OLIGOOXATETRAAZACORONANDS (REVIEW)

V. M. Ostrovskaya and I. A. D'yakonova

UDC 547.898(047)

Information on methods of synthesis and the physicochemical and chemical properties of tetraazamacroheterocycles from classes of crown ethers, viz., amides and thioamides, urethanes, azomethines, formazans, and depsipeptides, that contain two or more oxygen atoms in their loops is correlated. The unique characteristics of their complexing with various groups of metals are noted.

In previous reviews [1, 2] a great deal of attention was directed to tetraazamacrocycles, particularly as models of natural compounds, and to their metal complexes. References to oxygen-containing tetraazamacrocycles began to appear later [3]. The present paper is devoted to macrocycles that contain in their loops four nitrogen atoms and two or more oxygen atoms in the form of groups such as oxa, carboxylato, iminocarboxylato, imino, nitrilo, amido, ureylene, thioureylene, azo, enamino, hydrazo, and formazan and do not have other condensed-on, bridged, anchor, and other such macroheterocycles. According to the nomenclature of Weber and Vogtle [4], they belong to the monocoronand series and can be designated as follows: {I} <O_nN_4-coronands>, where $n \geq 2$.

The methods used to obtain macrocycles are divided into two principal types: with the use of reactions involving the cyclization of two or more molecules and reactions involving intramolecular cyclization [5]. One should also take into account an additional method with the use of reactions involving the transformation of groupings, both those that are included in the loop of the macroheterocycle and those that are separated from it. Each of these methods may include acylation, arylation, and alkylation involving the oxygen and nitrogen atoms, condensation with the formation of C=N bonds, diazo coupling, etc. In the case of cyclization of two molecules, or the "usual two-component method" [6], the mechanism of the synthesis is not always clear: it is not known if it proceeds in two steps that include linear addition of the starting molecules with subsequent intramolecular cyclization or in one step with simultaneous orientation about the template cation.

The synthesis and properties of each class of oligooxatetraazamacrocycles are examined below.

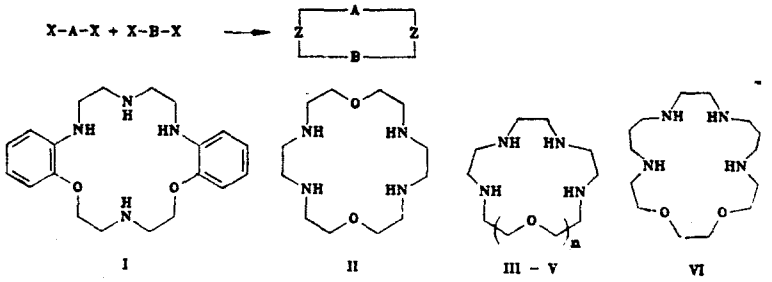
Tetraazacrown Ethers

Saturated polyaza polyethers are obtained by intramolecular cyclization of oligoethylene glycols that include primary and secondary amino groups or of α,ω-diamino compounds and polyamines with oligoethylene glycols or α,ω- dihaloalkanes, sometimes with the use of tosyl, trifluoroacetyl, or mesyl protection of the functional groups.

Cyclization proceeds under the condition of high dilution or the template effect. The method gives the best results for monoaza- and diazacrown ethers; the yields are lower in the case of triazacrown ethers, and approximately one half of the starting substances is recovered unchanged from the reaction mass. It is assumed [7] that this is due to a decrease in the template effect because of the softer (as compared with an O-donor) N-donor, which is not capable of complexing with the hard cation of an alkali metal. This assumption is even more valid for tetraazacrown ethers, viz., unsymmetrical I [8] and symmetrical II [9], and attempts to synthesize dibenzo-18-crown-6 analogs that contain five of six nitrogen atoms in place of oxygen atoms were unsuccessful [8].

All-Union Scientific-Research Institute of Chemical Reagents and Ultrapure Chemical Substances, Moscow 107258. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 7, pp. 867-882, July, 1987. Original article submitted August 23, 1985.

0009-3122/87/2307-0711$12.50



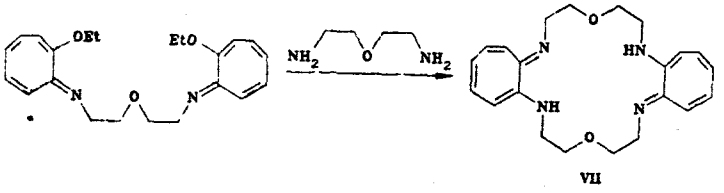
I II III – V VI

X=OH, OTs, NH_2, NHTs, NHMs, $NHCOCF_3$, Cl, Br; Z=O, NH; III n=2, IV n=3, V n=5

Serial tetraazacrown ethers III-V were obtained in two steps: by cyclization of tosylated triethylenetetraamines with tosylated polyethylene glycols [10] and subsequent removal of the tosyl protective group by sulfuric acid hydrolysis at 100°C [11]. The reaction is complicated by partial cleavage of the cyclic ethers. Of significance for stability is steric hindrance associated with the formation of NH...N hydrogen bridges, which can protonate an oxygen atom, thereby retarding the decomposition reaction.

A modification of the method of obtaining III and VI consists in the reaction of N-tosyltrialkylenetetraamines with dibromooxaalkanes in a two-phase catalytic system under conditions of interphase catalysis by tetrabutylammonium hydroxide with subsequent removal of the tosyl protective group with hydrogen bromide in glacial acetic acid or lithium aluminum hydride [12, 13].

Of great interest is a method of synthesis of azacrown compounds by cyclization that includes aminolysis of ether groups, as, for example, in the synthesis of tropocoronand VII [14, 15].



VII

X-ray diffraction analysis [14] of a complex of nickel with the tropocoronand showed that the ligand can realize a tetrahedral structure with elongated Ni–N bonds (1.946 Å) without participation of an oxygen atom in coordination.

Macrocycle III was also obtained by reduction of 1,4-dioxa-7,10,13,16-tetraazacyclooctadecane-6,17-dione with lithium aluminum hydride or diborane in tetrahydrofuran [16, 17].

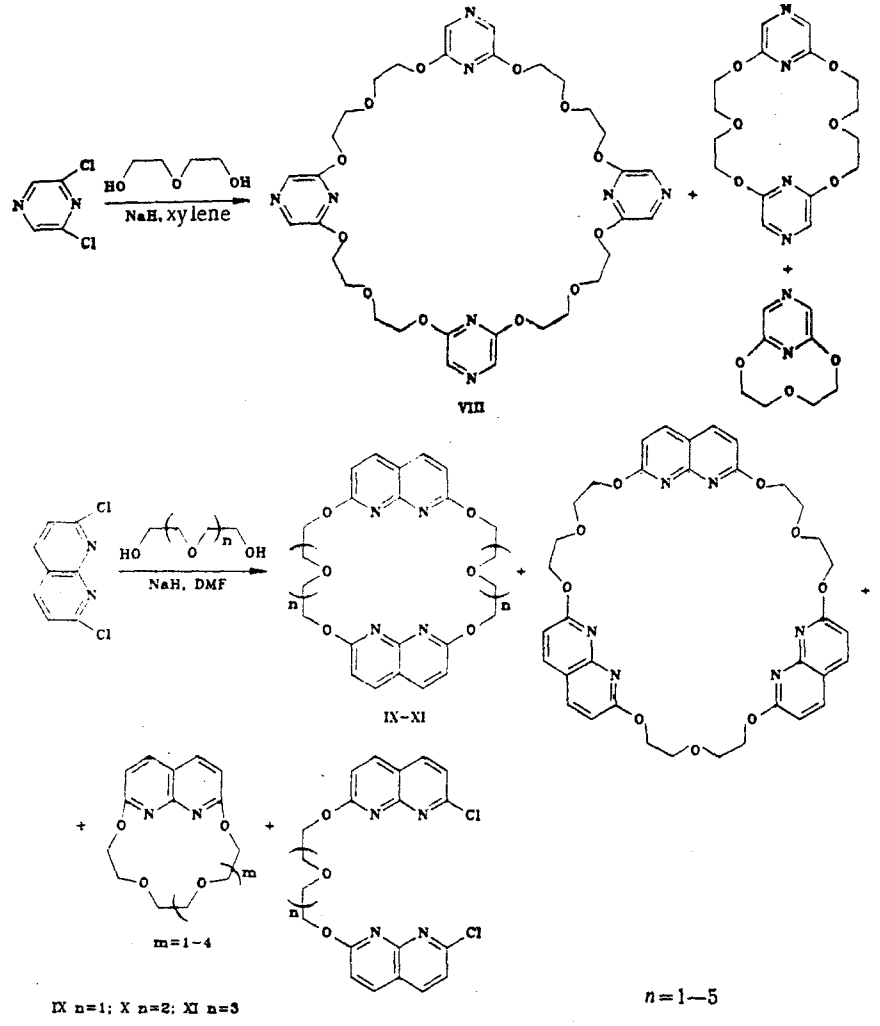
Condensed Heterocyclic Tetraazacrown Ethers

Tetraazacrown ethers with condensed-on six-membered nitrogen-containing heterocycles, the nitrogen atoms of which are included in the loop of the macrocycle, are obtained by [2 + 2]-cyclization of dihaloheterocycles with oligoethylene glycols or their heteroanalogs, of heterocyclic bases with α,ω-dihalo- or α,ω-ditosylatooligoethylene glycols, and of heterocyclic dicarboxylic acid chlorides with α,ω-diaminooligoethylene glycols.

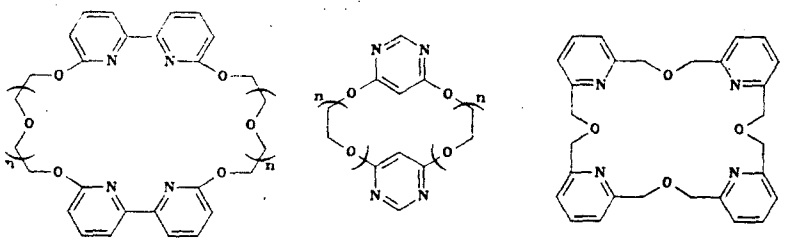
A series of such macrocycles was obtained by Newkome and co-workers [18-21]. Thus macrocycle VIII with four pyrazine fragments was isolated in 3% yield along with smaller macrocyclic analogs in the reaction of 2,6-dichloropyrazine with diethylene glycol [18] (see scheme VIII on following page).

(1,8-Naphthyridino)macrocycles IX-XI were isolated [19] from the complex mixtures of products of the reaction of 2,7-dichloro-1,8-naphthyridine with polyethylene glycols. The yields of macrocyclic products of [2 + 2]- and [1 + 1]-addition when n = 3-5 were, respectively 2% and 30-38%, whereas the yields when n = 1-2, like the yield of the [3 + 3]-analog, were insignificant (see scheme IX on following page).

Oligooxatetraazamacrocycles XII [20] and XIII [21], respectively, along with their diaza analogs, were obtained by the reaction of 6,6'-dibromo-2,2'-dipyridyl [20] or 4,6-dichloropyrimidine [21] with oligoethylene glycols.



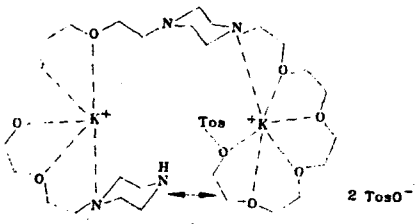
Tetrapyridyl-24-crown-8 XIV was synthesized by intracyclic alkylation of 2,6-bis(hydroxymethyl)pyridine with 2,6-bis(bromomethyl)pyridine in absolute THF with sodium hydride. This macrocycle undergoes "guest-host" complexing with tert-$BuNH_3^+SCN^-$. The constants and free energy of association were calculated for the complex, and these characteristics were compared with the characteristics of analogous macrocycles of other sizes [22].



1,2,8,9-(Diphthalyl)tetraaza-5,12-dioxacyclotetradecane, 1,2,8,9-(diphthalyl)tetraaza-5,12,15-trioxacycloheptadecane, and 1,2,11,12-(diphathalyl)tetraaza-5,8,15,18-tetraoxacyclodecane were obtained [23] from 3,8-dioxobenzopyridazine and the corresponding dichlorides — di-, tri-, and tetraethyl glycol derivatives — in DMF at 90-95°C in the presence of lithium hydride; the yields were, respectively, 26, 12, and 5%.

Azacrowns with piperazine fragments — 1,10,13,22-tetraaza-4,7,16,18-tetraxoatricyclo [20.2.2^{10,13,1,22}]octacosane, 1,13,16,28-tetraaza-4,7,10,19,22,25-hexaxatricyclo[26.2.2^{13,16,1,28}]-triacontane, and 1,16,19,34-tetraaza-4,7,10,13,22,25,28,31-octaoxatricylo[32.2.2^{16,19,1,34}] tetracontaine — were obtained by the reaction of piperazine of N,N'-bis(2-hydroxyethyl)piper-

azine with polyethylene glycol ditosylates in the presence of LiH/Na, NaH, and KH, respectively, in 15, 29, and 42% yields [24]. Chenevert and Plante [24] explain the high yield of the 36-membered macrocycle by the double template effect of the doubly charged potassium complex.



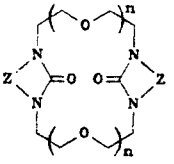
These mixed ligands have the ability to tie up ions of alkali, alkaline-earth, and transition metals [24].

1,11-Dioxo-5,8-dioxa-2,12-diaza[12](6,6')-2,2'-bipyridinophan and 1,15-dioxo-5,8,11-trioxa-2,14-diaza[15](6')-2,2'-bipyridinophan were obtained in 59 and 24% yields, respectively, from (6,6')-dichloroformyl-2,2'-dipyridyl and the corresponding diamine under high-dilution conditions [25].

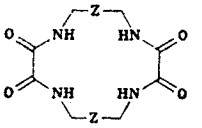
Amide Crown Compounds

The interest in crown ether ligand systems with CO—NH groups is due to the fact that they are found in natural compounds and to their specific complexing properties [26]. They can be obtained by [2 + 2]-cyclization of the ready-made amides with α,ω-dihalo- or ditosylato-oligoethylene glycols, as well as by the intracyclic formation of amide groups in the process of aminolysis of the ester groups and acylation of the amino groups. The technique of high dilution or the template method with appropriate protection of the nitrogen atoms is usually employed.

Macrocycles XV-XVII were synthesized by alkylation of, respectively, benzimidazolone with oligohydroxyethylene α-ω-dichlorides in DMF in the presence of lithium hydride [27, 28] and 2(1H)-tetrahydropyrimidinone with hexaethylene glycol ditosylate in THF in the presence of sodium hydride [29]. The principal products in these reactions were monomeric analogs with one urea fragment in the ring.



XV–XVII



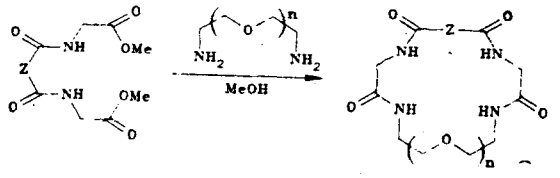
XVIII–XX

XV n=1, Z=o-C_6H_4; XVI n=2, Z=o-C_6H_4; XVII n=5, Z=$(CH_2)_3$; XVIII Z=CH_2OCH_2; XIX Z=$(CH_2OCH_2)_2$; XX Z=$(CH_2)_2OCH_2C(CH_3)_2CH_2O(CH_2)_2$

The complexing ability of macrocycle XV decreases in the order $Na^+ > Ba^{2+} > Ca^{2+}$, $Li^+ > Mg^{2+}$, Sr^{2+}, while that of macrocycle XVI decreases in the order Li^+, Na^+, $Sr^{2+} > Mg^{2+}$, Ba^{2+}, NH_4^+ Ca^{2+} [30]. Both the ether and carbonyl oxygen atoms participate in coordination with the hard ions [27-30].

1,10-Dioxa-4,7,13,16-tetraazacyclooctadecane-5,6,14,15-tetraone (SVIII), 1,4,13,16-tetraoxa-7,10,19,22-tetraazacyclotetracosa-8,9,20,21-tetraone (XIX), and 3,3,18,18-tetramethyl-1,5,16,20-tetraoxa-9,12,24,27-tetraazacyclotriaconta-10,11,25,26-tetraone (XX) were synthesized [31] by aminolysis of dimethyl oxalate with, respectively, 3-oxa-1,5-pentanediamine, 3,6-dioxa-1,8-octanediamine, and 6,6-dimethyl-4,8-dioxa-1,11-undecanediamine in methanol under high-dilution conditions; the yields were 60-75%.

Macrocyclic tetraamides XXI-XXIII were obtained by the reaction of oxalic, succinic, adipic, diglycolic, and triglycolic acid N,N'-bis(methoxycarbonylmethyl)diamides (the concentration of the reacting substances was 0.3 mole/liter). A decrease in the reagent concentration does not affect the yields of the macrocycles, which range from 8 to 16% [32]. 7,10-Dioxa-1,4,11,14-tetraazacycloicosanyl-3,14,17,20-tetraone was also previously obtained [33] from succinic acid N,N-bis(methoxycarbonylmethyl)diamide and 1,10-diamino-4,7-dioxadecane.



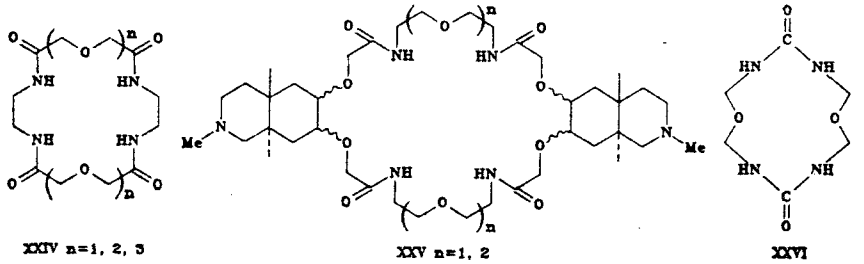
XXI–XXIII

XXI n=1, Z=$(CH_2)_2$; n=2, Z=–; n=1, Z=$(CH_2)_4$; n=2, Z=$(CH_2)_4$; n=1, Z=CH_2OCH_2; n=2, Z=$(CH_2OCH_2)_2$; XXII n=2, Z=$(CH_2)_2$; XXIII n=2, Z=$(CH_2OCH_2)_2$

A shift of all of the groups of signals to weak field is observed in the PMR spectra when alkali and alkaline-earth metal salts are added to solutions of macrocyclic tetraamides in deuteromethanol; this is associated with the formation of complexes [33]. Macrocycle XXIII is a membrane-active selective complexone in dialysis and electrodialysis [34]. Its sensitivity to cations changes in the order $Cu^{2+} > Ca^{2+} > Ni^{2+} > Zn^{2+} > Li^{+} > K^{+} > Na^{+} > Cs^{+}$ [35].

Macrocycles XXIV were obtained by acylation of ethylenediamine with oligoethylene glycol dicarboxylic acid chlorides under high-dilution conditions [36], while macrocycles XXV, which form complexes with alkali-metal salts, were obtained by acylation of 1,5- and 1,8-diaminoethylene glycols with stereoisomeric 2-methyl-6,7-bis(carboxymethoxy)perhydroisoquinolines [37].

The cyclization of diisocyanatodimethyl ether with its hydrolysis product leads to 1,7-dioxa-3,5,9,11-tetraazacyclododecane-4,10-dione (XXVI) [38].



XXIV n=1, 2, 3 XXV n=1, 2 XXVI

However, Tabushi and co-workers [16, 17] feel that the most convenient general synthetic method for obtaining macrocyclic amides that contain oxygen atoms is cyclization through aminolysis of the easily obtainable α-ω-dicarboxylic acid diethyl esters by commercially available polyethylene polyamines.

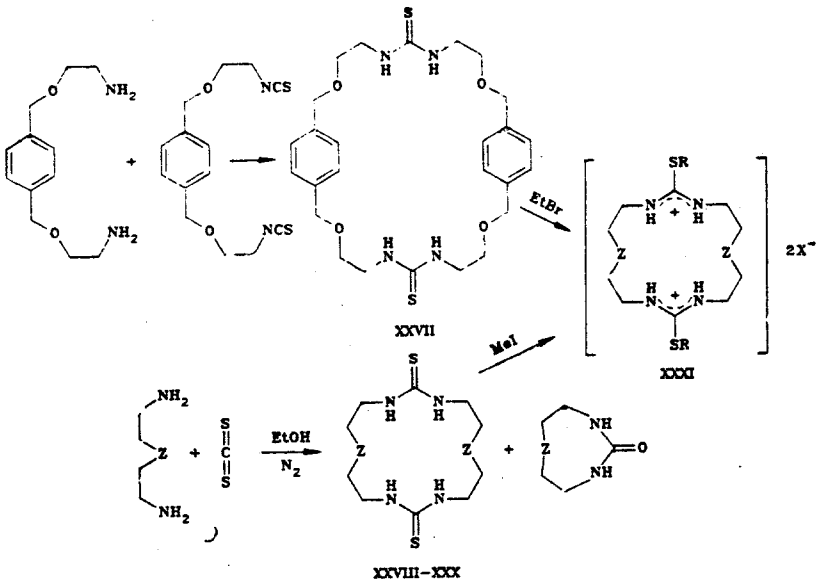
Macrocyclic Oligooxathioureas

Macrocycles that contain thiourea and crown-ether fragments are of interest as ligands and valuable intermediate reagents. They were obtained by the reaction of diamines with diisothiocyanates [39] or with carbon disulfide [40, 41] under high-dilution conditions (see scheme on following page).

The yield of coronand XXVII was 80%. Dithiones XXVIII-XXX were obtained in 18, 8, and 5% yields, respectively, i.e., the yield decreases with an increase in the ring size, since the principal reaction products are monomers. Macrocycle XXVIII undergoes ion-molecular reactions with the ions of the acetylacetonates of some rare-earth elements in the gas phase [42]. Compounds XXVIII and XXIX have ion-selective properties and membrane-active activity in the transfer of Li^{+}, K^{+}, Cs^{+}, Rb^{+}, Ca^{2+}, Cu^{2+}, and Zn^{2+} ions in dialysis and electrodialysis [34]. Macrocyclic thioureas XXVIII-XXX react with $CoCl_2$ in butanol or in a mixture of butanol with acetone [43] to form pseudotetrahedral complexes with a CoS_2Cl_2 coordination node; both sulfur atoms are coordinated in the bidentate ligands. The complexes are not electrolytes, and consequently, the atoms are coordinated with the metal. The fact that the bands of the stretching vibrations are shifted to the lower-frequency region in the absorption spectra in the case of complexing constitutes evidence for the absence of a nitrogen–metal interaction.

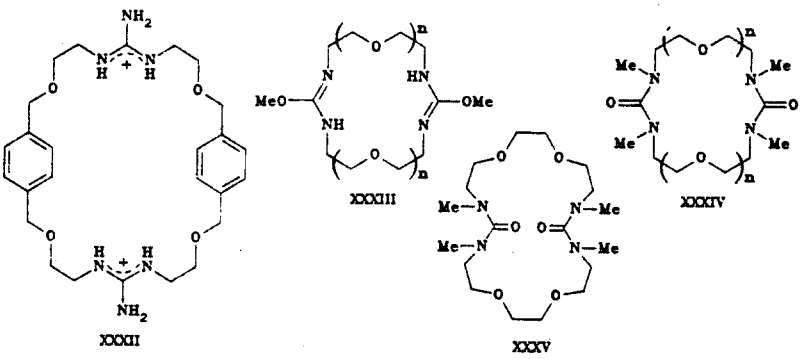
1,3,12,14-Tetramethyl-6,9,17,20-tetraoxa-1,3,12,14-tetraazacyclodocosane-2,13-dithione was obtained by methylation of macrocycle XXIX under conditions of phase-transition catalysis in the absence of water [44].

The action of ethyl bromide in ethanol on macrocycle XXVII [39] and the action of methyl iodide in methanol on macrocycles XXVIII-XXX [45-47] lead to the formation of S-alkylthiuronium



VIII Z=O, XXIX Z=O(CH$_2$)$_2$O, XXX Z=O(CH$_2$)$_2$O(CH$_2$)$_2$O, XXXI X=Br, R=Et; X=I, R=Me

salts XXXI [45-47], of which the bromides are converted to bis(guanidinium) salt XXXII under the influence of ammonia [39], while the iodides are converted to macrocyclic polyhydroxyethyleneisoureas XXXIII [45] under the influence of anhydrous sodium carbonate or sodium methoxide under interphase-catalysis conditions with triethylbenzylammonium chloride and crown ethers as the catalysts [45] or to cyclic N-N'-dialkylureas XXXIV under the influence of aqueous alkali and the same catalysts [46, 47].



XXXIII, XXXIV n=1,2

Macroheterocycles XXXIV are complexing agents for ions and take on conformation XXXV upon complexing with lithium; this conformation results in the decrease in the size of the cavity that is necessary to ensure complexing with ions of the metal [48].

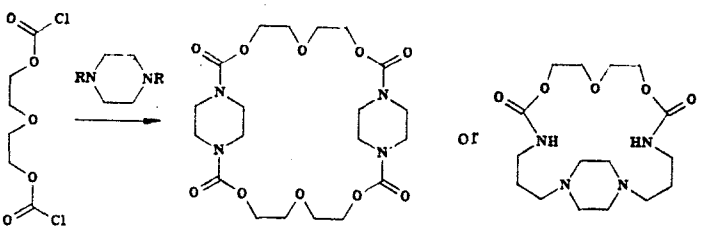
Anionic ligand XXXII reacts with PO_4^{3-} to form a 1:1 complex with manifestation of chelate and macrocyclic effects [39].

Macrocyclic Urethanes

Crown compounds with urethane structural fragments — 2,10,15,23-tetraoxo-1,11,14,24-tetraaza-3,6,9,16,19,22-dexaoxatricyclo[22.2.2^{11,14,1,20}]triacontane and 6,14-dioxo-1,5,15,19-tetraaza-7,10,13-trioxabicyclo[17.2.2^{1,19}]tricosane — were obtained [26] by cyclization of the bis(chlorocarbonyl) derivative of diethylene glycol with diamines under high-dilution conditions; the yields were 35 and 59%, respectively. Without the use of the dilution principle the yields of these crown compounds do not exceed 10%.

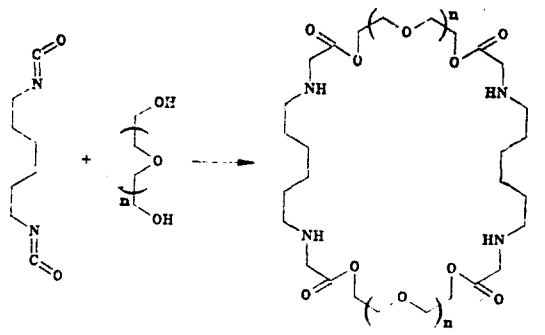
These macrocycles were found to be ligands that are incapable of dissolving potassium and sodium permanganates in chloroform (see scheme on following page).

Cyclic urethanes XXXVI were obtained by the reaction of two molecules of diethylene glycol or triethylene glycol with two molecules of hexamethylene diisocyanate under high-dilution



R=H, $(CH_2)_3NH_2$

conditions [49]. They form complexes with the composition $(ZnCl_2 \cdot L)_n$, where n = 1-3. A shift of the signals of the protons to weak field as compared with the free ligand is observed in the PMR spectra of the resulting complexes; the maximum shifts were noted for the CH_2OCH_2 ($\Delta\delta$ = 0.06 ppm) and CH_2OCO ($\Delta\delta$ = 0.04 ppm) groups. The values for the protons attached to the nitrogen atom of the urethane group and to the methylene groups remained unchanged. On the basis of these data it was concluded that only the oxygen atoms of the cyclic urethanes participate in complexing.

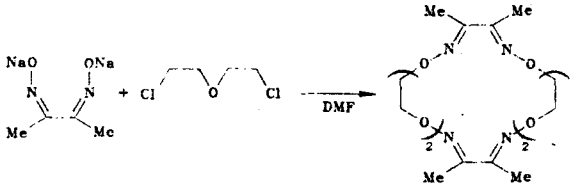


XXXVI n = 1,2

Crown Azomethines

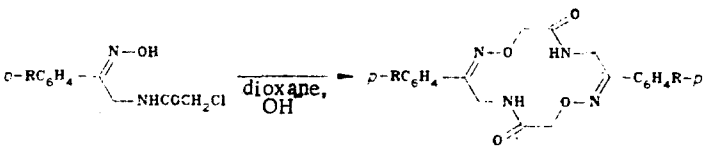
Advances in the synthesis and coordination chemistry of macrocyclic Schiff bases have been noted [50]. These macrocycles can be obtained by two methods: by cyclization of oximes with dichlorides or by template C=N condensation of dialdehydes with diamines.

Thus 14,15,20,21-tetramethyl-1,4,7,12,15,18-hexaoxa-13,16,19,20-tetraazacyclodocosatetraene (XXXVII) was obtained in 1.7% yield by cyclization of sodium dimethylglyoximate with 1,5-dichloro-3-oxapentane [51].



XXXVII

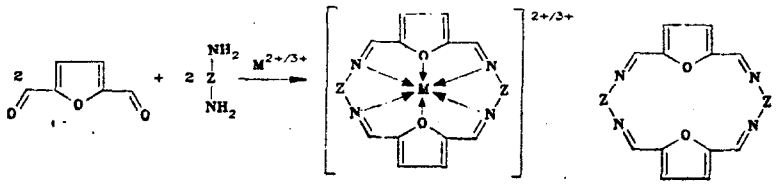
1,10-Diaryl-1,8-dioxa-2,5,9,12-tetraazacyclotetradeca-2,4-diene-6,13-diones XXXVIII were obtained in 29-35% yields by self-cyclization of α-(chloroacetamido)acetophenone oximes.



R=H, Me, OMe

XXXVIII

Reactions involving condensation between dicarbonyl compounds and diamines have played an important role in the development of the synthesis of tetraazamethine macrocycles [53], which is realized most effectively in the presence of template metal ions. Complexes of <<N_4O_2>>-macrocyclic ligands with alkaline-earth and rare-earth metals were obtained by [2 + 2]-condensation of 2,5-diformylfuran with diamines in the presence of these metals [54-57].



Z = $(CH_2)_2$, $(CH_2)_3$, CH=CH—CH_2, o-C_6H_4

The effectiveness of the template activity of the metal depends on the type of diamine; thus cyclization with ethylenediamine proceeds in the presence of La^{3+}, Ce^{3+}, Pr^{3+}, Nd^{3+}, Sm^{3+}, and Eu^{3+}, with 1,3-propanediamine in the presence of La^{3+}, Ce^{3+}, Pr^{3+} [53], and Ba^{2+} [55], and with o-phenylenediamine in the presence of Ba^{2+}, Ca^{2+}, Sr^{2+}, and Rb^{2+} [57]. It was found that Li^+, Na^+, and Mg^{2+} and the transition-metal ions Mn^{2+}, Zn^{2+}, Ag^+, and Cd^{2+} are ineffective [57]. Viscous oils with oligomeric or polymeric structures are formed in the absence of metals [53, 57]. In all cases the complexes had a 1:1 metal—macrocycle composition, except for the complex with barium $BaQ_2(ClO_4)_2$ (Q = o-C_6H_4), which has a sandwich structure, is quite stable, and does not dissociate in solution. These complexes are matrices for obtaining other complexes by reactions involving transmetallation by $Cu^{+/2+}$, Co^{2+}, and Ni^{2+} ions with the formation of various mixed complexes [53, 55, 56], which could not be obtained by the direct template method [57].

X-ray diffraction analysis shows that for each macrocycle in the molecules of the Cu and Co complexes [53, 55, 56, 58, 59] there are two metal atoms, which are bonded to two nitrogen atoms in the 2 and 3 positions of the macrocycle and to bridged atoms of additional ligands. In the Ba complexes [57, 60] each metal atoms is bonded to two molecules of the macrocycle through both nitrogen and oxygen atoms.

Crown Formazans

Crown formazans are of interest as potentially multidentate reagents with increased structural rigidity and different sizes of the inner coordination cavity of the ring and as chromogenic redox indicators.

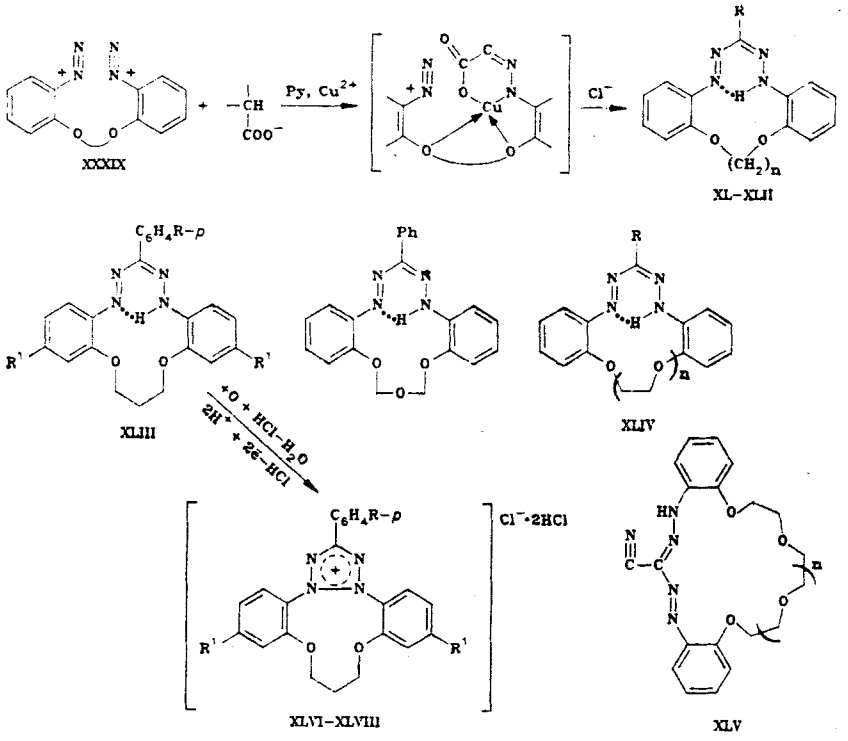
A series of oxygen-containing macrocycles of the do-, tri-, tetra-, penta-, hexa-, hepta-, and nonadecene and docosene systems that include in their rings a chromophoric redox-formazan grouping with H, CN, CH_3CO [61, 62], and Ar [63, 64] groups in the meso position was synthesized. They were obtained by diazo coupling of bis(diazotized) bis(2-aminoaryl)oligooxaalkanes XXXIX with compounds that contain active methylene and methylidyne groups — malonic, acetoacetic, cyanoacetic, phenylmalonic, and 4-nitrophenylacetic acids — in an alkaline medium with the addition of pyridine in the presence of small amounts of Cu(II).

An increase in the amount of Cu(II) in the reaction up to and beyond the stoichiometric amount leads to a decrease in the yields, while crown formazans are not formed in the absence of a metal under these conditions. The yields of crown formazans increase with a decrease in the ring size: for example, from 2% for the 22-membered crown formazan to 46% for the 13-membered compound (see scheme on the following page).

Regardless of the substitutents in the meso position, all of the 12- to 16-membered macrocycles have a stable intramolecular hydrogen bond of the "quasi-aromatic" formazan ring, which is weakened both with an increase in the size of the macrocycle and with intensification of the acceptor effect and a decrease in the size of the substituent in the meso position of the formazan group. A phenyl radical promotes the fixation of a chelate form [65, 66], while a cyano group weakens the hydrogen bond [67]. This effect is so strong for 19- to 22-membered macrocycles that cyanocrown formazans XLV exist in the open form. This is confirmed by the spectral data, which are in good agreement with one another. Weakening of the hydrogen bond is also indicated by the presence in the PMR spectra of narrow signals of NH protons, which are shifted from 18.9 ppm to 14.0 ppm with an increase in the size of the inner cavity of the macrocycle from 13 to 16 members.

The maxima of the curves of the absorption spectra of meso-phenylcrown formazans lie at 490-510 nm, as compared with 450-480 nm for meso-cyanocrown formazans [62]. With an increase in the ring size the principal maximum is shifted to the short-wave region; this is associated with weakening of the intramolecular NH...N bond.

Crown formazans with a small ring size (XL, XLII) do not form colored complexes with metals. Crown formazans XLI and XLIII, which have acceptor substituents, selectively give colored 1:1 complexes with lithium [62, 63].



XL R=Ph, n=1, 4—6; XLI R=CN, n=3; XLII R=H, n=3; XLIV R=Ph, n=1—4; R=CN, n=1, 2; XLV n=1, 2; XLVI R=R¹=H; XLVII R=NO_2, R¹=H; XLVIII R=H, R¹=NO_2

Cycloformazans XLIV not only form colored complexes [68, 69] with copper and mercury but also extract these metals from aqueous solutions of their nitrates and chlorides. Extraction depends to a greater degree on the nature of the substituent in the meso position than on the length of the crownlike chain. Copper is extracted by phenyl-substituted reagents in the form of 1:2 complexes and by cyano-substituted reagents in the form of 1:1 complexes. A 1:1 complex is formed with mercury.

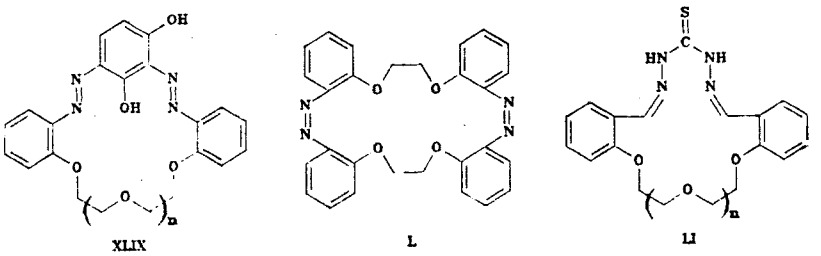
The reversible redox properties of meso-phenylcrown formazans have been studied [70]. The polarographic potentials of the half waves of their oxidation $E_{1/2}$ = 0.545-0.690 V and increase with an increase in the size of the macrocycle. Colorless condensed macrocyclic 2H-tetrazolium salts are formed by the action of chlorine or N-bromosuccinimide on solutions of intensely colored phenylcrown formazans in ethanol or chloroform.

Thus the oxidation of 16,17-dihydro-7-phenyl-5H-dibenzo[b, i][1, 11, 4, 5, 7, 8]dioxatetraazacyclotetradecene in ethanol with chlorine gave 10,11-dihydro-2-phenyldibenzo[b, f]-2H-tetrazolo[2, 3-d][1, 8, 4, 5]dioxadiazacycloundecenium chloride dihydrochloride (—0.31 V), which, like its nitro (XLVIII, —0.36 V) and dinitro (XXVIII, —0.28 V) analogs, is suitable for use as a chromogrenic indicator of the viability of seeds and living bacteria.

Azo- and Azinocrown Compounds

Bisazocrown compounds XLIX were obtained by diazo coupling of bis(2-aminophenyl)oligooxaalkanes XXXIX with resorcinol under high-dilution conditions [71], while L was obtained by the reaction of 2,2'-dihydroxyazobenzene with ethylene glycol ditosylate in THF in the presence of the calculated amount of potassium butoxide [72]; the yields were low.

Macrocyclic thiocarbohydrazides LI were synthesized by the reaction of dialdehyde with thiocarbohydrazide in aqueous alcohol.



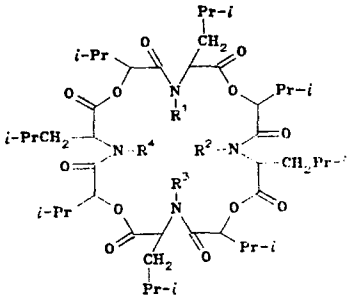
XLIX, LI n=1, 2

The complexing abilities of LI were studied. Depending on the nature of the metal, the reaction occurs with the sulfur atoms, the nitrogen atoms of the azomethine groups, or the oxygen atoms. Macrocycle LI (n = 2) is used as an extractant for the extraction of thallium [73].

Cyclooctadepsipeptides

Natural compounds and their analogs that contain amide and ester groupings in the loop of the ring are interesting.

The insecticide bassianolide (LII), which was isolated [74] from the mycelium of insectivorous fungi by repeated chromatography, exists in the form of two conformational isomers, which undergo cis–trans isomerization with respect to the amide bonds. The compound displays high biological activity: the lethal dose for silkworm larvae is 5-10 μg/1.2 g of their mass.

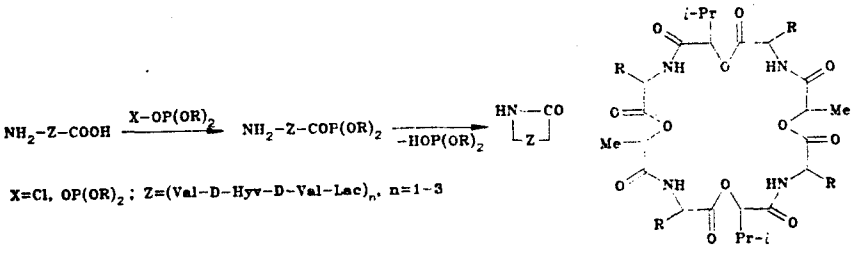


LII–LIV

LII $R^1=R^2=R^3=R^4=Me$; LIII $R^1=R^2=R^3=Me$, $R^4=H$; $R^1=R^2=Me$, $R^3=R^4=H$; $R^1=R^3=Me$, $R^2=R^4=H$; $R^1=Me$, $R^2=R^3=R^4=H$; LIV $R^1=R^2=R^4=H$

Analogs LIII, which contain less than four methyl groups, and analog LIV were obtained by cyclization of linear depsipeptides by the acyl-chloride method in benzene under high-dilution conditions. It was established that the presence of four methyl groups and a 24-membered ring is responsible for the biological activity of the depsipeptide [75].

A number of cyclodepsipeptides were obtained in order to ascertain the effect of the size of the ring and individual fragments on the biological activity of synthetic analogs of the ionophoric antibiotic valinomycin. Tetravalinomycin (n = 1), octavalinomycin LV (n = 2), and valinomycin (n = 3) were obtained by the phosphite method by reaction of unsubstituted linear depsipeptides with chlorophosphites and pyrophosphites to give mixed anhydrides, which underwent spontaneous intramolecular cyclization with yields of 52, 74, and 56%, respectively; this indicates the most stable conformation of the cyclooctadepsipeptide [76].



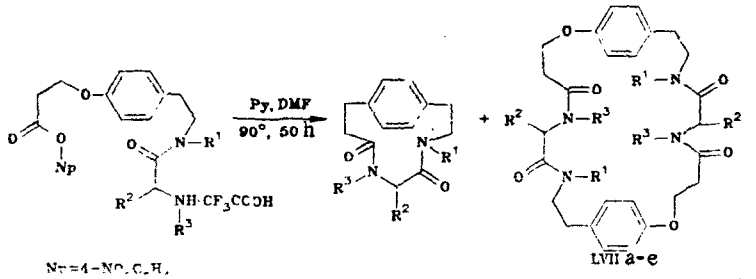
X=Cl, $OP(OR)_2$; Z=(Val–D–Hyv–D–Val–Lac)$_n$, n=1–3

LV R=*i*-Pr, LVI R=*s*-Bu

Octaisoleucinomycin LVI was obtained by cyclization of the linear depsipeptide by the acyl-chloride method under high-dilution conditions [77].

The ring size does not have a substantial effect on the conformation of the depsipeptide chain but does have a decisive effect on the selectivity of complexing with alkali-metal ions. Thus the 12-membered tetravalinomycin does not form complexes with Na^+, K^+, and Rb^+, while the 24-membered octavalinomycin and octaisoleucinomycin form more stable complexes with Na^+, which has effective radius R_e = 0.98 Å; the 36-membered valinomycin forms complexes with K^+ (R_e = 1.33 Å) and Rb^+ (R_e = 1.49 Å); and the 48-membered hexadecavalinomycin forms complexes with Cs^+ (R_e = 1.65 Å). Hexavalinomycin is also capable of transferring bulky organic cations: tetramethylammonium, chlorine, and acetylcholine.

It has been shown [78] that replacement of the isopropyl groups of valine and α-hydroxyisovaleric acid by smaller methyl groups leads to a certain decrease in the stability of potassium complexes and to a decrease in the tendency of macrocycles to be incorporated into the lipid zones of membranes due to a decrease in the overall hydrophobic character of the molecule. Although it is accompanied by an increase in the stability of the complex, replacement of the methyl groups of lactic acid residues by isopropyl groups retards the rates of its formation and destruction, and this leads to a decrease in the effectiveness of the ionophoric activity in two-layer membranes. The role of amino acid side chains in shielding of a cation bonded in the molecular cavity as a function of the interaction with the solvent and the manifestation of surface-active properties by the complex was ascertained.



LVII a R^1=Me, $R^2-R^3=(CH_2)_3$; b R^1=Me, R^2=*i*-Bu, R^3=H; c $R^1=R^3$=Me, R^2=*i*-Bu; d R^1=H, $R^2-R^3=(CH_2)_3$; $R^1=R^3$=H, R^2=*i*-Bu

Twenty-eight-membered cyclodesipeptides are obtained in low yields in the synthesis of 14-membered cyclopeptide alkaloids by cyclization of linear peptides with β elimination of a 3-phenoxypropanate grouping [79].

The highest yield (34%) was obtained for cyclo{3-[4-(2-aminoethyl)phenoxy]propanoyl-L-propyl}$_2$ (LVIId).

It has been demonstrated by circular dichroism that only 14-membered alkaloids display complexing properties with respect to Mg^{2+}, Ca^{2+}, and Li^+.

The synthesis of O_nN_4 macroheterocycles ($n \geq 2$) by cyclization of bifunctional reagents is complicated by the competitive formation of $O_{n/2}N_2$ macroheterocycles, products of linear polycondensation, and, to a small extent, $O_{3n/2}N_{4+2}$ and $O_{n/4}N$ macroheterocycles. Increases in the yields of oligooxatetraazamacrocycles can be achieved by the use of the high-dilution method, as well as interphase-catalysis conditions, in the synthesis of the template cations. At first glance, opposite tendencies are observed in the synthesis of O_nN_4 coronands: in some series of analogs the yield decreases with an increase in the ring size, whereas in others it increases and then may decrease; in the latter case this is sometimes caused by such strong steric factors that the formation of the smallest rings becomes impossible.

The complexing abilities of macroheterocycles depend on the presence of heteroatoms and functional groupings in the macrocyclic ring and, to a lesser degree, on the size of the ring itself and are manifested in different ways with respect to alkali, alkaline-earth, transition, heavy, and other metals. The complexing of O_nN_4 macroheterocycles with alkali metals occurs with the participation of an oxygen atom, and the nitrogen atom is ignored, even if it is in the loop of the macroheterocycle. Both the nitrogen and oxygen atoms may participate in the complexing of alkaline-earth and rare-earth elements. The interaction of the macroheterocycles with transition metals generally occurs with the participation of the donor nitrogen atoms, and the coordination number of the metal in the complex is satisfied not through the oxygen atoms but rather by additional clathrate molecules or anions with which the metal was bonded prior to complexing. The frequent assertion of the authors that the size of the macroring and the number of heteroatoms in it play the paramount role in coordination evidently is hardly true for transition and heavy metals. Thus, for example, Cu, Ag, Ni, and Co upon coordination often do not enter into the cavity of the tetraazaoligooxamacrocycle but rather are situated above the cavity, where each of them interacts with two close-lying nitrogen atoms situated along the sides of the ring or with nitrogen atoms from different molecules of the macrocycle. This exception in the coordination with the ether atoms of an O_nN_4 donor macrocycle is also responsible for the absence of a clearly expressed macrocyclic effect. Systematic results with respect to the dependence of the complexing properties on the structures of macrocycles of this type have not been accumulated to a sufficient extent.

Anionic ligands of this type form more stable complexes with a number of anions of mineral and organic acids than their acyclic analogs. Of particular interest is the ability of these compounds to form stable complexes with amino acids and nucleotides; this opens up the possibility of the selective extraction of the latter and their transport through artificial and biological membranes. The indicated compounds form stable complexes with anions in the range of neutral pH values; this is important with respect to their biological application [48].

A particularly great deal of attention is being directed to the selectivity of macrocycles with respect to their membrane activity, the biological activity of complexes, the chromogenic indicator properties, extraction in the separation of ions in analytical chemistry and technology, and obtaining catalysts. In this respect particularly interesting results were obtained in an investigation of analogs of natural compounds. Inasmuch as they are less accessible and more complex than crown ethers, diazacrown ethers, and tetraazamacrocycles, O_nN_4 macrocycles as yet remain virtually unused as effective synthetic tools in improving the yields of products, investigating new reactions, and monitoring the regio- and stereoselectivity of chemical reactions. Research regarding the preparation of redox indicators has been published, but there has been virtually no research dealing with the redox properties of macrocyclic ligands and their complexes as models of respiratory systems.

In a theoretical and practical respect the possibilities of this series of macroheterocycles have not been exhausted, and research in this direction is promising.

LITERATURE CITED

1. L. F. Lindoy, Chem. Soc. Rev., 4, 421 (1975).
2. F. Vögtle and E. Weber, Angew. Chem., Int. Ed., 18, 753 (1979).
3. G. W. Gokel, D. M. Dishong, R. A. Schultz, and V. J. Gatto, Synthesis, No. 12, 997 (1982).
4. E. Weber and F. Vögtle, Inorg. Chim. Acta, 45, 65 (1980).
5. M. Okahara, Chem. Ind., 33, 715 (1982).
6. F. Vögtle, E. Weber, and U. Elben, Kontakte, Merck (1980), No. 2, p. 36.
7. H. Maeda, S. Furuyoshi, Y. Nakatsuji, and M. Okahara, Bull. Chem. Soc. Hps., 56, 3073 (1983).
8. S. A. G. Högberg and D. J. Cram, J. Org. Chem., 40, 151 (1975).
9. C. J. Pedersen and M. H. Bromels, US Patent No. 3 847-949; Chem. Abstr., 82, 73049 (1975).
10. W. Rasshofer, W. Wehner, and F. Vögtle, Ann. Chem., No. 5, 916 (1976).
11. W. Rasshofer and F. Vögtle, Ann., No. 8, 1340 (1977).
12. A. V. Bogatskii, N. G. Luk'yanenko, S. S. Basok, and L. K. Ostrovskaya, in: 4th All-Union Symposium on Organic Synthesis [in Russian], Moscow (1984).
13. A. V. Bogatskii (Bogatsky), N. G. Luk'yanenko (Lukyanenko), S. S. Basok (Basoc), and L. K. Ostrovskaya, Synthesis, No. 2, 138 (1984).
14. S. Imajo and K. Nakanishi, J. Am. Chem. Soc., 105, 2071 (1983).
15. S. Imaki, T. Nodzoe, K. Nakanishi, and K. K. Santori, Japanese Patent No. 58-121285; Ref. Zh. Khim., 13N229P (1984).
16. I. Tabushi, H. Okino, and Y. Kuroda, Tetrahedron Lett., No. 48, 4339 (1976).
17. H. Kato, T. Hirai, I. Tabushi, Y. Kuroda, and H. Okino, Japanese Patent No. 77 106 882; Chem. Abstr., 88, 89730 (1978).
18. G. R. Newkome and A. T. Nayak, J. Org. Chem., 43, 409 (1978).
19. G. R. Newkome, S. J. Garbis, and V. K. Majestic, J. Org. Chem., 46, 833 (1981).
20. G. R. Newkome, A. Nayak, F. Fronczek, T. Kawata, H. C. R. Taylor, L. Maede, and W. Mattice, J. Am. Chem. Soc., 101, 4472 (1979).
21. G. R. Newkome, A. Nayak, M. G. Sorci, and W. H. Benton, J. Org. Chem., 44, 3812 (1979).
22. M. Newcomb, J. M. Timko, D. M. Walba, and D. J. Cram, J. Am. Chem. Soc., 99, 6392 (1977).
23. S. A. Vartanyan, T. R. Akopyan, E. G. Paronikyan, and G. M. Paronikyan, Armyansk. Khim. Zh., 34, 64 (1981).
24. R. Chenevert and R. Plante, Synthesis, No. 10, 847 (1983).
25. E. Buhleier, W. Wehner, and F. Vögtle, Chem. Ber., 111, 200 (1978).
26. E. Buhleier, K. Frensch, F. Luppertz, and F. Vögtle, Ann. Chem., No. 10, 1586 (1978).
27. M. M. Htay and O. Meth-Cohn, Tetrahedron Lett., No. 1, 79 (1976).
28. R. J. Hayword, M. M. Htay, and O. Meth-Cohn, Chem. Ind., No. 8, 373 (1977).
29. L. J. Kaplan, G. R. Weisman, and D. J. Cram, J. Org. Chem., 44, 2226 (1979).
30. M. M. Htay and O. Meth-Cohn, Tetrahedron Lett., No. 6, 469 (1976).
31. F. Vögtle and P. Dix, Ann. Chem., No. 10, 1698 (1977).

32. N. G. Luk'yanenko, A. V. Bogatskii, and Yu. A. Popkov, Khim. Geterotsikl. Soedin., No. 8, 1132 (1981).
33. N. G. Luk'yanenko, Yu. A. Popkov, and A. V. Bogatskii, Dokl. Akad. Nauk SSSR, 244, 106 (1979).
34. V. N. Golubev, A. D. Gutsol, A. V. Bogatskii, N. G. Luk'yanenko, T. I. Kirichenko, Yu. A. Popkov, and V. A. Shapkin, Dokl. Akad. Nauk SSSR, 271, 642 (1983).
35. V. N. Golubev and A. D. Gutsol, Élektrokhimiya, 19, 1588 (1983).
36. A. V. Bogatskii, and N. G. Luk'yanenko, in: Abstracts of Papers and Reports Presented at the 12th Mendeleev Conference on General and Applied Chemistry [in Russian], Vol. 1, Moscow (1981), p. 335.
37. L. I. Ukhova, A. N. Sergeeva, T. M. Tsvetkova, and G. I. Krivko, in: Summaries of Papers Presented at the 2nd All-Union Conference on the Chemistry of Macrocycles [in Russian], Odessa (1984), p. 20.
38. N. I. Popov, A. A. Lobanova, Z. A. Dobronravova, and I. G. Kaufman, Zh. Org. Khim., 16, 1551 (1980).
39. B. Dietrech, T. M. Fyles, J. M. Lehn, L. G. Pease, and D. L. Fyles, Chem. Commun., No. 21, 934 (1978).
40. A. V. Bogatskii, N. G. Luk'yanenko, and T. I. Kirichenko, Zh. Org. Khim., 16, 1301 (1980).
41. A. V. Bogat-skii (Bogatsky), N. G. Luk'yanenko (Lukyanenko), and T. I. Kirichenko, Tetrahedron Lett., No. 3, 313 (1980).
42. O. S. Timofeev, N. G. Luk'yanenko (Lukyanenko), T. I. Kirichenko, V. S. Kalishevich, A. V. Bogatskii,(Bogatsky), A. I. Gren, D. V. Zagorevskii, and Yu. S. Nekrasov, Inorg. Chim. Acta, 77, 245 (1983).
43. T. I. Kirichenko, A. V. Bogatskii and N. G. Luk'yanenko, Dokl. Akad. Nauk SSSR, 255, 594 (1980).
44. A. V. Bogatskii (Bogatsky), N. G. Luk'yanenko (Lukyanenko), T. I. Kirichenko, and V. V. Limich, Synthesis, No. 2, 136 (1984).
45. N. G. Luk'yanenko, A. V. Bogat-skii, T. I. Kirichenko, and S. V. Shcherbakov, Zh. Org. Khim., 17, 1279 (1981).
46. A. V. Bogatskii,(Bogatsky), N. G. Luk'yanenko (Lukyanenko), and T. I. Kirichenko, Synthesis, No. 6, 464 (1982).
47. A. V. Bogatskii N. G. Luk'yanenko, T. I. Kirichenko, V. V. Limich, and L. P. Karpenko, Zh. Org. Khim., 20, 101 (1984).
48. A. V. Bogatskii, Bioorg. Khim., 9, 1445 (1983).
49. T. E. Lipatova, L. F. Kosyanchuk, and T. S. Khramova, Teor. Éksp. Khim., No. 3, 323 (1983).
50. S. M. Nelson, Pure Appl. Chem., 52, 2461 (1980).
51. W. Rasshofer, W. M. Müller, and G. Oepen, J. Chem. Res., No. 2, 72 (1978).
52. H. Gnichtel and C. Graphoff, Ann. Chem., No. 11, 2038 (1983).
53. I. K. Bhoon and R. P. Singh, J. Inorg. Nucl. Chem., 43, 1685 (1981).
54. K. K. Abid and D. E. Fenton, Inorg. Chem. Acta, 82, 223 (1984).
55. S. M. Nelson, F. S. Esho, and M. G. B. Drew, Chem. Commun., No. 8, 388 (1981).
56. S. M. Nelson, F. S. Esho, A. Lavery, and M. G. B. Drew, J. Am. Chem. Soc., 105, 5693 (1983)
57. S. M. Nelson, F. S. Esho, and M. G. B. Drew, J. Chem. Soc., Dalton Trans., No. 9, 1857 (1983).
58. M. G. B. Drew, F. S. Esho, and S. M. Nelson, Inorg. Chim. Acta, 76, 269 (1983).
59. M. G. B. Drew, F. S. Esho, and S. M. Nelson, Chem. Commun., No. 23, 1347 (1982).
60. M. G. B. Drew, J. Chem. Soc., Dalton Trans., No. 8, 1653 (1983).
61. V. M. Dziomko, V. M. Ostrovskaya, and T. E. Zhukova, USSR Inventor's Certificate No. 682517; Byull. Izobret., No. 32 (1979).
62. V. M. Dziomko, V. M. Ostrovskaya, T. E. Zhukova, and Yu. S. Ryabokobylko, Zh. Obshch. Khim., 51, 2323 (1981).
63. V. M. Ostrovskaya, I. A. D'yakonova, and T. S. Palilova, USSR Inventor's Certificate No. 105700; Byull. Ozobret., No. 44 (1983).
64. V. M. Ostrovskaya and I. A. D'yakonova, in: Summaries of Papers Presented at the 2nd All-Union Conference on the Chemistry of Macrocycles [in Russian], Odessa (1984), p. 51.
65. N. P. Bednyagina, I. Ya. Postovskii, A. D. Garnovskii, and O. A. Osipov, Usp. Khim., 49, 1053 (1975).
66. I. Ya. Postovskii, I. V. Podgornaya, V. A. Popova, M. I. Ermakova, and O. V. Fedorova, Khim. Geterotsikl. Soedin., No. 11, 1479 (1981).
67. V. M. Dziomko, V. M. Ostrovskaya, and T. E. Zhukova, Khim. Geterotsikl. Soedin., No. 5, 530 (1979).
68. Yu. A. Zolotov, N. V. Niz'eva, V. P. Ionov, V. M. Dziomko, V. M. Ostrovskaya, and I. A. D'yakonova, USSR Inventor's Certificate No. 1060200; Byull. Izobr., No. 46 (1983).

69. N. V. Niz'eva, V. P. Ionov, I. V. Pletnev, D. M. Kumina, V. M. Ostrovskaya, I. A. D'yakova, and Yu. A. Zolotov, Dokl. Akad. Nauk SSSR, 274, 611 (1984).
70. V. M. Ostrovskaya, I. A. D'yakonova, and T. D. Nikolaeva, in: Summaries of Papers Presented at the 2nd All-Union Confernece on the Chemistry of Macrocycles [in Russian], Odessa (1984), p. 52.
71. A. V. Sultanov and S. B. Savvin, in: Summaries of Papers Presented at the 2nd All-Union Conference on the Chemistry of Macrocycles [in Russian], Odessa (1984), p. 205.
72. M. Shiga, M. Takagi, and K. Ueno, Chem. Lett., No. 8, 1021 (1980).
73. I. V. Podgornaya, Yu. A. Zolotov, V. A. Popova, V. A. Ionov, and O. V. Fedorova, USSR Inventor's Certificate No. 1122657; Byull. Izobr., No. 41 (1984).
74. M. Kanaoka, A. Isogai, S. Murakoshi, M. Ichinol, A. Suzuki, and S. Tamura, Agric. Biol. Chem., 42, 629 (1978).
75. A. Isogai, M. Kanaoka, and A. Suzuki, Pept. Chem., 16, 165 (1978); Chem. Abstr., 94, 103802 (1981).
76. M. Rothe and W. Kreiss, in: Peptides. Proceedings of the European Peptide Symposium (1976), p. 71.
77. L. A. Fonina, I. S. Savelov (Sawelow), G. G. Avotin' (Avotina), V. T. Ivanov (Ivanow), and Yu. A. Ovchinnikov, in: Peptides. Proceedings of the European Peptide Symposium (1976), p. 636.
78. L. A. Fonina, G. Ya. Avotin', T. A. Balashova, N. V. Starovoitova, L. B. Senyavina, I. S. Savelov, V. F. Bystrov, V. T. Ivanov, and Yu. A. Ovchinnikov, Bioorg. Khim., 6, 1285 (1980).
79. J. C. Lagarias, R. A. Houghten, and H. Rapoport, J. Am. Chem. Soc., 100, 8202 (1978).

WITTIG REARRANGEMENT OF ALLYL FURFURYL AND ALLYL THIENYL ETHERS AND SULFIDES AND THEIR BENZO-DERIVATIVES

A. V. Anisimov, L. V. Mozhaeva, N. B. Kazennova, S. V. Kuznetsova, and E. A. Viktorova

UDC 547.722'728'732.04:543.422.25

Treatment of allyl furfuryl ethers and sulfides with butyllithium results in metallation at the free α-position of the heterocycle, with partial Wittig rearrangement to the isomeric alcohols and sulfides and ring opening. With the benzo-derivatives, Wittig rearrangement and ring opening takes place.

The possibility of using the Wittig rearrangement in the synthesis of unsaturated hydroxy- and mercapto-derivatives of the aromatic series has demonstrated in the treatment of benzyl allyl ethers and sulfides with strong bases [1, 2]. The extension of this reaction to furans and thiophens provides a convenient method for the functionalization of these systems.

For this purpose, we examined the reactions of some allyl furfuryl and allyl thienyl ethers and sulfides, together with their benzo-derivatives, with the strong base butyllithium, which is widely employed for the generation of anionoid species.

It would be expected from the results of basic deuterium exchange experiments carried out with some of the starting compounds as a preliminary, (Table 1), that deprotonation on treatment with bases would take place for the most part at the methylene group between the heterocycle and the hetero-atom, and at the free α-position of the heterocyclic system.

The principal pathway in the reactions of 2-allyloxy-methyl- and 2-allylthiomethylbenzofurans (I) and (II) with butyllithium is metallation at the free 5-position of the furan ring, giving following silylation the 5-trimethylsilylfurans (III) and (VII). Additionally, deprotonation takes place at the methylene group located between the heterocycle and the hetero-

M. V. Lomonosov Moscow State University, Moscow 119899. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 7, pp. 883-888, July, 1987. Original article submitted January 15, 1986.

 0009-3122/87/2307-0724$12.50