POLYFUNCTIONAL MACROHETEROCYCLES. 7.* SYNTHETIC ENZYME ANALOGS. SYNTHESIS OF 16- AND 22-MEMBERED NITROGEN AND SULFUR CROWN COMPOUNDS CONTAINING EXOCYCLIC HISTAMINE AND HISTIDINE FRAGMENTS AND CARBOXYL GROUPS

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The acid hydrolysis of 9,14-bis(2-methoxycarbonylethyl)-11-12-benzo-3,4-(4',5'-dimethylbenzo)-10,13-dioxo-1,6-dithia-9,14-diazacyclohexadeca-3,11-diene leads to the corresponding 9,14-biscarboxy derivative. The reaction of 4,9,15,20-tetrakis-(2-methoxycarbonylethyl)-6,7,17,18-dibenzo-5,8,16,19-tetraoxo-1,12-dithia-4,9,15,20-tetraazacyclodocosa-6,17-diene with hydrazine hydrate and subsequent treatment with $NaNO_2$ gave the corresponding tetraazide. The reaction of this tetraazide with histamine and histidine leads to macroheterocycles, containing exocyclic histamine and histidine fragments.

The rapid progress in the chemistry of polyfunctional macroheterocycles is attributed to the possibility of their use in supramolecular chemistry as endo- and exoreceptors for binding cations, anions, or neutral molecules [2, 3]. Thus, macrocyclic receptors are capable of binding a substrate in the macrocycle cavity and catalyzing the hydrolysis of its peptide or ester bonds using exocyclic catalytically active functional groups [2-4]. Such compounds are models for the active sites of papain and α-chymotrypsin [3, 4]. Complexes of macroheterocycles with metal ions are models for the active sites of metalloenzymes [5]. The metal ion with the macroheterocycle environment may act as a Lewis acid site and bind nucleophilic species such as hydroxide and thiolate anions (cascade type of anion binding by the macroheterocycle). Then, the nucleophile becomes capable of adding to the carbon atom of an ester group, accelerating its hydrolysis [6]. The use of macroheterocycles and their complexes with metals for obtaining models of enzyme action holds considerable promise in the development of biomimetic chemistry and the chemistry of synthetic enzymes (synzymes) [7].

We have developed methods for the synthesis of polyfunctional nitrogen macroheterocycles [8-13]. The complexes of these compounds with cupric ions have spectral characteristics and oxidation—reduction potentials corresponding to the active sites of blue proteins and may be used as models in the study of metalloenzymes [14]. In previous work [1], we reported a synthesis for a nitrogen- and sulfur-containing macroheterocycle with exocyclic L-serine and histamine fragments. This macroheterocycle is a structural model for α-chymotrypsin.

The hydrolytic enzymes, carboxypeptidase and carboanhydrase, have a zinc ion at the active site, which is surrounded by donor carboxyl oxygen atoms or imidazole nitrogen atoms [15]. In order to obtain synzyme models for zinc-containing enzymes, we prepared nitrogen- and sulfur-containing crown compounds with exocyclic carboxyethyl groups and histamine or histidine fragments.

Macroheterocycles I and III were synthesized in our previous work [9, 13].

*For Communication 6, see [1].

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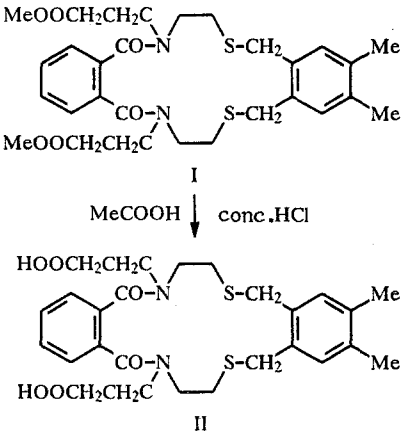
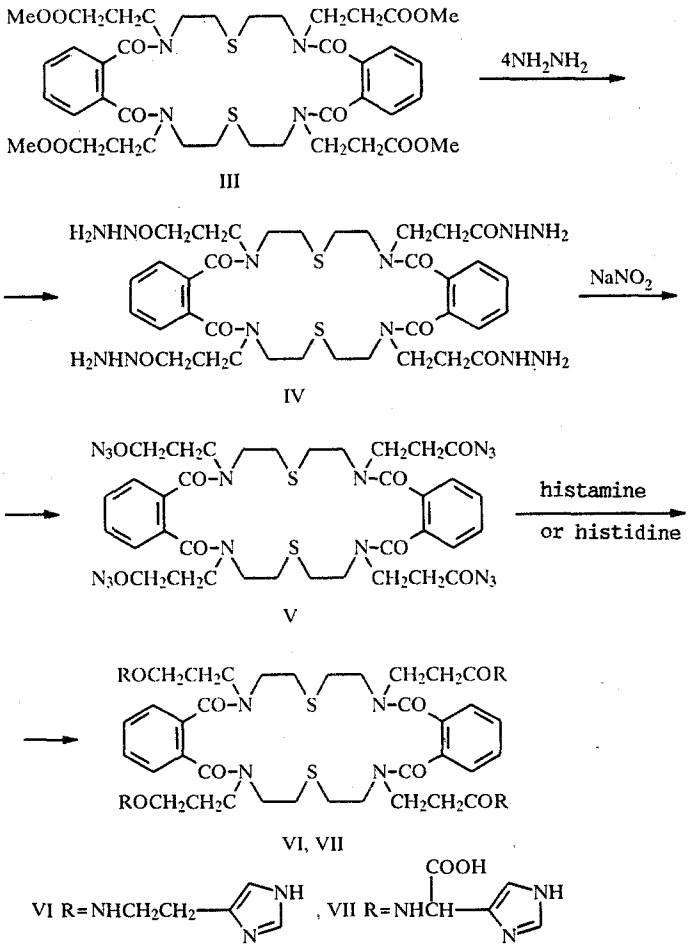


Acid hydrolysis of crown compound I affects only the exocyclic ether groups. The endocyclic amide groups are not hydrolyzed under these conditions due to steric hindrance by the benzene rings of the macrocycle and 2-methoxycarbonylethyl groups. The yield of macrocycle II is 70%.



The reaction of macroheterocycle III with hydrazine hydrate upon heating in absolute ethanol leads to tetrahydrazide IV. The treatment of IV with $NaNO_2$ leads to unstable tetraazide V. The reaction of V used without prior purification and histamine leads to macrocycle VI, while the reaction with histidine gives crown compound VII.

The IR spectra of macroheterocycles II, IV, VI, and VII have amide group bands at 1645 cm^{-1}. The spectrum of crown compound II has a broad band at 3030-2400 cm^{-1} as well as bands at 1730 and 1410 cm^{-1} characteristic for the CO_2H

group. The NH groups in macrocycles IV, VI, and VII absorb at 3300 cm^{-1}, while the frequency for the C=N bond in VI and VII is at 1660 cm^{-1}. The spectrum of macroheterocycle VII has bands for the N^+H_2 group at 3070, 1645, and 1560 cm^{-1}. The bands for the ionized carboxyl group are found at 1590 and 1375 cm^{-1}.

EXPERIMENTAL

The IR spectra were taken on a UR-20 spectrometer. The PMR spectra were taken on a Tesla BS-497 spectrometer at 100 MHz with $CDCl_3$ as the solvent and HMDS as the internal standard.

9,14-Bis(2-carboxyethyl)-11,12-benzo-3,4-(4′,5′-dimethylbenzo)-10,13-dioxo-1,6-dithia-9,14-diazacyclohexadeca-3,11-diene (II, $C_{28}H_{30}N_2O_6S_2$). A mixture of 5.82 g (0.01 mole) macroheterocycle I in 50 ml glacial acetic acid and 10 ml concentrated hydrochloric acid was heated at 100°C for 2 h. The solvent was distilled off and the residue was recrystallized from ethanol, mp 268-270°C. The yield of II was 3.9 g (70%).

4,9,15,20-Tetrakis[(3′-oxohydrazonium)propyl]-6,7,17,18-dibenzo-5,8,16,19-tetraoxo-1,12-dithia-4,9,15,20-tetraazacyclodocosa-6,17-diene (IV, $C_{36}H_{56}N_{12}O_{12}S_2$). A solution of 0.84 g (1 mmole) macrocycle III in 20 ml dry ethanol was added slowly to a solution of 0.5 g hydrazine hydrate in 20 ml ethanol at reflux. The mixture was heated at reflux for 5 min. The oily product was precipitated by the addition of ether. The yield of IV was 0.69 g (80%).

4,9,15,20-Tetrakis[(3′-oxo-4′-aza-6′-imidazolium)hexyl]-6,7,17,18-dibenzo-5,8,16,19-tetraoxo-1,12-dithia-4,9,15,20-tetraazacyclodocosa-6,17-diene (VI, $C_{56}H_{72}N_{16}O_8S_2$). A sample of 0.86 g (1 mmole) macrocycle IV in 5 ml chloroform was added to a flask containing 2 ml concentrated hydrochloric acid and 4.0 g crushed ice. A sample of 0.6 g $NaNO_2$ in 15 ml water was added to the vigorously stirred mixture, maintaining the temperature at ≤ 10°C. The solution turned pink and then V precipitated out as a pink oil. The solvent was decanted off and the residue was dissolved in 50 ml DMF. A sample of 0.4 g histamine in 50 ml DMF was added. The mixture was stirred at room temperature for 6 h and the greenish oil product was precipitated by the addition of ether. PMR spectrum: 2.74 (m, SCH_2), 2.92 (m, NCH_2), 7.21 ppm (m, C_6H_4). The yield of VI was 0.81 g (71%).

4,9,15,20-Tetrakis[(3′-oxo-4′-aza-5′-carboxy-5′-imidazolium)pentyl]6,7,17,18-dibenzo-5,8,16,19-tetraoxo-1,12-dithia-4,9,15,20-tetraazacyclodocosa-6,17-diene (VII, $C_{56}H_{64}N_{16}O_{16}S_2$). A sample of 0.56 g (4 mmoles) α-histidine in a mixture of 50 ml DMF and 20 ml water was added to a solution of 1.28 g (1 mmole) macrocycle V in 50 ml DMF. The mixture was stirred for 6 h. The solvent was distilled off. The residue was dissolved in DMF and precipitated by the addition of ether. PMR spectrum: 2.75 (m, SCH_2), 2.90 (m, NCH_2), 7.35 (m, C_6H_4), 9.61 ppm (s, CO_2H), mp 240-242°C. The yield of VII was 1.2 g (75%).

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