THREE-MEMBERED HETEROCYCLES IN THE SYNTHESIS OF CROWN COMPOUNDS AND CRYPTANDS (REVIEW)

M. G. Voronkov, V. I. Knutov, and O. N. Shevko

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The cyclo-oligomerization of oxirane and aziridine and their derivatives in the presence of BF_3 *leads to the corresponding macroheterocyclic compounds. Crown compounds with exocyclic alkyl, aryl, or functional substituents are formed in the reaction of alkyl-, aryl-, and functionally substituted oxiranes or aziridines with dinucleophilic reagents with subsequent intramolecular cyclocondensation of the reaction products. Methods for the synthesis of cryptands that are based on the reaction of diazacrown compounds with diglycidyl ethers of oligoethyleneglycols are described. The reaction of tosylaziridine with α,ω-alkylenediamines leads to tetrakis(p-toluenesulfamidoethyl)alkylenediamines, the cyclocondensation of which in the presence of 1,2-dibromomethane under interphase-catalysis conditions gives the corresponding cryptands.*

In 1967, the American chemist Pedersen synthesized macrocyclic polyethers (crown ethers) and investigated their complexing properties with ions of alkali and alkaline-earth metals [1]. The carcasses of crown ethers consist primarily of oligomers of oxirane that are bonded with one or several benzene or cyclohexane rings. Each heteroatom in the macroring is separated from the adjacent heteroatom by two carbon atoms; the most effective complexing agents have been found to be macrocyclic polyethers that contain from 5 to 10 oxygen atoms [2]. Most crown ethers have been obtained using the Williamson reaction as applied to bifunctional compounds, i.e., by the reaction of aromatic diols with α,ω-dihalo-oligoethyleneglycols in the presence of alkali metal hydroxides [1-4]. The principal methods for the synthesis of crown ethers that are not bonded with benzene or cyclohexane rings are the reactions of oligoethyleneglycols with ditosylates [5, 6] or with oligoethyleneglycol dichlorides [7-9]. The enumerated methods require the use of relatively costly starting substances. In this connection, of great attraction is a method for the direct cyclic oligomerization of oxirane and its derivatives, which leads to crown ethers based on cheap and accessible industrial products. Of great promise is the use of diglycidyl ethers of oligoethyleneglycols, which have high reactivities, as well as aziridine and its derivatives, in the synthesis of nitrogen-containing crown compounds. At the present time one can single out four basic pathways for the synthesis of macroheterocycles that use three-membered heterocycles as synthones: 1) the cyclooligomerization of oxirane and aziridine and their derivatives; 2) the cyclocondensation of acyclic derivatives of three-membered heterocycles; 3) the cyclization of bisoxiranes and bisaziridines; 4) the synthesis of cryptands on the basis of oxirane and aziridine derivatives.

A partial description of these methods of synthesis has been presented in several review papers and monographs [10-15]. In the present review data to the use of three-membered heterocycles in the synthesis of crown compounds and cryptands that have been published up to the end of 1988 have, as far as possible, been exhaustively correlated and systematized.

CYCLOOLIGOMERIZATION OF OXIRANE AND AZIRIDINE AND THEIR DERIVATIVES

The cyclooligomerization of oxirane has been studied in detail [16, 17]. In the presence of BF_3 at room temperature and atmospheric pressure oxirane gives a mixture of cyclic oligomers that consists primarily of dioxane (40%) and macrocyclic polyethers. The yield of the latter is relatively low, with the exception of 12-crown-4, which is formed in 15% yield.

Irkutsk Institute of Organic Chemistry, Siberian Branch, Academy of Sciences of the USSR, Irkutsk, 664033.
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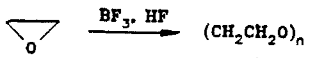


1

n	2	3	4	5	6	7	8	9	10	11	More than II
Relative yield, %	40	1	15	5	4	3	2	2	1	1	25

The reaction proceeds in inert solvents such as benzene, dioxane, and alkanes. Dry hydrogen fluoride is used as a cocatalyst. Phosphorus and antimony fluorides have also been found to be effective catalysts, while only polymerization products were obtained when $SnCl_4$ and $SbCl_3$ were used. The Lewis acids $AlCl_3$ and $FeCl_3$ have been found to be ineffective, while chlorosulfonic acid and p-toluenesulfonic acid react with oxirane to give polyethyleneglycol polyethers.

Higher yields of crown ethers are observed when tetrafluoroborates, fluorophosphates, or fluoroantimonates of alkali, alkaline-earth, and some transition metals are added (Table 1).

The products of cyclooligomerization of oxirane in this case are complexes of crown ethers with metal salts. The isolation of the free ligands is accomplished by pyrolysis at reduced pressure. The metal salts act as template agents; it has been established that halide and sulfate anions of the salts, being relatively highly basic, neutralize Lewis catalysts rapidly and are therefore unsuitable for the cyclooligomerization of oxirane. In addition to this, these anions decompose the crown ethers during the pyrolysis, which leads to additional chromatographic purification and a decrease in the yields of the final reaction products. The use of tetrafluoroborates, fluorophosphates, or fluoroantimonates of metals satisfies many requirements. The anions of these salts, just like the catalysts, do not form terminal groups that can hinder cyclization and promote the formation of polymers. Complexes with such anions are easily isolated from solution, since they are only slightly soluble in neutral solvents as compared with complexes that contain halide or sulfate anions. The BF_4^-, PF_6^-, and SbF_6^- anions are inert and do not decompose the cyclopolyethers during pyrolysis of the complexes.

The cyclooligomerization of oxirane catalyzed by a trialkylaluminum leads to the formation of dioxane, 12-crown-4, and polymeric reaction products [18].

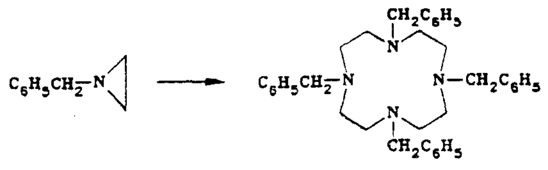
The cationic cyclooligomerization of some alkylene oxides, including oxirane, has been studied relatively recently [19, 20]. When KBF_4 is used as the template agent, oxirane undergoes oligomerization to give a mixture of 15-crown-5 and 18-crown-6 in a ratio of 1:9, respectively. The reaction products are isolated in the form of complexes. A significant part of the products of oligomerization of oxirane is the linear oligomer. The authors (Lebedev and coworkers) feel that the nature of the monomer and the catalyst and the conditions under which cationic oligomerization is carried out affect the yields of the crown ethers to a significant degree.

Propylene oxide in the presence of $(C_2H_5)_3OBF_4$ or BF_3 undergoes oligomerization to give primarily cyclic tetramers and pentamers, while 1,2-butylene oxide and epichlorohydrin are converted primarily to 12-membered cyclopolyethers [21, 22].

Aziridine derivatives undergo oligomerization primarily with the formation of cyclic tetramers. Thus, for example, 1-benzylaziridine is converted almost quantitatively to 1,4,7,10-tetrabenzyl-1,4,7,10-tetraazacyclododecane (2) by the action of p-toluenesulfonic acid in refluxing ethanol [23] (see scheme at top of following page).

TABLE 1. Yields of Products in the Cyclooligomerization of Oxirane in the Presence of Metal Salts

Salt	Relative yield, %			Salt	Relative yield, %		
	12-crown-4	15-crown-5	18-crown-6		12-crown-4	15-crown-5	18-crown-6
$LiBF_4$	30	70	—	$Sr(BF_4)_2$	10	45	45
$NaBF_4$	25	50	25	$Ba(BF_4)_2$	10	30	60
KBF_4	—	50	50	$AgBF_4$	35	30	35
KPF_6	20	40	40	$Hg(BF_4)_2$	20	70	10
$KSbF_6$	40	20	40	$Ni(BF_4)_2$	20	80	—
$RbBF_4$	—	—	100	$Cu(BF_4)_2$	5	90	5
$CsBF_4$	—	—	100	$Zn(BF_4)_2$	5	90	5
$Ca(BF_4)_2$	50	50	—				



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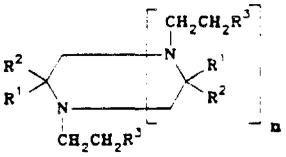
Cyclic tetramers were also obtained by oligomerization of 1-benzyl-2-ethyl- and 1-benzyl-2-(ethoxycarbonylmethyl)aziridines in the presence of boron trifluoride etherate [24-26]. The resulting mixture of isomers of chiral macroheterocycles was separated into stereoisomers, which were isolated and identified.

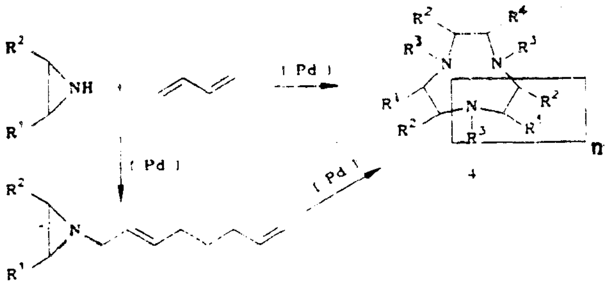
The oligomerization of substituted aziridines, the principal products of which are not only cyclic tetramers but also cyclopentameric polyamines 3, has been described [27].



3

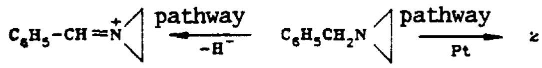
n = 2-7; $R^1 = R^2 = H$, alkyl $R^3 = H, OH, CN, RCO_2, NHCOR, CONHR, NHCONHR, NHCO_2R, OR$ (R = alkyl, aryl, alaryl, aralkyl, alkenyl, or OH)

The reaction of aziridines with 1,3-dienes catalyzed by palladium leads to cyclic polyamines 4 in high yields [28].

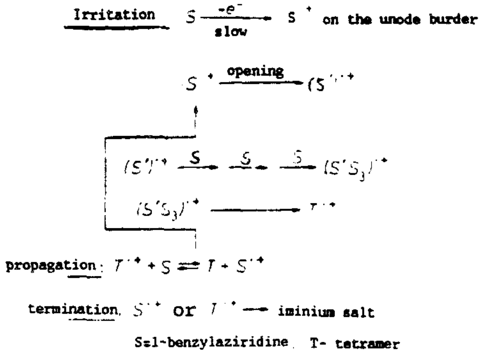


n = 0, 1, 2; $R^3 = CH_2–CH=CH(CH_2)_3CH=CH_2$

An electrochemical method for obtaining macrocyclic polyamines, which is based on the anode oxidation of substituted aziridines, is unique [29].



The oxidation of tertiary amines usually leads to iminium salts (pathway 2) [30, 31]. At the same time, the anode oxidation of 1-benzylaziridine, depending on the conditions, gives macrocyclic polyamine 2 in 43-80% yields (pathway 1). Elec-



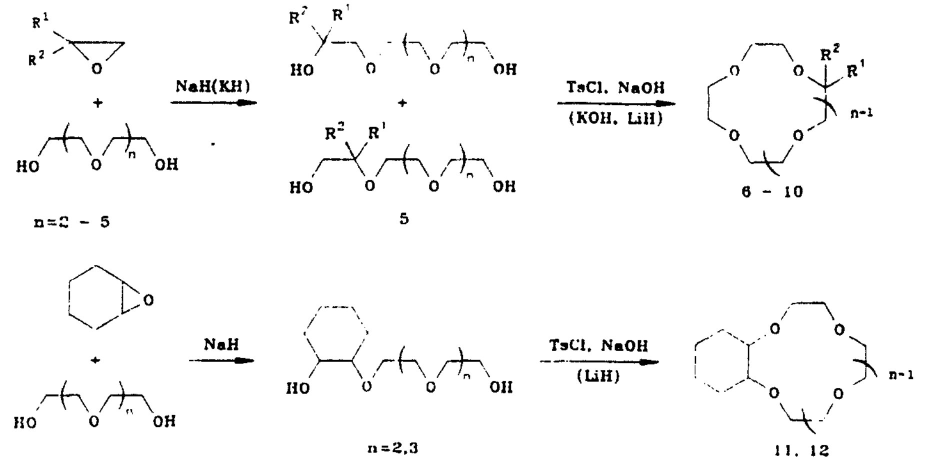
trochemical tetramerization proceeds through the formation of a radical cation via the direct or indirect transfer of an electron (see scheme on bottom of preceding page).

On the other hand, this transition is possible as a result of chemical oxidation (H^+ or some metal cations), which is accelerated by means of photoillumination. The experimental results show that the deprotonation of the cation radical, which leads, in the case with tertiary amines, to iminium salts, is excluded in anode oxidation, and the reaction proceeds as a result of rapid opening of the three-membered ring, which leads to the formation of cyclic tetramer 2.

CYCLOCONDENSATION OF ACYCLIC DERIVATIVES OF THREE-MEMBERED HETEROCYCLES

The development of the chemistry of crown compounds and cryptands has led to the synthesis of a large number of new polyfunctional hetero-containing acyclic compounds that are the principal starting components in the formation of macroheterocycles. In this connection three-membered heterocycles find extensive application as synthones. Their reaction with bifunctional nucleophilic reagents leads to an increase in the chain length and functionalization of the resulting linear compounds due to opening of the three-membered ring. The cyclocondensation of the latter leads to macroheterocycles with exocyclic substituents.

A large number of crown ethers **6-12** with exocyclic alkyl, phenyl, allyloxy, butoxy, phenoxy, and benzyloxymethyl substituents as well as cyclohexane rings, have been obtained on the basis of substituted oxiranes [32, 33].

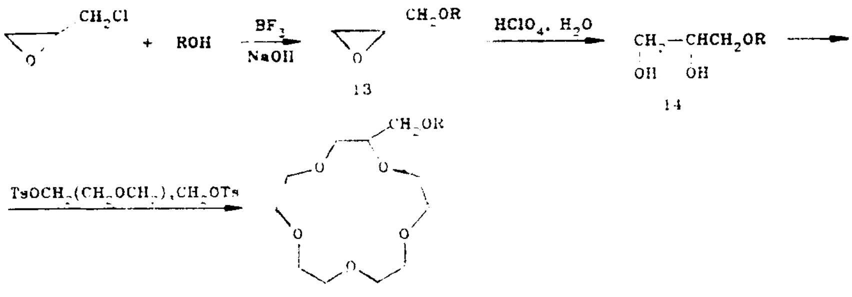


6 $R^1=H$, $n=3$, $R^2=CH_3$, C_2H_5, C_6H_{13}, C_8H_{17}, $C_{10}H_{21}$, $C_{12}H_{25}$, C_6H_5, $CH_2{=}CHCH_2OCH_2$, $C_4H_9OCH_2$, $C_6H_5OCH_2$, $C_6H_5CH_2OCH_2$; **7** $R^1=H$, $n=2$, $R^2=C_6H_5$, $C_6H_5CH_2OCH_2$; **8** $R^1=H$, $n=4$, $R^2=C_6H_5$, C_8H_{17}, $C_{10}H_{21}$; **9** $R^1=H$, $n=5$, $R^2=C_{10}H_{21}$, $C_{12}H_{25}$; **10** $R^1=R^2=CH_3$, $n=3$; **11** $n=2$; **12** $n=3$

Substituted oxiranes react with oligoethyleneglycols in the presence of sodium or potassium hydride on heating in dioxane to give mixtures of oligoethyleneglycols **5** in a maximum yields of 73%. The intramolecular cyclization of isomeric oligoethyleneglycols **5** was carried out without their prior separation by means of p-toluenesulfonyl chloride and alkali metal hydroxides or lithium hydride. The yields of substituted crown ethers **6-10** range from 19 to 70%. Cyclohexane crown ethers **11** and **12** were similarly obtained in a maximum yield of 61%.

Macroheterocycles that contain additional donor atoms in the side chain have been called lariat (lasso) crown ethers [34-36]. During complexing with alkali metal cations cyclopolyethers of this type encapsulate the cation into the hollow of the macroring and throw a "lasso" on it – a flexible side substituent, the donor atom of which forms an additional bond with the metal ion. The stability of the complex is increased due to this. The introduction of side substituents into the macroring is accomplished by using fucntionally substituted oxiranes as the starting compounds. Thus, the scheme of the synthesis of lariat-15-crown-5 has the form shown in the scheme at the top of the following page.

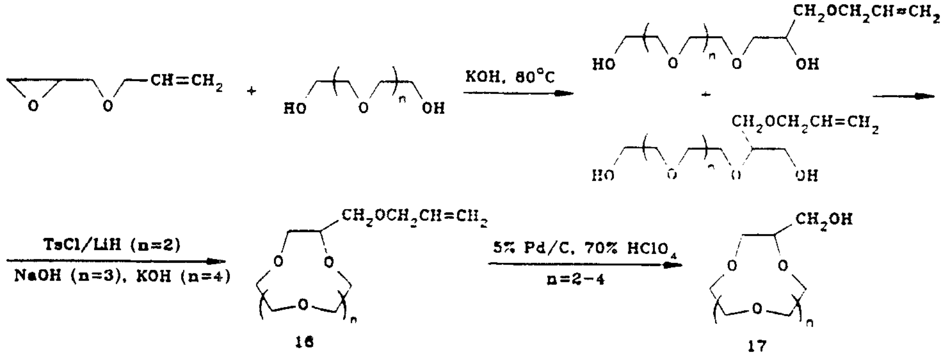
The reaction of epichlorohydrin with alcohols or carboxylic acids in the presence of BF_3 leads to monoglycidyl ethers **13** which, as a result of opening of the three-membered ring under the influence of $HClO_4$, form substituted diols **14**. The reaction of the latter with tetraethyleneglycol ditosylates or dimesylates in THF in the presence of NaOH leads to lariat-15-crown-5 **15** in 30-70% yields.



13 14 15

R = CH_3, $CH_2CH{=}CH_2$, C_3H_7, C_4H_9, i-C_4H_9, $Si(CH_3)_3$, $C_{16}H_{33}$, $OCCH_3$, OCC_3H_7, $OCC_{15}H_3$, $CH_2CH_2OCH_3$, $CH_2CH_2OC_4H_9$, $CH_2CH(OH)CH_3$, $(CH_2CH_2O)_2CH_3$, $(CH_2CH_2O)_3H$, $(CH_2CH_2O)_3CH_3$, C_6H_5, $C_6H_5CH_2$, 2-, 3- and 4 methoxyphenyl, 2-maphthyl, 8-xynolyl, OCC_6H_5, $OCC_6H_4OCH_3$-4, $OCC_6H_4NO_2$-4, 2-$CH_3OC_6H_4(CH_2)_2$, 2-$CH_3OC_6H_4CH_2CH(OH)$—

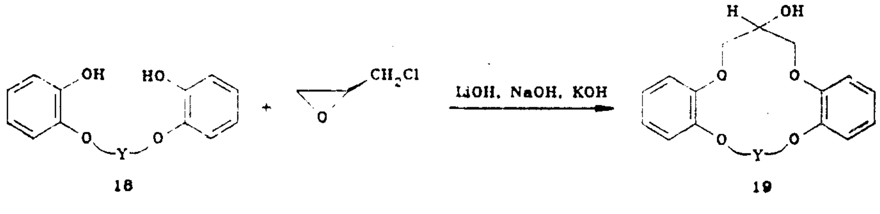
Hydroxymethyl-substituted crown ethers **17** were obtained on the basis of the industrially accessible allylglycidyl ether and oligoethylene glycols [37].



16 17

The reaction proceeds in the corresponding glycol at 80°C in the presence of KOH. The allyloxymethyloligoethyleneglycols obtained in this way underwent cyclization in the presence of p-toluenesulfonyl chloride. Lithium hydride and sodium and potassium hydroxides have been used as template agents. Thus allyloxymethyl-12-crown-4 was obtained in the presence of lithium hydride. Sodium hydroxide has been used for the synthesis of allyloxymethyl-15-crown-5, while potassium hydroxide has been used to obtain allyloxymethyl-18-crown-6 (45-66% yields). Deblocking of the allyloxymethyl-substituted crown ethers **16** includes a step involving isomerization of the allyl ether to 2-methylvinyl ether by the action of 5% Pd/C and subsequent acidic hydrolysis. The yields of hydroxymethyl-substituted crown ethers **17** ranged from 79 to 90%.

Hydroxy-containing crown ethers were also obtained by the reaction of epichlorohydrin with diphenols **18** [38, 39].



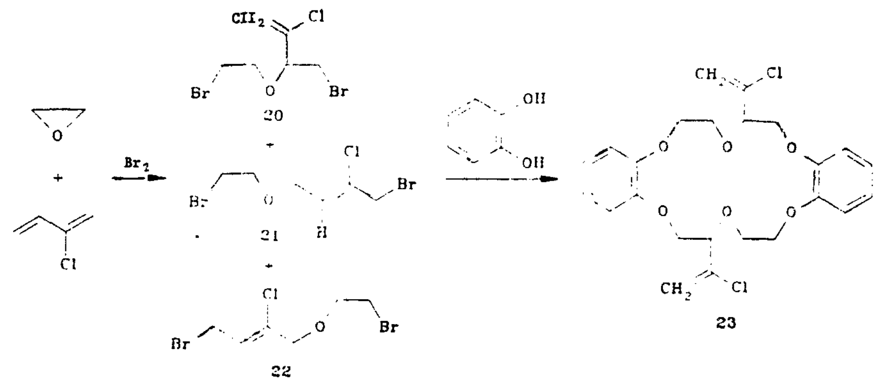
18 19

19 Y = CH_2CH_2, $CH_2CH_2CH_2$, $CH_2CH(OH)CH_2$, $CH_2CH_2OCH_2CH_2$, $CH_2CH(CH_3)OCH_2CH_2$, $CH_2CH(C_2H_5)OCH_2CH_2$, $CH_2CH_2OCH_2CH_2OCH_2CH_2$, $CH_2C(O)NHCH_2NHC(O)CH_2$

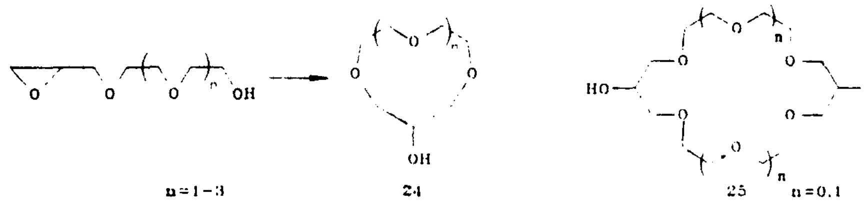
The reaction proceeds in aqueous solutions of alkali metal hydroxides, which act as template agents, to give hydroxydibenzocrown ethers **19** in 39-60% yields.

The concerted bromination of chloroprene with oxirane, which leads to the formation of a mixture of three reaction products (**20-22**), has been studied [40].

Dibenzo-18-crown-6 (**23**), which contains α-chlorovinyl groups in the polyether ring, was obtained by the reaction of **20** with 1,2-dihydroxybenzene under high-dilution conditions.

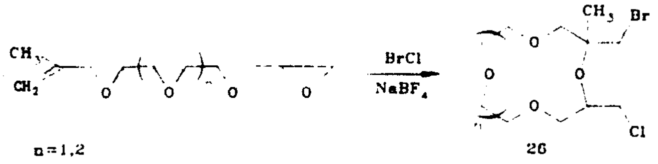


The use of monoglycidyl ethers of oligoethyleneglycols in the synthesis of crown ethers is promising owing to their accessibility and high reactivities. The intramolecular cyclization of these compounds in the presence of boron fluorides, alkali metal hydroxides, or alkali metals leads to monohydroxy-containing crown ethers **24** in 35-48% yields [41-43].

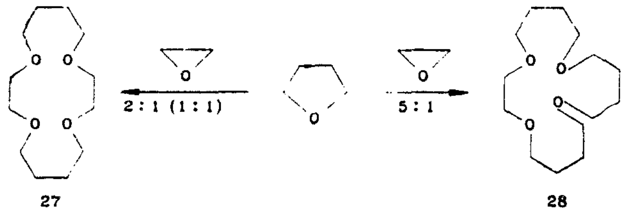


When LiOH and KOH are used, monoglycidyl ethers of ethyleneglycol and diethyleneglycol undergo cyclodimerization to give dihydroxy-containing crown ethers **25**.

The concerted cyclization of methallylglycidyl ethers of di- and triethyleneglycols and bromine chloride gives crown ethers **26**, which contain chloro- and bromomethyl groups in the side chains. The yields of macrocyclic polyethers **26** amount to 31-35%.

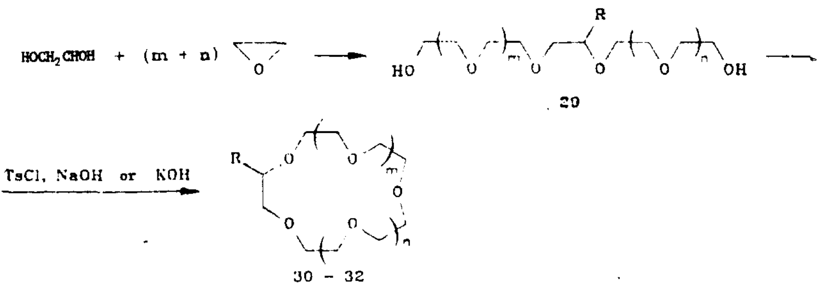


Oxirane reacts with tetrahydrofuran in the presence of trifluoromethanesulfonic acid as the catalyst to give macroheterocycles **27** and **28** [44].



Adduct **27** (2:2) is formed in the reaction of 2 moles of THF with 1 or 2 moles of oxirane, whereas adduct **28** (3:1) was obtained in 32% yield when the ratio of the starting compounds was 5:1.

The reaction of oxirane with 1,2-propanediol or 3-(allyloxymethyl)propane-1,2-diol leads to the previously difficult-to-obtain substituted oligoethyleneglycols **29** with different chain lengths [45]. The reaction proceeds in the presence of boron trifluoride etherate. The oligoethyleneglycols **29** obtained were separated by means of fractional distillation.

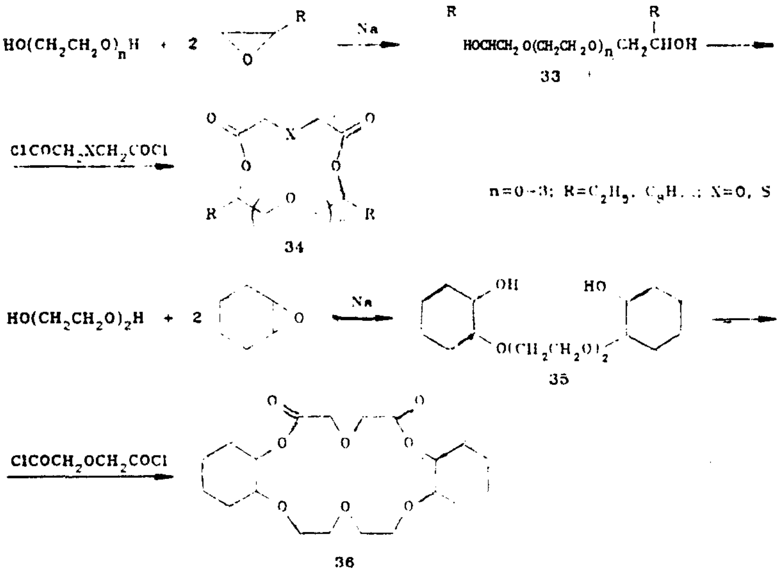


30 $R=CH_3$, $m+n=2$; 31 $R=CH_3$, $m+n=3$; 32 $R=CH_2OCH_2CH=CH_2$, $m+n=2$

Complexes of substituted crown ethers (30-32) with alkali metal p-toluenesulfonates are obtained by their cyclization in the presence of p-toluenesulfonyl chloride and alkali metal hydroxides. The free crown ethers were isolated by pyrolysis of the complexes in vacuo.

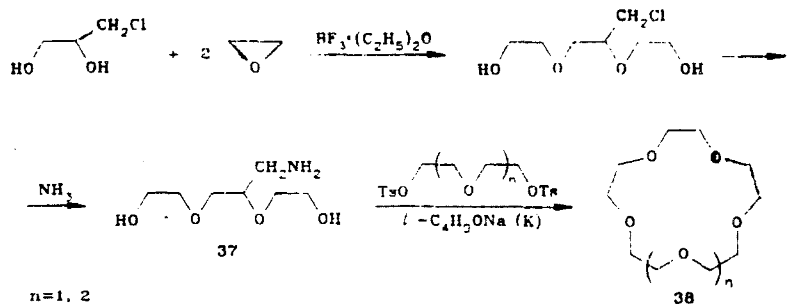
Oxirane also reacts with pyrocatechol in the presence of alkaline catalysts to give mono- or oligohydroxyethyl-substituted benzenes [46]. Cyclization of the latter takes place with the formation of dibenzo-12-crown-4, dibenzo-18-crown-6, and tetrabenzo-24-crown-8.

Dialkyl-substituted oligoethyleneglycols were obtained by the reaction of oligoethyleneglycols with 2 moles of alkyloxiranes in the presence of sodium metal [47].



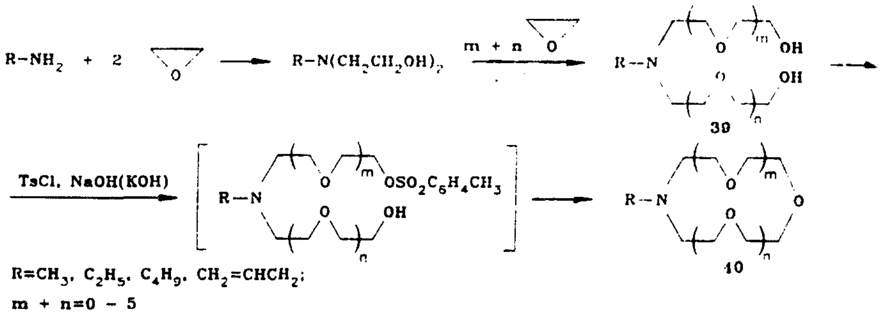
They have been used for the synthesis of crown ethers that contain endocyclic ester groups. Thus the reaction of oligoethyleneglycols 33 with 3-oxa- and 3-thiaglutaric acid dichlorides under high-dilution conditions leads to macroheterocycles 34 in 55% yields. Oligoethyleneglycol 35 reacts with 3-oxaglutaric acid dichloride to give dicyclohexanodioxo-18-crown-6 (36) in 60% yield.

A method for the synthesis of crown ethers 38, which contain an amiomethyl group, has been developed [48].

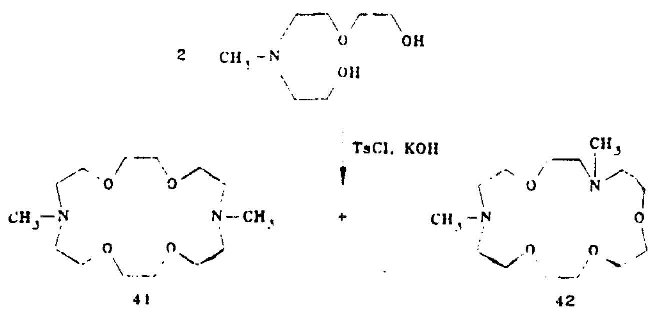


Bis(polyhydroxyethylene)alkylamines **39** were obtained as a result of the stepwise building up of the chain in the reaction of primary alkylamines with oxirane [49] (see scheme at bottom of previous page).

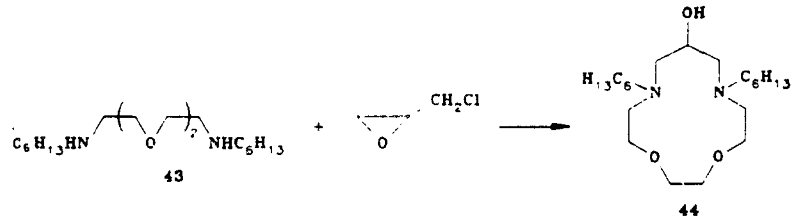
Their cyclocondensation in the presence of p-toluenesulfonyl chloride and sodium and potassium hydroxides leads to complexes of monoazacrown ethers with alkali metal p-toluenesulfonates. Alkyl-substituted monoazacrown ethers 40 were obtained in 40-74% yields by pyrolysis of the complexes.



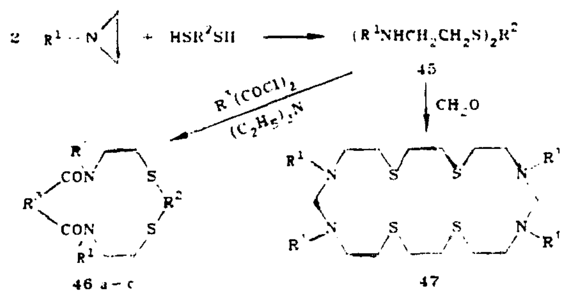
The cyclocondensation of amine **39** ($R = CH_3$, $m = 1$, $n = 0$) under similar conditions leads to a mixture of dimethyldiazacrown ethers **41** and **42** in 24% yield.



A one-step method for the synthesis of oxygen- and nitrogen-containing macrocycle **44** was developed on the basis of epichlorohydrin and secondary diamine **43** [42].



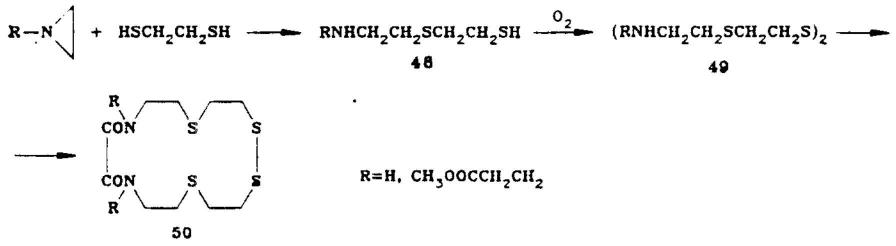
Nitrogen- and sulfur-containing macroheterocycles **46** were obtained by the reaction of primary and secondary diamines **45** with dicarboxylic acid dichlorides [50-60], while thiazacrown compounds **47** were obtained by cyclocondensation of secondary diamines with formaldehyde [61-63].



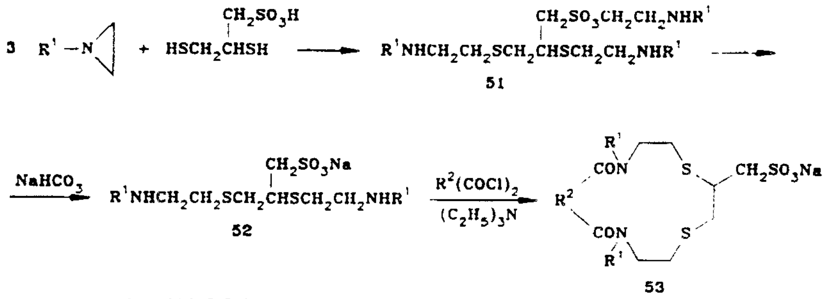
46 $R^1 = H$, $C_6H_5CH_2CH_2$, $CH_3OOCCH_2CH_2$, $NCCH_2CH_2$, $CH(COOCH_3)CH_2COOCH_3$, $CH(COOC_2H_5)CH_2COOC_2H_5$; $R^2 = CH_2CH_2$, 4,5-dimethylphenyl-1,2-dimethylene 1,3,4-thiadiazole-2,5-diyl; $R^3 = (CH_2)_4$, 1,2-C_6H_4; 1,4-C_6H_4, $(CH_2CH_2S)_2CH_2CH_2$; **47** R= $=CH_3OOCCH_2CH_2$, $CH(COOCH_3)CH_2COOCH_3$, CH_2CH_2CN, $C_6H_5CH_2CH_2$

Diamines **45** have become accessible on the basis of the reaction of aziridines with α,ω-aliphatic, aromatic, and heterocyclic dithiols [50-63]. Their cyclization with adipic, phthalic, terephthalic, and 3,6-dithiaoctanedicarboxylic acid dichlorides in dry benzene under high-dilution conditions leads to macroheterocycles **46** in 50-70% yields.

If the reaction of aziridines with 1,2-ethanedithiol is carried out in benzene, monoadducts, viz., amino thiols **48**, which are readily oxidized to diamino disulfides **49**, are formed. The reaction of the latter with oxalyl chloride in dry benzene gave 16-membered crown compounds **50**, which contain two nitrogen heteroatoms and four sulfur atoms in the ring, in 75-80% yields [50].



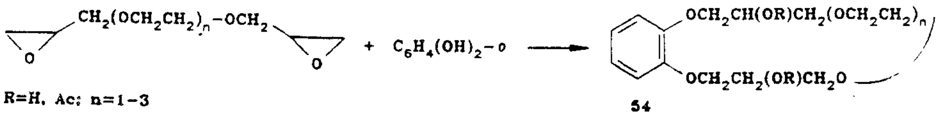
A method for the synthesis of C- and N-functionally substituted macroheterocycles **53**, which is based on the reaction of acyclic diamines **52** with phthalic and terephthalic acid dichlorides, has been developed. Diamines **52** were obtained from 2,3-dimercaptopropanesulfonic acid and aziridine or substituted aziridines with subsequent treatment of triamines **51** with sodium bicarbonate [64, 65].



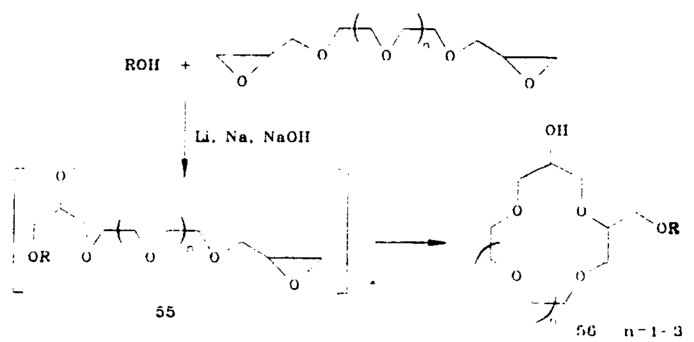
$R^1 = H$, $CH_3OOCCH_2CH_2$, $C_6H_5CH_2CH_2$; $R^2 = 1,2\text{-}C_6H_4$, $1,4\text{-}C_6H_4$

CYCLIZATION OF BISOXIRANES AND BISAZIRIDINES

The synthesis of functionally substituted crown ethers on the basis of accessible bisoxiranes is most simple and promising. Mono-, di-, and tetrahydroxy-substituted crown ethers are readily obtained by means of them. Difficult-to-obtain aza- and thiacrown compounds are formed in the reaction of bisoxiranes with nitrogen- or sulfur-containing nucleophilic reagents. Thus, diglycidyl ethers of oligoethyleneglycols react with pyrocatechol in the presence of alkali metal alkoxides to give dihydroxybenzocrown ethers **54**. Subsequent treatment with acetic anhydride and hydrolysis lead to substituted benzocrown ethers **54** [66].

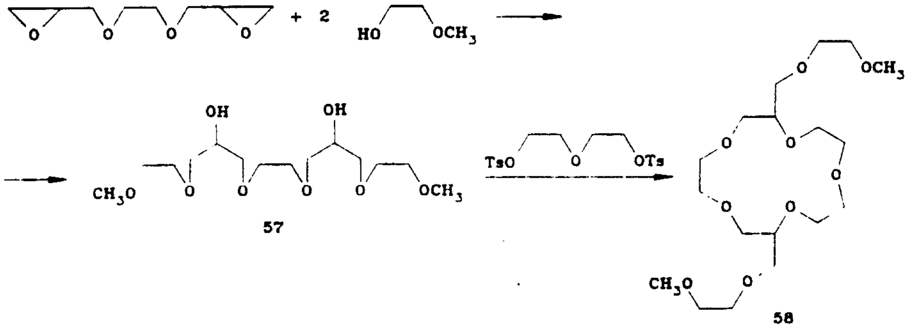


An original method for the synthesis of lariat crown ethers **56** (in 30-80% yields), which contain a hydroxy group, has been developed on the basis of the reaction of diglycidyl ethers of oligoethyleneglycols with alcohols [67].

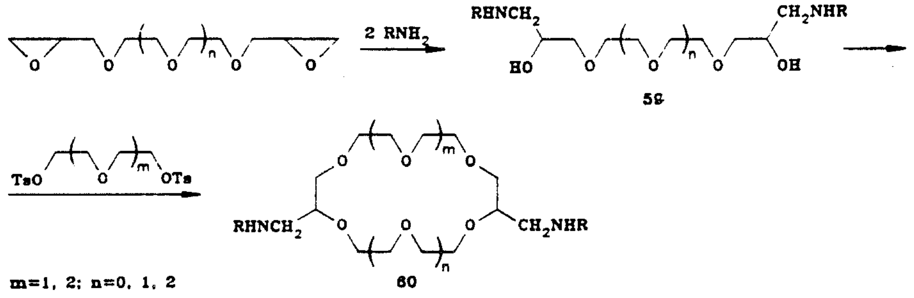


R = CH_3, C_3H_7, C_6H_{13}, $C_{12}H_{25}$, $C_{18}H_{37}$, $CH_2{=}CHCH_2$, C_6H_5, tetrahydrofurfuryl

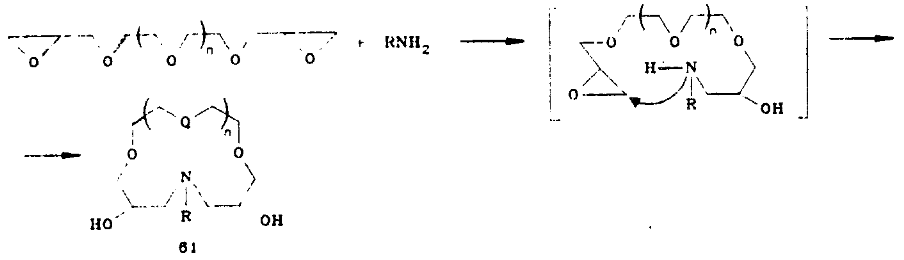
The reaction of ethyleneglycol diglycidyl ether with ethyleneglycol monomethyl ether leads to the formation of diol **57**. Its alkylation with diethyleneglycol ditosylate gives dimethoxyethyloxymethyl-substituted 15-crown-5 (**58**) [68].



Bis(aminomethyl)crown ethers **60** were obtained by a similar scheme [69].

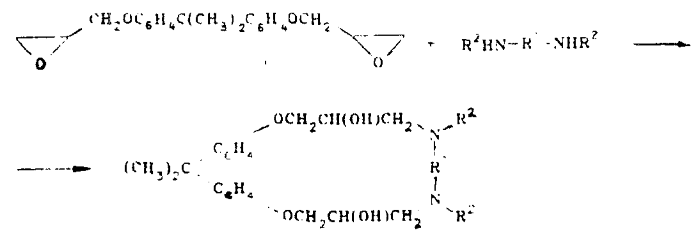


The direct cyclization of diglycidyl ethers of oligoethyleneglycols with primary amines in protic and aprotic solvents has been studied [70]. Water and methanol accelerate opening of the oxirane ring, while in aprotic solvents (benzene, dioxane, and trichloromethane) the reaction virtually does not take place. The maximum yield of dihydroxyazacrown ethers **61** reaches 50%.



R = H, C_2H_5, sec—C_4H_9, $C_{10}H_{21}$, C_6H_5, CH_2CH_2OH, n = 1—3

The possibility of obtaining macrocyclic compounds by the reaction of 2,2-bis[4-(2,3-epoxypropoxy)phenyl]propane with primary monoamines, 1,2-dimethylhydrazine, secondary diamines, and sodium sulfide under high-dilution conditions has been investigated [71].

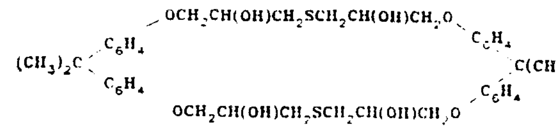


62

$R^1-CH_2CH_2$, $(CH_2)_3$, $(CH_2)_4$, $(CH_2)_6$, $CH_2-CH=CH-CH_2$, $CH_2-C\equiv C-CH_2$; $R^2=CH_3$, C_2H_5; $R^2N-R^1-NR^2$= piperazine-1,4-diyl

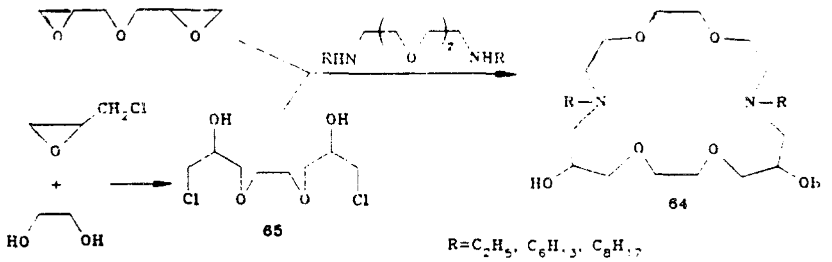
Macrocycles could not be obtained by the reaction of 2,2-bis[4-(2,3-epoxypropoxy)phenyl]propane with primary amines and 1,2-dimethylhydrazine because of steric hindrance formed by the benzene rings; only products of opening of one oxirane ring were isolated. At the same time, secondary aliphatic diamines, which have a long chain length, react with the formation of macrocyclic products (**62**) in 3-28% yields. The yields of the crown compounds increase with an increase in the chain length on passing from N,N'-dimethylethylenediamine to N,N'-dimethyltetramethylenediamine.

In contrast to primary monoamines, sodium sulfide reacts with 2,2-bis[4-(2,3-epoxypropoxy)phenyl]propane in methanol at 50°C to give 36-membered macroheterocycle **63**.



63

Secondary diamines have also been used in the reaction with ethyleneglycol diglycidyl ether to obtain dihydroxy-substituted diazacrown ethers **64** [42].



65

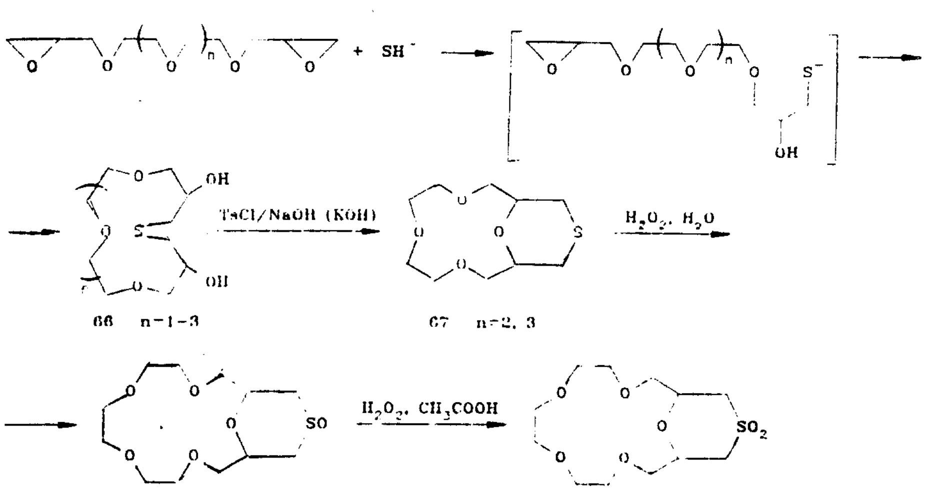
64

R=C_2H_5, C_6H_{13}, C_8H_{17}

The reaction takes place in methanol to give the diazacrown ethers **64** in 30-35% yield. The same macrocycles were obtained via the following scheme: the reaction of epichlorohydrin with ethylene glycol leads to dichloride **65**, which, on reaction with diamines in the presence of K_2CO_3, forms crown compound **64** in 23-28% yield.

The reaction of diglycidyl ethers of oligoethylene glycols with sodium hydrosulfide also takes place in protic solvents [72]. Dihydroxy-substituted thiacrown ethers **66** are formed in 52-63% yields. Macroheterocycles **66** are not formed in aprotic solvents such as dioxane (see scheme on following page).

Bicyclic compounds **67** are formed in 45-55% yields when dihydroxy-substituted crown compounds **66** (n = 2, 3) with p-toluenesulfonyl chloride in the presence of sodium or potassium hydroxide in dioxane. The oxidation of the sulfur atom with hydrogen peroxide in water leads to crown compound **68** with a sulfoxide group, while its subsequent treatment with H_2O_2 in CH_3COOH gives bicyclic sulfone **69**.



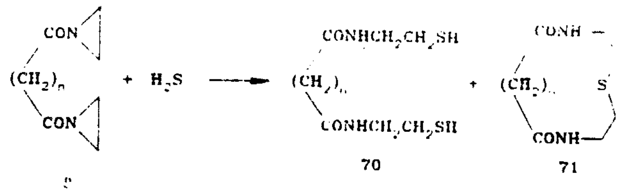
66 n = 1–3

67 n = 2, 3

68

69

Bis(ethyleneimides) of azelaic acid and sebacic acids react with excess hydrogen sulfide to give carboxylic acid bis(2-mercaptoethylamides) **70** and macrocyclic sulfides **71** [73].



70

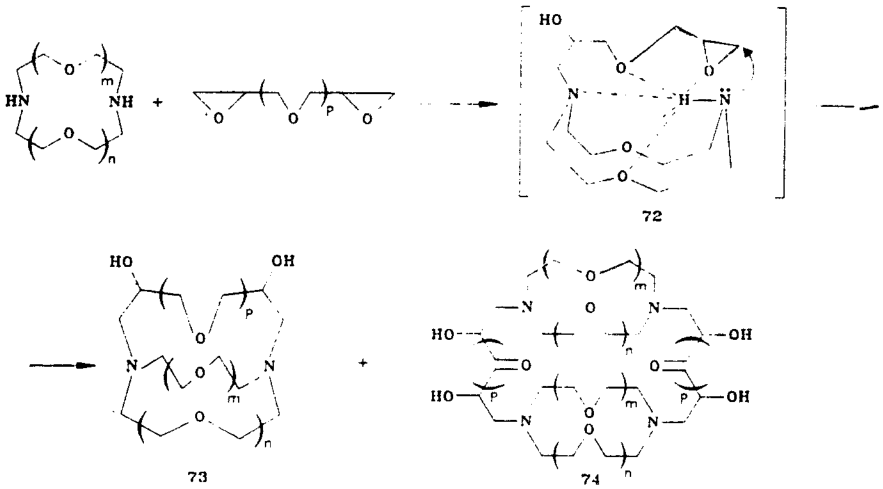
71

If, instead of hydrogen sulfide, 1,2-ethanedithiol is used in the reaction with adipic acid bis(ethyleneimide), macroheterocycle **46** [R^1 = H, R^2 = CH_2CH_2, R^3 = $(CH_2)_4$] is formed in 60% yield [59].

SYNTHESIS OF CRYPTANDS FROM OXIRANE AND AZIRIDINE DERIVATIVES

Diglycidyl ethers of oligoethyleneglycols are industrially accessible, and the synthesis of cryptands from them is therefore promising as compared with methods that have been previously developed [74-77].

New approaches to the synthesis of cryptands are presented in [78, 79]. They are based on the reaction of diazacrown ethers with diglycidyl ethers.

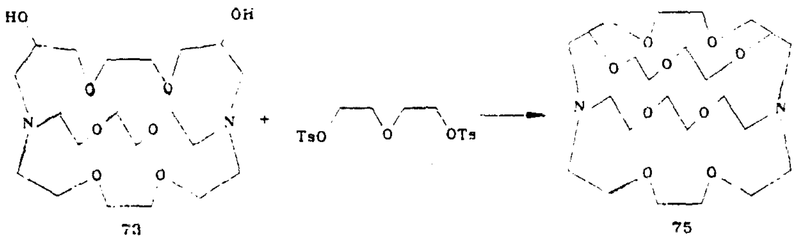


72

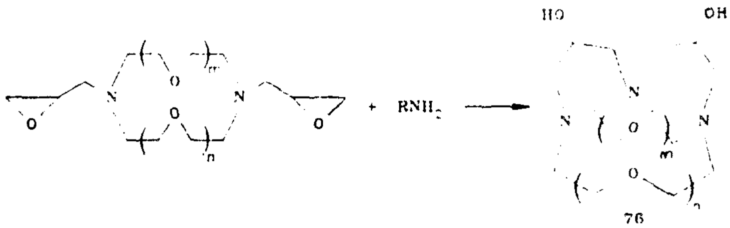
73

74

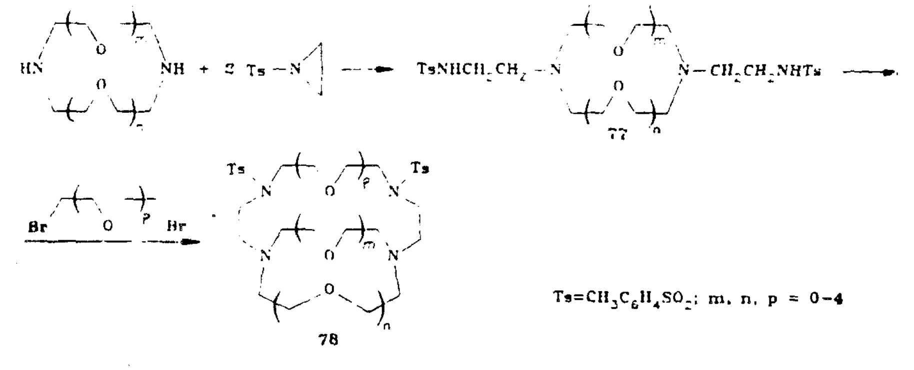
Cryptands 73 and 74 are formed as a result of intracomplex cyclization of intermediates 72, in which a spatial orientation of the reactions centers that is favorable is ensured. The reaction proceeds on heating in a mixture of dry ethanol and tetrahydrofuran (1:1). Compounds 73 and 74 were separated by chromatography. The yields of cryptands 73 are 69%. The hydroxy groups of cryptands have been used to obtain tricyclic compounds. Thus, dihydroxycryptand 73 (m = n = p = 2) was condensed with diethylene glycol ditosylate by refluxing in dioxane in the presence of sodium hydride to give cylindrical cryptand 75 in 19% yield [80].



Intramolecular cyclization has also been successfully used for obtaining dihydroxycryptands 76 [78]. Diazacrown ethers that contain exocyclic oxiranylmethyl groups, as well as primary amines, have been used as starting substances.



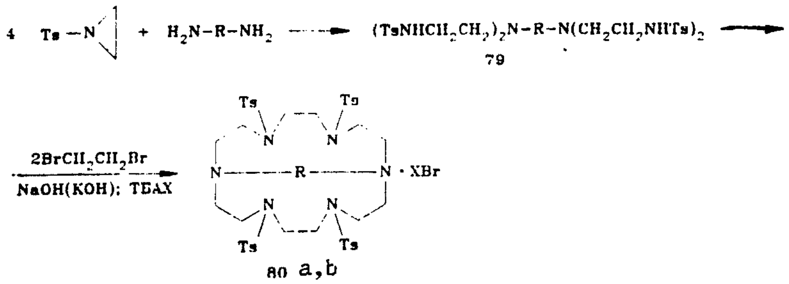
The reaction of the highly reactive tosylaziridine with diaza-18-crown-6 leads to the formation of bis(tosylethyleneamino)diaza-18-crown-6 77, which reacts readily with 1,5-dibromo-3-oxapentane in a two-phase system (aqueous alkali–toluene in the presence of quaternary ammonium salts) [78, 80, 81], resulting in the formation of cryptand 78 in 87% yield.



Ts=CH$_3$C$_6$H$_4$SO$_2$; m, n, p = 0–4

The most promising, in a practical respect because of the accessibility of the starting reagents, is a method for the synthesis of cryptands that was developed in [82-85] and is based on the reaction of tosylaziridine with a primary diamine at 80°C in DMF. The resulting (in 80-85% yield) tetrakis(p-toluenesulfonamidoethyl)alkylenediamines 79 react, under interphase-catalysis conditions, with 1,2-dibromoethane to give cryptands 80 in 60-65% yields (see scheme on following page).

The synthesis of crown compounds and cryptands on the basis of cheap petrochemical raw material is a promising direction in the area of the chemistry of macroheterocycles. The use, for these purposes, of highly reactive oxirane and aziridine and their derivatives makes it possible to obtain, in high yields, previously inaccessible alkyl-, aryl-, and functionally substituted crown compounds with relatively simple and accessible methods. Particular attention should be drawn to methods that involve the synthesis of bicyclic and tricyclic macroheterocycles based on oxirane and aziridine derivatives. In this instance,



Ts=$CH_3C_6H_4SO_2$; a R=CH_2CH_2, X=Na, K; R=$-(CH_2)_6-$, $(CH_2CH_2)_2S$, $(CH_2CH_2S-)_2$, X=H

no small role is played by such factors as realizing the synthesis of something without using the technique of high-dilution, as well as operating under interphase-catalysis conditions; this leads to high yields of the final products. This makes it possible to hope for the utilization of developed methods for the synthesis of cryptands, not only in a laboratory setting, but also in industry.

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