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SYNTHESIS OF NEW BI- AND TRICYCLIC AZAMACROCYCLES USING CYCLENE

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A method was developed for preparing bi- and tricyclic tetra- and hexaazamacrocycles using the reaction of 1,4,7,10-tetraazacyclododecane with various alkylating ditosylates.

Macrocyclic compounds continue to hold interest due to their unusual chemical properties. Special attention has been given to the synthesis and study of polymacro- and polycyclic structures such as cryptands, spherands, calixarenes in light of the great stability of their complexes, selectivity, and biological activity [1]. Study of the chemistry of the first-synthesized [2] three-dimensional macrocyclic compounds began with the development of new synthetic pathways and investigation of polycyclic aza compounds [3]. A method for the preparation of tricyclic oxygen and nitrogen ligands with various other heteroatoms and aromatic systems was shown by Wester [4] and Alberis [5]. A synthesis of bicyclic ligands displaying high selectivity toward alkali metal ions was based on the alkylation of ethylenediamine by triethyleneglycol ditosylates [6]. The synthesis of a tricyclic ligand termed a "cylindrical" cryptand was also described using a derivative of diaza-12-crown-4 only in the presence of a template agent [7].

We have developed a convenient synthesis for such polycyclic compounds based on the alkylation of 1,4,7,10-tetraazacyclododecane (cyclene) used as a matrix by diol and aminoglycol ditosylates. Bicyclic tetraaza derivatives II-V were obtained by the condensation of cyclene I with ditosyl derivatives of diethyleneglycol, triethyleneglycol, diethanolamine, and N,N′-bis(2-hydroxyethyl)ethylenediamine in dry acetonitrile in the presence of potassium carbonate with a 1:1 reagent ratio. "Cylindrical" cryptand VI was isolated in the reaction of a nitrogen analog of 12-crown-4 with two molecules of diethyleneglycol ditosylate. Thin-layer chromatography indicated that VI is also formed in the synthesis of II, which is an intermediate in the formation of this tricyclic product. In all cases, cyclic compounds were isolated by extraction and further purified by crystallization from saturated hydrocarbons. The relatively good yields (from 18 to 61%) and rather high reagent concentrations indicate a kinetic template mechanism for the formation of bi- and tricyclic products II-VI.

The role of the template agent in these reactions is apparently played by the H^+ ion due to intramolecular hydrogen bonding in the transition state. Such an effect was also observed in the synthesis of cryptand[1.1.1] [8]. Evidence for this hypothesis lies in the finding that the yield of cyclic products decreases is reduced several times in the presence of a proton acceptor stronger than potassium carbonate. We should note that these compounds are also found in the absence of metal salts. The nitrogen atoms play the role of the base in the alkylation reaction, which supports our hypothesis of a role for the hydrogen ion as a template agent.

The ion peaks* 169 and 143 are noted among the strong fragment ion peaks in the mass spectrum of tricyclic derivative VI. The precise masses for these peaks were 169.13410 and 143.11839, indicating chemical formulas $C_9H_{17}N_2O$ and $C_7H_{15}N_2O$. A strong peak (100%) is found for the parent ions in the spectra of the metastable ions of these fragments by accelerating voltage scanning, which corresponds to the molecular ion, while the peaks of other possible parent ions have 5-7% intensity. Hence, these fragments are formed from the molecular ions in a single step, i.e., we may conclude that the cylindrical model is characteristic for VI. The mass spectra of III and IV show strong fragmentation ion peaks 322 and 310 (for III) and

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*Here and subsequently, the *m/z* values are given for the ion peaks.

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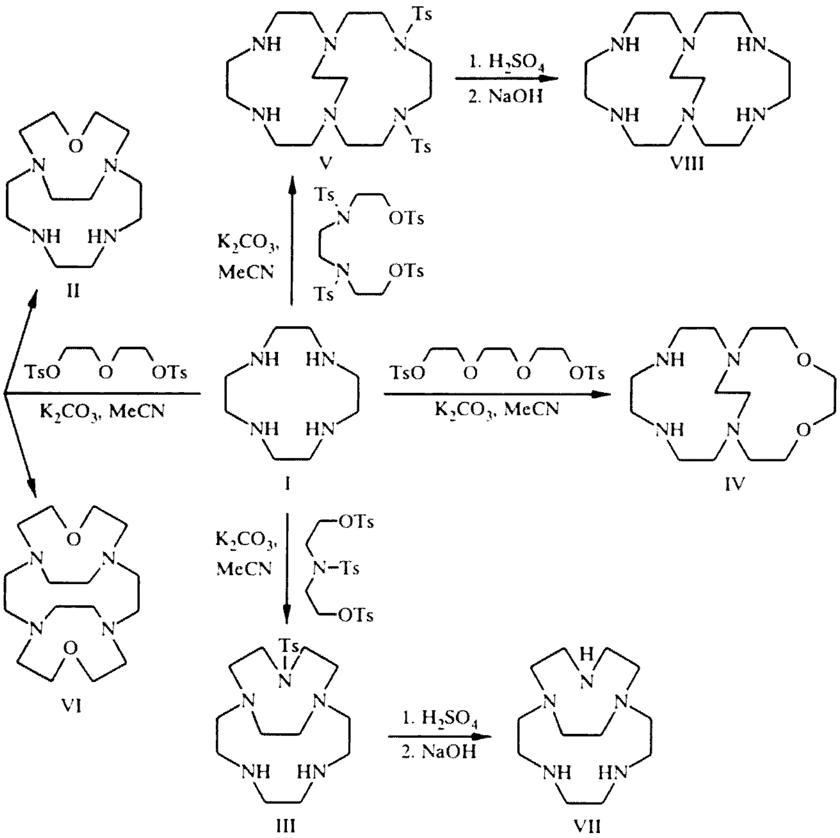

201 and 187 (for IV). The high-resolution mass spectral data and the metastable ion spectra indicate that the formation of the fragments noted above proceeds through one-step elimination of $C_3H_9N_2$ and $C_4H_9N_2$ (for III) and $C_4H_9N_2$ and $C_5H_{11}N_2$ (for IV).

The molecular ion peak of V has lower intensity than the corresponding peaks observed for III-VI. On the other hand, the decomposition channels are identical. The mass spectrum of V has fragmentation ions $[M - 56]^+$, $[M - 75]^+$, and $[M - 85]^+$, whose formation is related to the elimination of chain fragments containing secondary nitrogen atoms. On the other hand, a peak is observed for a fragment without a tosyl substituent $[M - 155]^+$, whose intensity is similar to the intensity of the peak in the spectrum of III.

Additional proof for the structures of II-VI is found in the ^{13}C NMR spectra. In the number of signals and intensities, these spectra indicate that the alkylation of cyclene proceeds predominantly at the nitrogen atoms at positions 1-2 and 3-4 and not at 1-3 and 2-4.

The removal of the tosyl fragments in III and V was carried out by the action of concentrated sulfuric acid upon prolonged heating at 100°C or by heating with $NaAlH_2(OCH_2CH_2OCH_3)_2$ in toluene. We should note that the yields of VII and VIII were higher in the former case. Products VII and VIII were also isolated by extraction.

EXPERIMENTAL

The PMR and ^{13}C NMR spectra were taken on a Bruker AM-250 spectrometer in $CDCl_3$. The mass spectra were taken on a Varian MAT CH-112 mass spectrometer. The spectral data are given in Table 1.

The reaction course and purity of the products were monitored by thin-layer chromatography on Silufol UV-254 with development by iodine vapor and ethereal ninhydrin using 10:3:5 ethanol–acetonitrile–aqueous ammonia as the eluent.

The elemental analysis for C, H, and N corresponded to the calculated values.

TABLE 1. Spectral Indices for Bi- and Tricyclic Products II-VIII

Compound	PMR spectrum, δ, ppm	^{13}C NMR spectrum, δ, ppm	Mass spectrum, Mt
II	2,40...2,59 (22H, m, CH_2N, N, H), 3,59...3,71 (4H,m, CH_2O)	45,30, 47,03, 50,48, 51,42, 55,90, 70,33	242
III	2,40 (3H, s, $ArCH_3$), 2,53...2,69 (22H, m, NCH_2, NH), 2,83...3,10 (4H, m, $TsNCH_2$), 7,27...7,66 (4H, d.d. C_6H_4)	22,14, 47,71, 48,09, 55,26, 55,98, 57,55, 127,77, 130,28, 136,13, 143,84	395
IV	2,47...2,78 (22H, m, CH_2N, NH), 3,54...3,80 (8H,m, CH_2O)	44,36, 46,85, 50,67, 51,80, 54,25, 68,57, 72,03	286
V	2,43 (6H, s, $ArCH_3$), 2,49...2,80 (22H, m, CH_2N, NH), 2,90...3,21 (4H, m, $TsNCH_2$), 3,30 (4H, s, $(TsNCH_2)_2$), 7,21...7,63 (8H,m, C_6H_4)	21,35, 44,99, 47,13, 47,71, 49,00, 50,28, 52,83, 55,72, 127,10, 129,40, 136,57, 142,91	592
VI	2,52...2,73 (24H,m, NCH_2), 3,67...3,81 (8H, m, OCH_2)	—	312
VII	2,10...2,19 (3H, s, NH), 2,60...2,84 (24H,m, CH_2N)	—	241
VIII	2,11...2,16 (4H, s, NH), 2,59...2,71 (28H,m, CH_2N)	—	284

Diethyleneglycol ditosylate, triethyleneglycol ditosylate, diethanolamine tritosylate and N,N′-bis(2-hydroxyethyl)-ethylenediamine tetratosylate were obtained according to Lobach et al. [9]. The physical indices of these compounds corresponded to reported values.

A sample of 1,4,7,10-tetraazacyclododecane (I) was obtained from Aldrich.

4-Oxa-1,7,10,13-tetraazabicyclo[8.5.2]heptadecane (II). A sample of 4 g finely ground potassium carbonate was added to a solution of 1.72 g (10 mmoles) cyclene I in 100 ml dry acetonitrile, heated to reflux, and then a solution of 3.32 g (8 mmoles) diethyleneglycol ditosylate in 40 ml acetonitrile was added slowly. The reaction mixture was maintained at this temperature for 4 h, cooled, and filtered. The residue was extracted with hot benzene and the solution was evaporated in vacuum. The oily residue was crystallized from heptane to give 0.35 g (18%) II, mp 127-129°C.

4-*p*-Toluenesulfonyl-1,4,7,10,13-pentaazabicyclo[8.5.2]heptadecane (III). A mixture of 0.86 g (5 mmoles) cyclene I and 3 g roasted potassium carbonate in 50 ml acetonitrile was heated with stirring to reflux and, then, 2.83 g (5 mmoles) diethanolamine tritosylate in 30 ml acetonitrile was added over 1 h. The reaction mixture was heated at reflux with stirring for 5 h. After cooling and filtration, the residue was treated with hot heptane. The crystalline product was recrystallized from hexane to give 0.61 g (37%) III, mp 141-143°C.

4,7-Dioxa-1,10,13,16-tetraazabicyclo[8.8.2]icosane (IV). A mixture of 1.72 g (10 mmoles) cyclene I and 3 g roasted potassium carbonate in 100 ml acetonitrile was heated to reflux, and then 4 12 g (9 mmoles) triethyleneglycol ditosylate in 50 ml acetonitrile was added dropwise. The mixture was stirred for an additional 4 h, cooled, and evaporated. The light yellow product was treated with hot hexane. The residue after decantation and distillation of the solvent in vacuum was recrystallized from pentane to give 1.00 g (39%) IV, mp 109-111°C.

4,7-Di-*p*-toluenesulfonyl-1,4,7,10,13,16-hexaazabicyclo[8.8.2]icosane (V). A sample of 3.44 g (20 mmoles) cyclene I was dissolved in 80 ml hot acetonitrile, and then 6 g potassium carbonate was added with stirring. A mixture of 15.28 g (20 mmoles) N,N′-bis(2-hydroxyethyl)ethylenediamine in 150 ml dry acetonitrile was added at reflux. The reaction mixture was maintained for an additional 4 h at reflux. The mixture was filtered upon cooling. The residue was washed with acetonitrile and the organic phase was evaporated at reduced pressure. The residue was recrystallized from 3:1 acetone—hexane to give 7.22 g (61%) V, mp 218-219°C.

4,4′,7,7′-Ethylenebis(1-oxa-4,7-diazacyclonone) (VI). A sample of 5 g finely ground potassium carbonate was added to a solution of 1.72 g (0.01 mole) 1,4,7,10-tetraazacyclododecane (I) in 100 ml dry acetonitrile and heated to reflux upon stirring. A solution of 8.29 g (0.02 mole) diethyleneglycol (II) in 50 ml dry acetonitrile was added slowly to the mixture at reflux. The reaction mixture was heated at reflux for 6 h, cooled, and filtered. The residue was washed with hot acetonitrile and combined with the filtrate. Evaporation in vacuum gave an oil, which was treated with hot hexane, which was then also evaporated. The pale oil obtained was recrystallized from pentane to give 1.30 g (42%) VI, mp 74-75°C.

1,4,7,10,13-Pentaazabicyclo[8.5.2]heptadecane (VII). A mixture of 1.97 g (5 mmoles) III in 10 ml concentrated sulfuric acid was heated with stirring to 100°C and maintained at this temperature for 24 h. After cooling, 100 ml cold ether was slowly added to the reaction mixture and filtered. The precipitate was dissolved in a minimal amount of water and saturated with granulated lye. The product was extracted with hot benzene. The extract was evaporated to give 0.62 g (51%).

1,4,7,10,13,16-Hexaazabicyclo[8.8.2]icosane (VIII) was obtained from 5.92 g (10 mmoles) V in 50 ml concentrated sulfuric acid by analogy to VII. The yield of the oily product, which begins to crystallize upon standing, was 1.67 g (59%).

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REFERENCES

1. M. Hiraoka, Crown Compounds [Russian translation], Mir, Moscow (1988), p. 77.
2. B. Dietrich, J. M. Lehn, J. P. Sauvage, and J. Blanzat, Tetrahedron, **29**, 1629 (1973).
3. N. Wester and F. Vogtle, Chem. Ber., **112**, 3723 (1979).
4. N. Wester and F. Vogtle, Chem. Ber., **113**, 1487 (1980).
5. A. H. Alberis, R. Annunziata, and J. M. Lehn, J. Am. Chem. Soc., **99**, 8502 (1977).
6. T. Alfheim, J. Dale, and P. Croth, J. Chem. Soc., Chem. Commun., No. 22, 1502 (1984).
7. M. J. Calverley and J. Dale, J. Chem. Soc., Chem. Commun., No. 20, 1084 (1981).
8. R. Annunziata, F. Montznari, and S. Quici, J. Chem. Soc., Chem. Commun., No. 15, 777 (1981).
9. A. V. Lobach, S. S. Basok, V. N. Shcherbakov, and L. K. Ostrovskaya, Reference Handbook for Reagents and High-Purity Substances [in Russian], NIITÉKhIM, Moscow (1983), No. 3, p. 41.