered off and the solvent was distilled off at reduced pressure. The residue was purified by chromatography on alumina using 5:1 benzene—methanol as the eluent. The solvent was distilled off and the residue was dissolved in chloroform and precipitated by the addition of petroleum ether upon cooling, mp 193-195°C. PMR spectrum: 1.38 (4H, m, CH_2), 2.71 (8H, m, SCH_2), 3.59 (16H, m, NCH_2), 7.30 ppm (4H, m, C_6H_4). Found: C, 61.38; H, 8.09; N, 10.78; S, 12.42%; M 485. Calculated: C, 61.64; H, 8.30; N, 11.06; S, 12.64%; M 506. The yield of V was 3.64 g (72%).

13,14-Benzo-1,4-dithia-7,11,16,20-tetraazabicyclo[8,12,6]octacos-13-ene (VI, $C_{26}H_{48}N_4S_2$) was obtained as an oil analogously to II from 5.06 g (0.01 mole) macrobicycle V and 1.9 g (0.05 mole) $LiAlH_4$. PMR spectrum: 1.61 (4H, m, CH_2), 3.34 (8H, m, SCH_2), 3.57 (2OH, m, NCH_2), 7.30 ppm (4H, m, C_6H_4). Found: C, 64.95; H, 9.36; N, 11.48; S, 13.02%; M 454. Calculated: C, 65.27; H, 9.62; N, 11.71; S, 13.38%; M 478. The yield of VI was 3.82 g (80%).

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