Phenylaza- and benzoazacrown compounds with a nitrogen atom conjugated with a benzene ring

S P Gromov, S N Dmitrieva, M V Churakova

Abstract. Data on the synthesis and properties of aza- and diazacrown compounds containing a phenyl group at a nitrogen atom or an o-phenylene fragment annelated to the macrocycle are generalised. The functional derivatives of these compounds and their heteroanalogues with O, S and N atoms are considered. The bibliography includes 217 references.

Contents

I. Introduction 461
II. N-Phenylazacrown compounds 462
III. Functional derivatives of N-phenylazacrown compounds 466
IV. N,N'-Diphenylazacrown compounds 469
V. Functional derivatives of N,N'-diphenylazacrown compounds 471
VI. Benzoazacrown compounds 473
VII. Functional derivatives of benzoazacrown compounds 477
VIII. Dibenzoazacrown compounds 478
IX. Functional derivatives of dibenzoazacrown compounds 484
X. Conclusion 485

I. Introduction

Crown compounds bind metal cations, organic cations and neutral molecules through multidentate coordination to heteroatoms incorporated in the macrocycle. Due to this feature, they are used successfully as selective ligands, for extraction and separation of metal cations, for ion transport through membranes, in ion selective electrodes, as phase transfer catalysts and as synzymes that simulate enzymic activity.

In this case, the macrocycle size is given as the subscript ([N], [O], [S] atoms or [15]N, [14]N, [13]N, etc.) aza' (for example, [9]N3O or [8]N2). For this reason, we summarise here the data on the synthesis of several classes of crown ethers, which firmly bind alkali and alkaline earth metal ions, and the properties of cyclams, which form stable complexes with heavy and transition metal ions.

Apart from the traditional applications of azacrown compounds, of special interest is the use of those fragments, in which the nitrogen atom is conjugated with the chromophore, as parts of photosensitive, chromogenic, fluorescent and photochromic ligands. These compounds can form the heart of optical sensors for metal and ammonium ions, optical information recording systems, photoswitched molecular devices and machines for molecular electronics, transporting agents for the photocontrolled transport of metal cations, etc. For this reason, we summarise here the data on the synthesis of several classes of azacrown compounds in which the macrocycle nitrogen atom is conjugated with the benzene ring.

A number of reviews on the methods of synthesis of azacrown compounds have been published. Two of these consider crown ether analogues containing only nitrogen atoms as heteroatoms and cover a period from 1967 to 1987. Among the latest studies, noteworthy is the review devoted to the synthesis of fused aza- and thiaazacrown compounds. However, none of the published reviews consider specially the synthesis of azacrown compounds in which at least one nitrogen atom of the macrocycle is conjugated with a benzene ring; no systematic data are currently available on this topic.

This review is devoted to the synthesis and chemical properties of azacrown compounds based on macrocycles of various sizes (starting with the smallest, nine-membered one) containing three or more heteroatoms. A special feature of the molecules of these compounds is the presence of not more than two phenyl or annelated o-phenylene fragments linked to the macrocycle...
II. N-Phenylazacrown compounds

There are three main approaches to the synthesis of phenylazacrown compounds differing by the type of reaction used, which include the condensation of two fragments, aromatic nucleophilic substitution and cross-coupling.

I. Methods based on the condensation of two fragments

The base-induced condensation of N-aryldiethanolamines or their derivatives with oligoethylene glycols or their aza or thia analogues is a widely used method for the synthesis of N-phenylazacrown compounds. Using this method, Vogtle and Dix performed the first synthesis \(^{19,20}\) of N-phenylaza-15(18)-crown-5 ethers. With dichlorides as the electrophilic component, NaOH is used most often as the base, while in the case of ditoluenesulfonate this is NaH.\(^{19–21}\)

Phenylazacrown ethers \(1c\) – containing Me, MeO, Cl or NO\(_2\) groups in the ortho- or para-position of the benzene ring were prepared by condensation of N-aryldiethanolamine with oligoethylene glycol dimethanesulfonates (or ditoluenesulfonates) in the presence of sodium hydride,\(^{22–26}\) or with dichlorides in the presence of sodium hydroxide;\(^{27–29}\) while 3-nitrophenoxy-azacrown \(1j\) was synthesised using sodium tert-butoxide as the base.\(^{30}\) The use of derivatives with hard oxygen-containing leaving groups (ditoluenesulfonates, dimethanesulfonates) and strong bases (sodium hydride and tert-butoxide) allows one to synthesise N-arylcrown ether derivatives \(1\) in higher yields than the use of dichlorides in the presence of alkali.

![Diagram](image-url)

(a) NaOH, dioxane; (b) NaH, THF; (c) Bu'ONa, dioxane.

<table>
<thead>
<tr>
<th>Compound</th>
<th>X</th>
<th>R(^1)</th>
<th>R(^2)</th>
<th>R(^3)</th>
<th>n</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>Cl</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>1</td>
<td>16</td>
</tr>
<tr>
<td>b</td>
<td>Cl</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>2</td>
<td>13</td>
</tr>
<tr>
<td>c</td>
<td>Cl</td>
<td>OMe</td>
<td>H</td>
<td>H</td>
<td>1</td>
<td>16</td>
</tr>
<tr>
<td>d</td>
<td>OMe</td>
<td>OMe</td>
<td>H</td>
<td>H</td>
<td>1</td>
<td>16</td>
</tr>
<tr>
<td>e</td>
<td>OMe</td>
<td>H</td>
<td>H</td>
<td>OMe</td>
<td>1</td>
<td>16</td>
</tr>
<tr>
<td>f</td>
<td>OMe</td>
<td>H</td>
<td>H</td>
<td>Cl</td>
<td>1</td>
<td>35</td>
</tr>
<tr>
<td>g</td>
<td>OTs</td>
<td>H</td>
<td>H</td>
<td>NO(_2)</td>
<td>0</td>
<td>55</td>
</tr>
<tr>
<td>h</td>
<td>OTs</td>
<td>H</td>
<td>H</td>
<td>NO(_2)</td>
<td>1</td>
<td>70</td>
</tr>
<tr>
<td>i</td>
<td>OTs</td>
<td>H</td>
<td>H</td>
<td>NO(_2)</td>
<td>1</td>
<td>38</td>
</tr>
</tbody>
</table>

Ms is MeSO\(_2\), Ts is 4-MeC\(_6\)H\(_4\)SO\(_2\). The same method was utilised to obtain azacrown ether \(3\) with a long alkyl chain from N-phenyldiethanolamine and ditoluene-sulfonate \(2\) under the action of potassium tert-butoxide.\(^{31}\)

Using a similar procedure, a series of benzophenylazacrown ethers \(4\) have been prepared (with NaH as the base).\(^{32}\) Interestingly, the methoxy derivative \(4\) (R\(^1\) = H, R\(^2\) = OMe) was also prepared using an alternative method of synthesis, namely, from N-aryldiethanolamine ditoluene-sulfonate and the corresponding diol. The yields of products \(4\) were moderate in all cases.

![Diagram](image-url)

R\(^1\) = H, Me; R\(^2\) = H, OMe, Me, Bu'.

N-Phenyltetraazacrown compound \(5\) was obtained by the reaction of ditoluene-sulfonate \(6\) with the disodium salt of tritosylamide \(7\). The tosyl groups were removed by refluxing with sodium metal in n-butanol.\(^{33}\)

![Diagram](image-url)

The condensation of N-phenyldiethanolamide dichlorides, ditoluene-sulfonates or dimethanesulfonates with dithiols under the action of sodium hydroxide or potassium carbonate gave N-phenylthiiazacrown compounds \(8\) (for the derivative with X = OMs, n = 1, the yield was 40%).\(^{34–37}\)

\[ \text{Ph} - N - \text{OTs} + 2\text{Na}^+ \text{N} - \text{Ts} \quad \text{DMF} \]

\[ \text{Ph} - \text{N} - \text{N} - \text{Ts} \quad \text{Na, Bu'OH} \quad \text{Ph} - \text{N} - \text{N} - \text{NH} \]

The condensation of N-phenyldiethanolamide dichlorides, ditoluene-sulfonates or dimethanesulfonates with dithiols under the action of sodium hydroxide or potassium carbonate gave N-phenylthiiazacrown compounds \(8\) (for the derivative with X = OMs, n = 1, the yield was 40%).\(^{34–37}\)
Compounds 9, containing oxygen and sulfur atoms in various combinations in the macrocycle, have been prepared.\(^2\) The starting compounds used for this purpose were N-(4-methoxyphenyl)diethanolamine ditoluenesulfonate and diols or dithiols.

[Diagram]

\(n = 1, 2; X = \text{Cl, OTs, OMs};\)  
(a) NaOH, dioxane – BuOH; (b) K\(_2\)CO\(_3\), MeCN.

\(N\)-Phenylpolythiaaza-12-crown-4 ether by the reaction of \(o\)-aminophenol with the dichloride prepared from tetraethylene glycol on refluxing in water.

\[
\text{PhNH}_2 + \text{Cl}_2 \xrightarrow{\text{H}_2\text{O, }\Delta} \text{PhOCl}_2
\]

The reaction of aniline and its derivatives with the diiodides prepared from tri-, tetra- or pentaethylene glycols in the presence of sodium carbonate in acetonitrile resulted in the synthesis of arylazaazacrowns \(13, 25, 26, 42 – 50\)

\[
\text{PhNH}_2 + \text{Cl}_2 \xrightarrow{\text{Na}_2\text{CO}_3, \text{MeCN}} \text{PhOCl}_2
\]

\(N\)-Phenylaza-14-crown-4 ether 14, which contains two hydroxyl groups in the macroheterocycle, is formed upon the reaction of aniline with diethylene glycol diglycidyl ether in methanol at room temperature.\(^{51, 52}\)

\[
\text{PhNH}_2 + \xrightarrow{\text{MeOH, 20 }^\circ\text{C}} \text{PhOCl}_2
\]

The synthesis of \(N\)-phenyl-3-oxoaza-15(18)-crown-5(6) ethers 15 by the two-step condensation of \(N\)-(polyoxyethylene)anilines with bromoacetic acid has been described;\(^{53}\) first, the reaction is induced by sodium or potassium carbonate and then by the carbonate and benzenesulfonyl chloride in dioxane. However, the yields were low.

\[
\text{PhNH}_2 + \xrightarrow{\text{Br, MeOH, 20 }^\circ\text{C}} \text{PhOCl}_2
\]

Yet another version of the condensation of two fragments is the cyclodialkylation of anilines.\(^{22, 24, 41 – 53}\) This approach is usually employed to prepare \(N\)-phenylazaazacrown ethers with small rings. An early study\(^{41}\) describes the synthesis (without indication of the yields) of \(N\)-(2-hydroxyphenyl)aza-12-crown-4 ether by the reaction of \(o\)-aminophenol with the dichloride prepared from tetraethylene glycol on refluxing in water.

\[
\text{PhNH}_2 + \text{Cl}_2 \xrightarrow{\text{H}_2\text{O, }\Delta} \text{PhOCl}_2
\]

2. The introduction of a macrocyclic fragment by aromatic nucleophilic substitution

Many derivatives of \(N\)-phenylazaazacrown compounds have been obtained by arylation of the nitrogen atom in the macrocycle. Halobenzenes containing electron-withdrawing substituents are employed most often for this purpose.

Arylazacrown ethers 16a–e have been prepared by the reaction of aza-15-crown-5 ether with various fluoro- and
chloro-substituted benzenes (Table 1). The process conditions (heating of a reactant mixture in a polar solvent or in a neutral solvent under the action of a base) depend on the nature of the arylating reagent. Dinitrophenyl derivatives 16f (see Table 1) with various macrocycle sizes are formed in high yields in the reaction of 2,4-dinitrochlorobenzene with N-unsubstituted azacrown ethers in the presence of tetrabutylammonium acetate in diethyl ether.62, 63

The synthesis of (4-cyanophenyl)cyclam 17 from cyclam and 4-fluorobenzonitrile has been reported;64 however, the product yield is not indicated in the publication.

Bis(azacrown) compounds can be synthesised from dihalobenzenes. For example, the reaction of 1,5-difluoro-2,4-dinitrobenzene with two equivalents of cyclen 19 yields mainly bis(cyclen) 21. A small amount of cyclen 22 was also isolated (Scheme 1).66

The meta- and para-chloro derivatives of phenyldiazacrown ethers were synthesised by the reaction of the dichlorobenzene complex with cyclopentadienyliron hexafluorophosphate and diazacrown ether. The subsequent demetallation of the compounds formed was attained by irradiation with a halogen quartz lamp (100 W).67

Table 1. Preparation of N-arylazacrown ethers by arylation.

<table>
<thead>
<tr>
<th>Compound</th>
<th>X</th>
<th>R1</th>
<th>R2</th>
<th>R3</th>
<th>n</th>
<th>Reaction conditions (%)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>F</td>
<td>H</td>
<td>CN</td>
<td>H</td>
<td>1</td>
<td>a</td>
<td>70</td>
</tr>
<tr>
<td>b</td>
<td>F</td>
<td>H</td>
<td>NO2</td>
<td>H</td>
<td>1</td>
<td>a</td>
<td>59</td>
</tr>
<tr>
<td>c</td>
<td>Cl</td>
<td>Bz</td>
<td>NO2</td>
<td>NO2</td>
<td>1</td>
<td>b</td>
<td>84</td>
</tr>
<tr>
<td>d</td>
<td>Cl</td>
<td>NO2</td>
<td>CO2Me</td>
<td>NO2</td>
<td>1</td>
<td>b</td>
<td>77</td>
</tr>
<tr>
<td>e</td>
<td>Cl</td>
<td>CO2H</td>
<td>NO2</td>
<td>H</td>
<td>1</td>
<td>c</td>
<td>26</td>
</tr>
<tr>
<td>f</td>
<td>Cl</td>
<td>NO2</td>
<td>NO2</td>
<td>H</td>
<td>0–2</td>
<td>d</td>
<td>~95</td>
</tr>
</tbody>
</table>

The synthesis of (4-cyanophenyl)cyclam 17 from cyclam and 4-fluorobenzonitrile has been reported;64 however, the product yield is not indicated in the publication.

2',4'-Dinitrophenylcyclen 18 was prepared in two stages and characterised as the trihydrochloride. The reaction of 1-fluoro-2,4-dinitrobenzene with cyclen 19 was carried out in the presence of sodium hydrogen carbonate and was followed by treatment of compound 20 with hydrochloric acid in methanol.65

Boc is tert-butoxycarbonyl.

The synthesis of (4-cyanophenyl)cyclam 17 from cyclam and 4-fluorobenzonitrile has been reported;64 however, the product yield is not indicated in the publication.

Bis(azacrown) compounds can be synthesised from dihalobenzenes. For example, the reaction of 1,5-difluoro-2,4-dinitrobenzene with two equivalents of cyclen 19 yields mainly bis(cyclen) 21. A small amount of cyclen 22 was also isolated (Scheme 1).66

The meta- and para-chloro derivatives of phenyldiazacrown ethers were synthesised by the reaction of the dichlorobenzene complex with cyclopentadienyliron hexafluorophosphate and diazacrown ether. The subsequent demetallation of the compounds formed was attained by irradiation with a halogen quartz lamp (100 W).67

Table 1. Preparation of N-arylazacrown ethers by arylation.

<table>
<thead>
<tr>
<th>Compound</th>
<th>X</th>
<th>R1</th>
<th>R2</th>
<th>R3</th>
<th>n</th>
<th>Reaction conditions (%)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>F</td>
<td>H</td>
<td>CN</td>
<td>H</td>
<td>1</td>
<td>a</td>
<td>70</td>
</tr>
<tr>
<td>b</td>
<td>F</td>
<td>H</td>
<td>NO2</td>
<td>H</td>
<td>1</td>
<td>a</td>
<td>59</td>
</tr>
<tr>
<td>c</td>
<td>Cl</td>
<td>Bz</td>
<td>NO2</td>
<td>NO2</td>
<td>1</td>
<td>b</td>
<td>84</td>
</tr>
<tr>
<td>d</td>
<td>Cl</td>
<td>NO2</td>
<td>CO2Me</td>
<td>NO2</td>
<td>1</td>
<td>b</td>
<td>77</td>
</tr>
<tr>
<td>e</td>
<td>Cl</td>
<td>CO2H</td>
<td>NO2</td>
<td>H</td>
<td>1</td>
<td>c</td>
<td>26</td>
</tr>
<tr>
<td>f</td>
<td>Cl</td>
<td>NO2</td>
<td>NO2</td>
<td>H</td>
<td>0–2</td>
<td>d</td>
<td>~95</td>
</tr>
</tbody>
</table>

The synthesis of (4-cyanophenyl)cyclam 17 from cyclam and 4-fluorobenzonitrile has been reported;64 however, the product yield is not indicated in the publication.

Bis(azacrown) compounds can be synthesised from dihalobenzenes. For example, the reaction of 1,5-difluoro-2,4-dinitrobenzene with two equivalents of cyclen 19 yields mainly bis(cyclen) 21. A small amount of cyclen 22 was also isolated (Scheme 1).66

The meta- and para-chloro derivatives of phenyldiazacrown ethers were synthesised by the reaction of the dichlorobenzene complex with cyclopentadienyliron hexafluorophosphate and diazacrown ether. The subsequent demetallation of the compounds formed was attained by irradiation with a halogen quartz lamp (100 W).67

Table 1. Preparation of N-arylazacrown ethers by arylation.

<table>
<thead>
<tr>
<th>Compound</th>
<th>X</th>
<th>R1</th>
<th>R2</th>
<th>R3</th>
<th>n</th>
<th>Reaction conditions (%)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>F</td>
<td>H</td>
<td>CN</td>
<td>H</td>
<td>1</td>
<td>a</td>
<td>70</td>
</tr>
<tr>
<td>b</td>
<td>F</td>
<td>H</td>
<td>NO2</td>
<td>H</td>
<td>1</td>
<td>a</td>
<td>59</td>
</tr>
<tr>
<td>c</td>
<td>Cl</td>
<td>Bz</td>
<td>NO2</td>
<td>NO2</td>
<td>1</td>
<td>b</td>
<td>84</td>
</tr>
<tr>
<td>d</td>
<td>Cl</td>
<td>NO2</td>
<td>CO2Me</td>
<td>NO2</td>
<td>1</td>
<td>b</td>
<td>77</td>
</tr>
<tr>
<td>e</td>
<td>Cl</td>
<td>CO2H</td>
<td>NO2</td>
<td>H</td>
<td>1</td>
<td>c</td>
<td>26</td>
</tr>
<tr>
<td>f</td>
<td>Cl</td>
<td>NO2</td>
<td>NO2</td>
<td>H</td>
<td>0–2</td>
<td>d</td>
<td>~95</td>
</tr>
</tbody>
</table>
The refluxing of a mixture of aza-15(18)-crown-5(6) ethers (or diaza-15-crown-5 ether) with phloroglucinol with azeotropic removal of water gave rise to N-(3,5-dihydroxyphenyl)azacrown ethers\(^\text{23}\). Compounds\(^\text{23}\) condense with squaric acid to give squarelium dyes\(^\text{68, 70}\).

### 3. Cross-coupling reactions

In recent years, a new approach to the preparation of the compounds in question, based on palladium-catalysed N-arylation of azacrown ethers, has been developed\(^\text{66, 71 – 73}\). The reaction is normally carried out in toluene in the presence of sodium tert-butoxide. The advantage of this method is the possibility of using non-activated or sterically hindered aryl halides.

The cross-coupling of azacrown ethers catalysed by systems including a palladium complex ([Pd]) and a phosphine ligand (L) was first carried out for 4-nitro- and 4-cyanobromobenzenes. Aza-18(15,12)-crown-6(5,4) ethers were used to give arylazacrown compounds\(^\text{24}\) (Table 2, method\(^\text{A}\)).\(^\text{71}\) The highest product yields (57% – 88%) were observed when a mixture of Pd(OAc)\(_2\) and PPh\(_3\) was used as the catalyst.

![Chemical structure of compounds](image)

<table>
<thead>
<tr>
<th>Method</th>
<th>[Pd]</th>
<th>L</th>
<th>R(^1) – R(^5)</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Pd(dba)(<em>3), PdTol(</em>{o})(_3), PBut(_3); R(^1) = R(^2) = R(^3) = R(^5) = H, 0 – 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pd(OAc)(_2), PPh(_3); R(^3) = NO(_2), R(^1) = R(^2) = R(^3) = R(^5) = H, 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pd(_2)(dba)(_3); R(^1) = H, Me, Et, OMe, 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CF(_3), Cl; R(^2) = H, Me, OMe; R(^3) = H, Bu(_t), OMe, CF(_3), NMe(_2); R(^4) = R(^5) = H, Me</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>Pd(_2)(dba)(_3), Ph</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>P(But)_2; R(^1) = H, Me, Et, OMe, 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CF(_3), Cl; R(^2) = H, Me, OMe; R(^3) = H, Bu(_t), OMe, CF(_3), NMe(_2); R(^4) = R(^5) = H, Me</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(X = O: n = 1 (16%), 2; X = NCH\(_2\)C\(_6\)H\(_4\)OMe-2, n = 1.)

In the cross-coupling of cyclen\(^\text{19}\) with mono- and dihalo-benzenes resulted in the isolation of N-aryl-substituted\(^\text{25}\) and phenylene-bridged cyclens\(^\text{26}\) in moderate yields\(^\text{66}\). In the former case, toluene, THF, bromobenzene and a toluene –18-crown-6 mixture were used as solvents.

![Chemical structure of cyclens](image)

### Table 2. Preparation of N-arylazacrown ethers by cross-coupling.

<table>
<thead>
<tr>
<th>Method</th>
<th>[Pd]</th>
<th>L</th>
<th>R(^1) – R(^3)</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Pd(dba)(<em>3), PdTol(</em>{o})(_3), PBut(_3); R(^1) = R(^2) = R(^3) = H, 0 – 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pd(OAc)(_2), PPh(_3); R(^3) = NO(_2), R(^1) = R(^2) = R(^3) = R(^5) = H, 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pd(_2)(dba)(_3); R(^1) = H, Me, Et, OMe, 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CF(_3), Cl; R(^2) = H, Me, OMe; R(^3) = H, Bu(_t), OMe, CF(_3), NMe(_2); R(^4) = R(^5) = H, Me</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(X = I, Br = H, NO\(_2\), CH(OCH\(_2\)CH\(_2\))O, CHO; [Pd] = Pd(dba)\(_3\), Pd(OAc)\(_2\); L = 2,2’-bis(diphenylphosphino)-1,1’-binaphthyl (BINAP), 1,1’-bis(diphenylphosphino)ferrocene (DPFF), PPh\(_3\), 2-(di-tert-butylphosphino)biphenyl.)

(4-Cyanophenyl)cyclam\(^\text{17}\) (see Section II.2) is also formed upon arylation of cyclam with 4-bromobenzonitrile in the presence of the Pd(dba)\(_2\)-1-(R)-1-methoxyethyl)-2-(S)-diphenylphosphinoferrrocene (PFF-OMe) catalyst system and sodium tert-butoxide (yield 22%).\(^\text{73}\)
III. Functional derivatives of N-phenylazacrown compounds

Many functional derivatives of N-phenylazacrown compounds are formed during the construction of the macrocycle (see Section II). An alternative way is to introduce functional groups into the benzene ring of pre-formed N-phenylazacrown compounds via electrophilic substitution or to modify the existing substituents. Reactions of this type are presented below.

1. Nitro, nitroso and amino derivatives of N-phenylazacrown compounds

Direct nitration of N-phenylaza-15-crown-5 ether 1a with nitric acid at low temperature resulted in the 2,4-dinitrophenyl derivative 27.63 When N-(m-methoxyphenylaza)-15(18)-crown-5(6) ethers 1c,e were made to react with sodium nitrite in aqueous AcOH, nitration products 28 were isolated in high yields instead of the expected nitro compounds.74 The direction of substitution is determined by the aniline nitrogen atom — the nitro group enters the para-position with respect to this atom. The researchers suggested that nitration gives a radical cation as an intermediate. It is of interest that the use of traditional nitrating agents (HNO₃, HNO₂ – H₂SO₄ or NO₂BF₄) results in very low yields of nitration products in this reaction.

4'-Nitroso-N-phenylaza-15-crown-5 ethers 29 were prepared by nitrosation of N-phenylaza-15-crown-5 ethers with sodium nitrite in hydrochloric acid.20,69

A major route of modification of the nitroso group in N-phenylazacrown ethers is reduction to the amino group. The nitroso group in 29a was reduced with tin(II) chloride in HCl with heating (yield 87%)20 or with hydrogen in the presence of Raney nickel (Ni-Ra) at room temperature and atmospheric pressure (the yield was not reported).76

Amino derivatives of N-phenylazacrown ethers can also be prepared by palladium-catalysed reduction of nitro compounds with hydrogen or by reduction with tin(II) chloride.74

A number of para- or ortho-substituted N-(aminophenyl)aza- and -diazacrown ethers were synthesised by nucleophilic aromatic substitution of chlorine in complexes 31, followed by demetallation on exposure to UV light.67,77 The total yields of amino derivatives in relation to the starting dichlorobenzene complex with [CpM]+PF₆ were 26% – 37% (for M = Ru) and 50% – 96% (for M = Fe).

Many functional derivatives of N-phenylazacrown compounds were used in condensations with various...
substituted benzaldehydes, giving rise to chromoionophoric Schiff’s bases.\textsuperscript{21, 50}

\[
\begin{align*}
\text{R}^1 \text{CHO} + \text{H}_2 \text{N} - \text{N} - \text{Ph}\text{aza-15-crown-5 (6)} \rightarrow \text{PhH or EtOH} \\
\text{OHC-} + \text{Br}_2 \\
\text{OHC-} + \text{Br}_2
\end{align*}
\]

\(n = 1: \text{R}^1 = \text{OH}, \text{R}^2 = \text{R}^3 = \text{R}^4 = \text{H} (84\%); \text{R}^1 = \text{OH}, \text{R}^2 = \text{R}^3 = \text{H}, \text{R}^4 = \text{H}_2\text{N}, \text{R}^5 = \text{N} = \text{CH-} (80\%); \)

\(n = 2: \text{R}^1 = \text{H}, \text{R}^2 = \text{H}, \text{OMe}; \text{R}^3 = \text{H}, \text{OMe}, \text{NO}_2, \text{NMe}_2; \)

\(\text{R}^4 = \text{R}^5 = \text{H} (20\% - 84\%).\)

Acylation of \(m\)-amino-N-phenylaza-15-crown-5 ether \(32\) with acyl chlorides or acid anhydrides provided the synthesis of a series of amphiphilic azacrown ethers able to form bilayer membranes.\textsuperscript{30, 78}

[N-(4\(^0\)-Aminophenyl)azacrown ethers can add to naphthoquinones \(54\) and dicyanovinyl-containing heterocycles \(79\) to afford chromoionophoric compounds.

2. Halogen derivatives of N-phenylaza-15-crown compounds

Examples of the synthesis of bromo derivatives of N-phenylaza-15-crown compounds via electrophilic substitution are documented. Different brominating agents were used and the product yields were often high.

For example, bromination of N-phenylaza-15(18)-crown-5(6) ethers with tetrabutylammonium tribromide in dichloromethane\textsuperscript{30} or with N-bromosuccinimide (NBS) in tetrachloromethane\textsuperscript{31} furnishes the corresponding 4-bromophenyl derivatives \(33\).

<table>
<thead>
<tr>
<th>Reaction conditions</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) Bu(_4)NBr(_3), CH(_2)_Cl(_2); (b) NBS, CCl(_4)</td>
<td>(n)</td>
</tr>
<tr>
<td>(S)</td>
<td>(\text{H})</td>
</tr>
</tbody>
</table>

The \(o\)-bromo derivative of \(N\)-(formylphenyl)aza-15-crown-5 ether \(34\) was prepared from aldehyde \(35\) using tetrabromocyclohexadienone as the brominating reagent.\textsuperscript{82}

3. Formyl derivatives of N-phenylaza-15-crown compounds

Numerous publications have been devoted to the introduction of a formyl group into N-phenylaza-15-crown compounds. The formyla- tion of N-phenylaza-15(18)-crown-5(6) ethers \(19, 20, 27 - 29, 49\) and N-phenylpolythiaazacrown compounds \(83, 84\) has been accomplished by the Vilsmeier reaction.

\[
\begin{align*}
\text{CHO} + \text{R}_1 \text{R}_2 \text{O} + \text{R}_3 \text{R}_4 \text{O} & \rightarrow \text{OHC-} + \text{Br}_2 \\
\text{OHC-} + \text{Br}_2
\end{align*}
\]

X \(\text{R}_1 \text{R}_2 \text{POCl}_3, \text{DMF} \)

\(n = 1, 2.\)

Hydrogenolysis of benzyl ether \(37a\) at room temperature and a pressure of 1 atm resulted in salicylaldehyde derivative \(38a\).
Treatment of dimethoxy derivative 37b with aluminium chloride in dichloromethane induces the selective demethylation of the methoxy group located in the ortho-position relative to the formyl group to give compound 38b. Hydroxylaldehydes 38 were used to prepare fluorophores, in particular, azacrown-containing coumarins.

\[
\begin{align*}
37a.b(R^1 = H, R^2 = OBn (a); R^1 = R^2 = OMe (b)).
\end{align*}
\]

The introduction of the reactive formyl group in the molecule opens the way for the preparation of other derivatives of azacrown compounds. Indeed, the reaction of aldehyde \(N\)-phenylaza-15-crown-5 ether 40 with hydroxylamine in aqueous ethanol affords oxime 39, which is reduced by zinc in acetic acid to yield aminomethylated \(N\)-phenylaza-15-crown-5 ether 40.28,29

\[
\begin{align*}
\text{OHC} & \text{N} \text{O} \\
\text{O} & \text{O} \\
\text{R}^1 & \text{R}^2 \\
\text{37a.b} & \text{NH}_2 \text{O} \text{HCl, K}_2 \text{CO}_3, \text{EtOH, H}_2 \text{O} \\
\text{HCl} & \text{Zn, AcOH} \\
\text{39} (96\%) \\
\text{H}_2\text{NCH}_2\text{CH}_2 & \text{O} \text{Me} \\
\text{40} (78\%) \\
\end{align*}
\]

By the reaction of 2,4-dinitro-6-trifluoromethylphenylhydrazone with the formyl derivatives 35 (\(X = O, n = 3\)) and 41 (\(X = S, n = 1, 3\)), the corresponding hydrazones have been obtained.83,85,88 These were used for the extraction of heavy and transition metal ions.83,85,87

\[
\begin{align*}
o & \text{NO}_2 \\
& \text{CF}_3 \\
\text{35, 41} & \text{NH}_2 \text{NHNH}_2 + \text{OHC} \\
& \text{AcOH, EtOH} \\
& \text{O} \text{N} \text{CF}_3 \\
& \text{X = O; n = 3 (49\%); X = S; n = 1 (39\%), 3 (52\%).}
\end{align*}
\]

The condensation of aldehyde 35 with para-substituted anilines provided the route to chromoionophoric Schiff’s bases.21

The aldehyde functional group in azacrown compounds can also be modified via reactions with \(C\)-nucleophiles. 4'-Formyl-\(N\)-phenylaza-15-crown-5 ether 35 reacts with acetone in an alkaline medium to give bis(crown ether) dibenzylideneacetone, which exhibits fluoroionophoric properties.88

Compounds containing an active methylene group can undergo Knoevenagel condensation with the formyl derivatives of \(N\)-phenylazacrown ethers. Under these conditions, 4'-formyl-\(N\)-phenylaza-18(15)-crown-6(5) ethers react with malononitrile to yield crown-containing benzylideneunonitriles.75

The nitroethylene derivative 42 has been prepared by the reaction of aldehyde 37c with nitromethane in an acetic acid–ammonium acetate mixture. The reduction of this product gives azacrown ether 43,26,29 which has found application as an intermediate en route to fluorescent indicators of sodium ions.

\[
\begin{align*}
\text{MeNO}_2 & \text{AcONH}_2, \text{AcOH} \\
\text{LiAlH}_4, \text{THF} \\
\text{42 (60\%)} \\
\text{H}_2\text{NCH}_2\text{CH}_2 & \text{O} \text{Me} \\
\text{43 (80\%–90\%)} \text{O} \text{Me} \\
\end{align*}
\]

The reduction76 of the formyl group in \(N\)-phenylaza-15-crown-5 ether 35 on treatment with sodium borohydride affords the corresponding alcohol, while the oxidation of this group89 with sodium permanganate in aceton affords crown-containing benzoic acid 44.

\[
\begin{align*}
\text{NaBH}_4 & \text{EtOH} \\
\text{35} & \text{HOCH}_2 \text{N} \text{O} (100\%) \\
\text{K}_{2} \text{MnO}_4, \text{MeCO} & \text{H}_2\text{O} \text{C} \text{N} (30\%) \\
\text{44} (30\%) \\
\end{align*}
\]

Cinnamaldehydes based on \(N\)-phenylazacrown ethers were prepared by two routes. One employs the Wittig reaction of aldehyde 35 with phosphonium salt 45.82 In the alternative procedure,90 the modified Vilsmeier reaction of \(N\)-phenylazacrown ethers with \(N\)-methyl-\(N\)-phenyl-3-aminoacrolein is used; the products are formed under mild conditions in 35\% (\(n = 1\)) and 37\% (\(n = 2\)) yields.
The formyl derivatives of N-phenylazacrown ethers are widely used in the synthesis of crown-containing stilbenes, diphenylbutadienes, and styryl merocyanine and butadienyl dyes. These compounds have chromo- and fluoroionophore properties and are distinguished by high sensitivity and selectivity with respect to alkali and alkaline earth metal cations.

4. Azacrown-containing benzoic acids

The preparation and chemical properties of azacrown compounds containing an N-(4-carboxy)phenyl group are considered only in two papers.

The synthesis of azacrown-containing benzoic acid 44 from the formyl derivative has been described above (see Section II.1). The same compound is produced when carbon dioxide is passed into a tetrahydrofuran solution of the lithium derivative of N-(p-bromophenyl)azacrown-5 ether.

Acid 44 has been converted to give diverse derivatives, namely, the methyl ester (by the reaction with dimethyl sulfate in the presence of potassium carbonate in acetone), the chloride (on treatment with SOCl₂ in a DMF–toluene mixture) and the amide (by the reaction of the chloride with 4-aminopyridine) (Scheme 2).

IV. N,N'-Diphenyldiazacrown compounds

Generally, the routes to N,N'-diphenyldiazacrown compounds differ little from the above methods used to prepare their analogues with one nitrogen atom in the macrocycle. Diphenyldiazacrown ethers are obtained most often by condensation of two fragments and by N-arylation of diazacrown ethers.

1. Routes based on the condensation of two fragments

The two versions of this type of condensation (the reactions of toluenesulfonates with alcohols under the action of bases) are presented below. The reaction of N-phenylazidiethanolamine ditoluenesulfonates with N-phenylazidiethanolamine or N-phenylazateatraethylene glycol derivatives in the presence of sodium hydride resulted in para-substituted N,N'-diphenyldiaza-12(18)-crown-6(4) ethers.

In a similar method, N-phenylazatetraethylene glycol ditoluene-nesulfonates react with N-phenylazidiethanolamine, which also gives N,N'-diphenyldiaza-18-crown-6 ether (n = 1). In this case, potassium tert-butoxide was used as the base.

The condensation of dihalide 47 with various dithiols affords N,N'-diphenyltetraazadiiaza-18-crown-6 ether 48 and N,N'-diphenyldiaza-15-crown-5 compound 49 containing two S atoms and one O atom in the macrocycle.

Hal = Br, X = Si(CH₃)₂S (48, 11%); X = O (49).

As noted above (see Section II.1), the N,N'-diphenyltetraazadiiaza-18-crown-6 compound 11, in which the nitrogen atoms in the macrocycle are separated by three ethylene units, has been isolated as a side product in 2% yield in the synthesis of N-phenylazidiethiaaziaza-9-crown-3 compound 10 (see Section II.1).

The condensation of diphenyldiamines 50a–g and 51 (prepared from the corresponding anilines) (Scheme 3) with the dichlorides of dibasic carboxylic acids followed by the reduction of the obtained diamides is another method for the
synthesis of \(N,N'\)-diphenyldiazacrown derivatives. The reactions of compounds \(50a - g\) were carried out in the presence of pyridine in benzene or toluene under high dilution conditions (Table 3). The reducing agents used included boron compounds (\(B_2H_6\), \(BH_3\) complexes with \(Me_2S\) or \(THF\), \(NaBH_4\)) and lithium tetrahydroaluminate. \(N,N'\)-Diphenyldiaza-24-crown-8 ethers \(52d\) (\(n = 2\), \(m = 2\)) and \(52g\) (\(R_1 = H; R_2 = Me, MeO, Br; n = 2; m = 2\)) were prepared in 18%–33% total yields relative to the starting 4-substituted aniline.\(^{124}\)

A similar reaction of dianiline \(51\) was carried out in benzene under the action of triethylamine.\(^ {123}\)

The removal of the tosyl protective groups from the nitrogen atoms in diazacrown compound \(52c\) was induced by sodium naphthalenide in tetrahydrofuran under mild conditions (yield 70%).\(^ {120}\) Diaza-15(18)-crown-5(6) ethers \(52e, f\) were used to prepare azo dyes.\(^ {126}\)

A series of macrocyclic \(N,N'\)-diaryldiaza(oligomethylene)diamides \(53\) has been obtained by condensation of diaryldiamines containing different numbers of methylene groups with dicarboxylic acid dichlorides on treatment with triethylamine in benzene under high dilution conditions (Scheme 4).\(^ {127,128}\) Compounds \(53\), when introduced into polyvinyl chloride membranes, have shown high selectivity for \(Li^+\) ions.

2. Aromatic nucleophilic substitution reactions

Like azacrown ethers, diaza derivatives can be prepared by aromatic nucleophilic substitution in which the amino group of the crown compound attacks the carbon atom bonded to a halogen in an activated aryl halide.

\(N,N'\)-Diphenyldiazacrown compounds \(54a - j\), containing electron-withdrawing substituents in the para- and ortho-positions of the benzene ring, have been synthesised by \(N,N'\)-diarylated diazacrown ethers.\(^ {60,61,122,129-131}\) The conditions of this reaction (the type of base and solvent) were mainly determined by the nature of the arylating agent. For example, the reaction of diaza-18-crown-6 ether with 2-chloro-5,5-dinitrobenzophenone

![Scheme 3](image-url)

![Scheme 4](image-url)

\(X = \text{CMe}_2\text{CMe}_2; n = 6, 10, 12, 14 (61%–85%); X = \text{CH}_2\text{CMe}_2\text{CH}_2; n = 10 (62%), 12 (58%).\)

**Table 3.** Diphenyldiazaether derivatives \(52\).

<table>
<thead>
<tr>
<th>Compounds</th>
<th>(R_1)</th>
<th>(R_2)</th>
<th>(m)</th>
<th>(n)</th>
<th>Yield (%)</th>
<th>(\text{[H]})</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>(50, 52)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a</td>
<td>H</td>
<td>Br</td>
<td>1</td>
<td>0</td>
<td>74</td>
<td>84</td>
<td>BH(_3)·Me(_2)S</td>
</tr>
<tr>
<td>b</td>
<td>H</td>
<td>Br</td>
<td>1</td>
<td>1</td>
<td>69</td>
<td>71</td>
<td>BH(_3)·Me(_2)S</td>
</tr>
<tr>
<td>c</td>
<td>NHTs</td>
<td>H</td>
<td>1</td>
<td>1</td>
<td>62</td>
<td>61</td>
<td>Li(\text{AlH}_4)</td>
</tr>
<tr>
<td>d</td>
<td>H</td>
<td>H</td>
<td>1</td>
<td>1</td>
<td>73</td>
<td>71</td>
<td>B(_3\text{H}_8)</td>
</tr>
<tr>
<td>e</td>
<td>H</td>
<td>H</td>
<td>1, 2</td>
<td>0–2</td>
<td>33–71</td>
<td>41–50</td>
<td>BH(_3)·THF</td>
</tr>
<tr>
<td>f</td>
<td>H</td>
<td>H</td>
<td>2</td>
<td>2</td>
<td>–</td>
<td>18–33*</td>
<td>BH(_3)·THF</td>
</tr>
<tr>
<td>g</td>
<td>OMe</td>
<td>H</td>
<td>1</td>
<td>0</td>
<td>67</td>
<td>98</td>
<td>Na(\text{BH}_4)</td>
</tr>
<tr>
<td>h</td>
<td>OMe</td>
<td>H</td>
<td>1</td>
<td>0</td>
<td>–</td>
<td>–</td>
<td>B(_3\text{H}_8)</td>
</tr>
<tr>
<td>i</td>
<td>OMe</td>
<td>H</td>
<td>1</td>
<td>1</td>
<td>73</td>
<td>92</td>
<td>Na(\text{BH}_4)</td>
</tr>
<tr>
<td>j</td>
<td>H</td>
<td>Me, MeO, Br</td>
<td>2</td>
<td>2</td>
<td>–</td>
<td>18–33*</td>
<td>BH(_3)·THF</td>
</tr>
</tbody>
</table>

*The yield is given in relation to the starting 4-substituted aniline.
or with methyl 4-chloro-3,5-dinitrobenzoate in the presence of triethylamine in benzene gives compounds 54a.b in high yields.60

Compounds 54c.d were prepared in a similar way.60

$N,N'$-Diphenyldiazacrown ethers 54e.f, containing ortho-nitro- and para-trifluoromethy groups, were prepared by the reaction of diazacrown ethers with the corresponding aryl chloride in the presence of triethylamine in THF under rigorous conditions (8 kbar pressure).129,130 Diaza-15-crown-5 ether reacts with 2-fluoro-5-nitroisole61 and diaza-18-crown-6 ether reacts with 4-fluoronitrobenzene 131 in pyridine, giving rise to $N,N'$-bis(nitrophenyl)diazacrown ethers 54g.h. The diaacetyl derivatives 54i.j were produced upon condensation of diaza-18(15)-crown-6(5) ethers with 4-fluoropropiophenone in the presence of tetra-n-butylammonium fluoride at 150 °C.121

### Cross-coupling reactions

The preparation of $N,N'$-diphenyldiazacrown compounds via cross-coupling has been reported.132 The arylation of diaza-18-crown-6 ether with $p$-bromobenzotrifluoride catalysed by $\text{Pd}_2(\text{dba})_3$ – Xantphos in the presence of the Carbopack C graph- 

without a solvent resulted in compound

3. Cross-coupling reactions

The preparation of $N,N'$-diphenyldiazacrown compounds via cross-coupling has been reported.132 The arylation of diaza-18-crown-6 ether with $p$-bromobenzotrifluoride catalysed by $\text{Pd}_2(\text{dba})_3$ – Xantphos in the presence of the Carbopack C graph- 

without a solvent resulted in compound 55.

### 4. The substitution of hydrogen by diazacrown compounds

This method for the synthesis of $N,N'$-diphenyldiazacrown ethers, which is seldom encountered in the literature, is based on the addition of diazacrown ethers to an activated double bond followed by oxidation of the resulting adduct with excess reagent. $N,N'$-Diphenyldiazacrown ethers 56a.b, containing ortho- and meta-methoxy groups in the benzene rings have been prepared by hydrogenation of crown-containing $p$-benzoquinones 57a.b. The reaction takes place in MeOH under atmospheric pressure at room temperature in the presence of palladium.61,133,134 Macro-

### V. Functional derivatives of $N,N'$-diphenyldiaza-

crown compounds

The transition from unsubstituted $N,N'$-diphenyldiazacrown compounds to their functional derivatives is similar to the reactions of $N$-phenylazacrown compounds.

1. Nitro and amino derivatives of $N,N'$-diphenyldiazacrown compounds

$N,N'$-Bis(nitrophenyl)diazacrown compounds can be prepared by the nitration of the aromatic ring. Treatment of $N,N'$-diallyl-

diazia-15-crown-5 ether 56a with an HNO$_3$ – AcOH mixture results in 4,4'-dinitro derivative 58.131 $N,N'$-Bis(n-methoxyphenyl)diaza-15(18)-crown-5(6) ethers 52e.f react with sodium nitrite in aqueous AcOH (see also Section III.1) to give compounds 59 containing one or two nitro groups, whose ratio depends on the macrocycle size.74 The researchers noted that the use of traditional nitrating agents (HNO$_3$, HNO$_3$ – H$_2$SO$_4$ or NO$_2$BF$_3$) results in a total yield of both mono- and dinitration products of only 5% – 10%.

![Diagram](image_url)
Amines 60a–d have been prepared by the reduction of nitro derivatives of N,N′-diaryldiazacrown ethers with hydrogen in the presence of a palladium catalyst in dimethylformamide or ethanol. Conducting the reaction in acetic anhydride gave 4,4′-diacetamide derivative 60e.

<table>
<thead>
<tr>
<th>Compound 60</th>
<th>R1</th>
<th>R2</th>
<th>R3</th>
<th>R4</th>
<th>R5</th>
<th>n</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>NO2</td>
<td>H</td>
<td>H</td>
<td>NH2</td>
<td>H</td>
<td>2</td>
<td>–</td>
</tr>
<tr>
<td>b</td>
<td>NO2</td>
<td>OMe</td>
<td>OMe</td>
<td>NH2</td>
<td>H</td>
<td>1</td>
<td>&gt;95</td>
</tr>
<tr>
<td>c</td>
<td>H</td>
<td>H</td>
<td>OMe</td>
<td>H</td>
<td>H</td>
<td>1</td>
<td>59</td>
</tr>
<tr>
<td>d</td>
<td>H</td>
<td>H</td>
<td>OMe</td>
<td>H</td>
<td>NHAc</td>
<td>2</td>
<td>75</td>
</tr>
<tr>
<td>e</td>
<td>NO2</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>Ac</td>
<td>1</td>
<td>82</td>
</tr>
</tbody>
</table>

The bromine atom in compound 52g is easily replaced by the morpholine residue in the presence of a palladium catalyst.

The acylation of diamine 61 with succinic anhydride in pyridine gave the corresponding disuccinic acid.

2. Formyl derivatives of N,N′-diphenyldiazacrown compounds

The formyl derivatives of N,N′-diphenyldiazacrown ethers 63a–e and N,N′-diphenylthiadiazacrown compounds 64 and 65 were obtained by the Vilsmeier reaction.
On treatment with boron trichloride, compounds 63b,c undergo selective demethylation of the methoxy groups that occupy the ortho positions with respect to the formyl functions. Dinaldehyde 66 thus formed was used to prepare fluorescent reagents for Na⁺ and K⁺ ions.61,133,134

The condensation of diformyl derivatives of N,N’-diphenyldiazao-18-crown-6 ether 63c and N,N’-diphenyltetraazadiaco-18-crown-6 compound 64 with dinitromethoxyphenylhydrazine affords hydrazones that are used as fluorescent indicators for the Na⁺ and K⁺ ions.61,133,134

3. Acyl derivatives of N,N’-diphenyldiazacrown compounds
Diazacrown-containing α,β-unsaturated ketones 69a,b were prepared by converting the methyl groups of the propionyl substituent of compounds 54a,b into methylene groups (see Section IV.2).122 The reaction took place via selenium derivatives 70a.b. The enolates, obtained by deprotonation of ketones 54 under the action of lithium disopropylamide, reacted with phenylselenenyl chloride under mild conditions. The oxidation of diselenides 70 with sodium periodate was accompanied by elimination of organoselenenyl residues. Compounds 69a,b thus formed react with arylhydrazines to give pyrazolines that are used as fluorescent indicators for the Na⁺ and K⁺ ions.

VI. Benzoazacrown compounds

Benzoazacrown compounds that contain one or two nitrogen atoms conjugated with the benzene ring are obtained most often by [1+1]-condensation. In some cases, intramolecular cyclisation of podands (open-chain analogues of crown ethers) is used.

1. Condensation of two fragments

One method of synthesis of benzoaza- and benzodiazaacrown compounds is the reaction of 2-aminophenols or α-phenylenediamines with oligoethylene glycol derivatives.41,136–143

Thus by condensation of 2-aminophenols and α-phenylenediamine with the dichlorides, obtained from oligoethylene glycols, in DMF or water. Lockhart et al.41,136,137 performed the first synthesis of azacrown compounds 71 with different macrocycle sizes (the yields were not reported). More recently, the same researchers described the synthesis138 of benzodiaza-15-crown-5 ether 71 by the condensation of α-phenylenediamine with tetraethylenglycol ditoluenesulfonate under the action of potassium carbonate in dimethylformamide on heating; however, the product yield was low.

By the reaction of 2-aminophenol with the dichlorides prepared from tri- and tetraethylene glycol in aqueous butanol in the presence of sodium hydroxide, Pedersen and Bromels139 have synthesised benzoaza-15(18)-crown-5(6) ethers 71 in moderate yields (25% and 16%, respectively). The same method140 resulted in isolation of benzoaza-15-crown-5-ether in only 8% yield.

Benzodiaza-9-crown-3 compounds 72a–d have been prepared by condensation of N,N’-disubstituted α-phenylenediamines with chlorex.141,142 The tosyl groups in compound 72c are removed by heating in concentrated H2SO4 (yield 48%).
Mesyl protection has also been used for the synthesis of nitrogen-containing benzocrown compounds. Mesylamides form crown compounds in higher yields than the corresponding tosylamides; however, it is difficult to prepare N-unsubstituted products from them. No data on the successful removal of mesyl groups from compounds 73 can be found in the literature.

Several examples of the synthesis of benzazacrown compounds based on their linear analogues have been reported. Thus podands 80 and 81, containing two terminal NH or SH groups, have been converted into benzopolyaza- and benzopolythiaaza-crown compounds 82 and 83. The removal of the tosyl groups in compound 82 was accomplished under acidic conditions as for sulfonamide 72c, namely, by heating the compound in concentrated H$_2$SO$_4$ (yield 94%).

The condensation of podand 84 with diethanolamine tritoluene sulfonate induced by potassium tert-butoxide in tert-b Butler alcohol furnished the tosyl derivative of benzodiaza-18-crown-6 ether 85. In this case, the N-tosyl group was removed by treatment with lithium tetrahydroaluminate.

Acylation of benzodiaza-18-crown-6 ether 86 with $O,O'$-ethylenediglycolic acid dichloride in THF in the presence of pyridine, followed by the reduction of the resulting diamide 87 with the borane complex with THF, afforded the corresponding benzocryptand 88.
2. Arylation of 2,0-diamino compounds with 1,2-dihalobenzenes

The reactions of o-dihalobenzenes with diamines deserve a separate section. In these cases, the bonds between the nitrogen atoms and the benzene ring are formed as a result of nucleophilic aromatic replacement of halogen atoms in activated alky halides or as a result of C=N cross-coupling.

The benzodithiadiazacrown compound 89, containing two nitrile groups on the benzene ring, has been prepared by the reaction of 4,5-dichlorophthalonitrile with an acyclic ditosylamide under the action of potassium carbonate in DMF. The benzodithiadiazacrown compound 90, containing two nitrile groups on the benzene ring, has been prepared by the reaction of 4,5-dichlorophthalonitrile with an acyclic ditosylamide under the action of potassium carbonate in DMF.

Benzocyclam 90 and benzoazacyclam compounds 91a – e with different macrocycle sizes were prepared by amination of 1,2-di- or 1,2,3-trihalobenzenes with linear polyamines in the presence of the Pd(dba)2 – BINAP catalyst system. In addition to the macrocycles, linear products were also isolated in these reactions. The attempts to prepare benzocyclam-15-crown-5 ether derivatives from 2,6-dichlorobromobenzene and the corresponding trioxadiamino compounds with the same catalyst system have not met with success. Only the linear product was isolated in this case.

3. Intramolecular cyclisation of podands

This method of synthesis is based on the transformation of a linear molecule into a macrocycle with an annelated benzene ring. Urethane-type benzoazacrown compounds 92 are obtained from betaines 93. Under drastic conditions, these products rearrange into intermediate, readily cyclisable N-aryl isocyanates. The addition of template salts (NaBF₄, KBF₄) was found to affect only slightly the yields of these crown compounds.

Hydrogenation of nitrobenzenes containing an aldehyde function in the peripheral substituent, over a platinum or a palladium catalyst in ethanol, furnished a large series of benzoazacrown compounds 94a – g. Apart from compounds 94, the reaction mixture contained in some cases debenzoazacrown compounds 95b – g and polymerisation products. It was shown that the formation of nine- or ten-membered macrocycles is less favourable than the formation of dimers 95 with a macrocycle comprising 18 – 20 units (see below, Section VIII.2.a, synthesis of compounds 95h – o). After the introduction of an N-benzoyl group into the nitroaldehyde molecule, this reaction gives only the nine-membered compound 94a. Monomers 94f,g with a macrocycle size of 15 and 16 units are formed more readily than the corresponding dimers 95f,g (30- and 32-membered rings). In these cases, the 94/95 ratio in the products varies from 1.5 : 1 to 3 : 1. It is noteworthy that 11-, 13- and 14-membered benzoazacrown compounds 94c – e were synthesised in high yields without dimer formation (except for slight amounts of 95e).

<table>
<thead>
<tr>
<th>Compound 91</th>
<th>X</th>
<th>Y</th>
<th>n</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>CH₃CH₂</td>
<td>CH₂</td>
<td>1</td>
<td>47</td>
</tr>
<tr>
<td>b</td>
<td>CH₃</td>
<td>CH₂</td>
<td>1</td>
<td>27</td>
</tr>
<tr>
<td>c</td>
<td>CH₃</td>
<td>CH₂CH₂</td>
<td>1</td>
<td>17</td>
</tr>
<tr>
<td>d</td>
<td>CH₂</td>
<td>CH₂</td>
<td>2</td>
<td>12</td>
</tr>
<tr>
<td>e</td>
<td>CH₂</td>
<td>CH₂</td>
<td>3</td>
<td>10</td>
</tr>
</tbody>
</table>

4. Synthesis of benzoazacrown ethers by the transformation of the benzoazacyclam macrocycle

We proposed a new methodology for the synthesis of benzoazacrown ethers based on a stepwise ring transformation of benzoazacrown ethers. A distinctive feature of this method is macrocycle opening upon cleavage of the Ar–O bond followed by ring closure to give the corresponding aza analogues. The starting compounds used were benzoazacrown ethers whose benzene ring contained an electron-withdrawing group (nitro or formyl group), which activated the regioselective macrocycle opening induced by amines.

For successful recyclisation, the hydroxyl group present in the nitrogen-containing podands thus formed was
replaced by a better leaving group such as a chlorine or an iodine atom. The general pattern of the stepwise ring transformation in benzocrown ethers can be represented by Scheme 5.

The key step of this reaction sequence is ring closure in the podands to give the azamacrocycle. Several procedures differing in the reaction conditions were developed. Ring closure in the halogen derivatives of azapodands can take place both under the action of bases and without bases. Most often, iodine derivatives of azapodands are used to prepare benzoazacrown ethers.

Heating of formyl-containing iodides in the presence of alkali metal carbonates affords N-methylbenzoazacrown ethers together with N-demethylated benzoazacrown ethers as side products (yields 11%–18%). However, in the absence of bases, the reaction gives mainly (in some cases, only) N-demethylated benzoazacrown ethers. A drawback of the two methods of ring closure is the very long duration: the reaction does not go to completion even after 150 h. An increase in the time of heating results in a pronounced decrease in the yield of products.

As an example of another application of podands in the synthesis of benzoazacrown ethers, one can consider the synthesis of compound 100, which contains an ester group in the macrocycle. This azacrown ether was prepared in two ways: by intramolecular esterification of acid 101 under the action of N,N'-dicyclohexylcarbodiimide (DCC) and by transesterification of podand 102 in the presence of p-toluene sulfonic acid as the catalyst (Scheme 6). The resulting N-methylated benzoazacrown ethers form complexes with metal cations characterised by high stability constants, due to the specific features of their conformations. The complexity properties of these compounds substantially exceed those of widely used N-phenylazacrown ethers (and in many cases, benzocrown ethers, too) with the same macrocycle size.

Owing to the presence of a nitro or a formyl group in the products, heating results in a pronounced decrease in the yield of products. The use of alkali metal hydroxides or NaH, which are stronger bases than alkali metal carbonates, allows selective preparation of these compounds substantially exceed those of widely used N-phenylazacrown ethers (and in many cases, benzocrown ethers, too) with the same macrocycle size.

As an example of another application of podands in the synthesis of benzoazacrown ethers, one can consider the synthesis of compound 100, which contains an ester group in the macrocycle. This azacrown ether was prepared in two ways: by intramolecular esterification of acid 101 under the action of N,N'-dicyclohexylcarbodiimide (DCC) and by transesterification of podand 102 in the presence of p-toluene sulfonic acid as the catalyst (Scheme 6). The resulting N-methylated benzoazacrown ethers form complexes with metal cations characterised by high stability constants, due to the specific features of their conformations. The complexity properties of these compounds substantially exceed those of widely used N-phenylazacrown ethers (and in many cases, benzocrown ethers, too) with the same macrocycle size. Owing to the presence of a nitro or a formyl group in the products obtained, it is possible to convert them into diverse derivatives containing benzoazacrown ether fragments. These can be used as selective ligands for metal cations, for the extraction of metal ions.

---

**Table 4. Methods for the preparation of azacrown ethers from halopodands.**

<table>
<thead>
<tr>
<th>Compounds</th>
<th>n</th>
<th>Reaction conditions</th>
<th>Yield of 97 (%)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>a (X = CHO)</td>
<td>0 I</td>
<td>M_2CO_3 (M = Li, Na, K, Rb, Cs), MeCN</td>
<td>53–67</td>
<td>159–161</td>
</tr>
<tr>
<td>1 I</td>
<td>NaH, THF</td>
<td>61–68</td>
<td>166</td>
<td></td>
</tr>
<tr>
<td>1 I</td>
<td>NaOH, dioxane</td>
<td>52–63</td>
<td>162–165</td>
<td></td>
</tr>
<tr>
<td>2 I</td>
<td>M_2CO_3 (M = Li, Na, K, Rb), MeCN</td>
<td>53–61</td>
<td>159–161</td>
<td></td>
</tr>
<tr>
<td>2 I</td>
<td>NaH, THF</td>
<td>61–63</td>
<td>166</td>
<td></td>
</tr>
<tr>
<td>2 I</td>
<td>M_2CO_3 (M = Li, Na, K, Rb), MeCN</td>
<td>52–56</td>
<td>159–161</td>
<td></td>
</tr>
<tr>
<td>b (X = NO_2)</td>
<td>0 I</td>
<td>NaH, THF</td>
<td>51–57</td>
<td>166</td>
</tr>
<tr>
<td>1 I</td>
<td>NaOH, dioxane</td>
<td>36</td>
<td>162–165</td>
<td></td>
</tr>
<tr>
<td>1 I</td>
<td>Na_2CO_3, MeCN</td>
<td>54</td>
<td>165</td>
<td></td>
</tr>
<tr>
<td>1 I</td>
<td>NaH, THF</td>
<td>74–80</td>
<td>162–165</td>
<td></td>
</tr>
<tr>
<td>1 I</td>
<td>NaOH, dioxane</td>
<td>56</td>
<td>162, 165</td>
<td></td>
</tr>
<tr>
<td>2 I</td>
<td>NaH, THF</td>
<td>71</td>
<td>162–165</td>
<td></td>
</tr>
</tbody>
</table>

---

**Scheme 5**

---

**Notes:**

- The use of alkali metal hydroxides or NaH, which are stronger bases than alkali metal carbonates, allows selective preparation of N-methylbenzoazacrown ethers 97a–161 together with N-demethylated benzoazacrown ethers 98a as side products (yields 11%–18%). However, in the absence of bases, the reaction gives mainly (in some cases, only) N-demethylated benzoazacrown ethers. A drawback of the two methods of ring closure is the very long duration: the reaction does not go to completion even after 150 h. An increase in the time of heating results in a pronounced decrease in the yield of products.

- As an example of another application of podands in the synthesis of benzoazacrown ethers, one can consider the synthesis of compound 100, which contains an ester group in the macrocycle. This azacrown ether was prepared in two ways: by intramolecular esterification of acid 101 under the action of N,N'-dicyclohexylcarbodiimide (DCC) and by transesterification of podand 102 in the presence of p-toluene sulfonic acid as the catalyst (Scheme 6). The resulting N-methylated benzoazacrown ethers form complexes with metal cations characterised by high stability constants, due to the specific features of their conformations. The complexity properties of these compounds substantially exceed those of widely used N-phenylazacrown ethers (and in many cases, benzocrown ethers, too) with the same macrocycle size. Owing to the presence of a nitro or a formyl group in the products obtained, it is possible to convert them into diverse derivatives containing benzoazacrown ether fragments. These can be used as selective ligands for metal cations, for the extraction of metal ions.
from water and for membrane transport of metal ions, as ion selective dyes and fluoroionophores, in ion selective electrodes, and as parts of polymer films and Langmuir–Blodgett films.

VII. Functional derivatives of benzoazacrown compounds

1. Synthesis of benzoazacrown compounds with substituents in the benzene ring

Only a few examples of the synthesis of benzoazacrown derivatives by electrophilic substitution in the benzene ring have been reported.

On treatment with sodium nitrite in hydrochloric acid under mild conditions, benzoaza-15-crown-5 ether $\text{71}$ is converted into $N$-nitroso derivative $\text{103}$, which isomerises in the presence of cold concentrated HCl to give 3′-nitrosobenzo derivative $\text{104}$.\(^{139}\)

Azo coupling of benzoaza-12-crown-4 with $p$-nitrophenyldiazonium chloride leads to crown-containing azobenzene in which the substituent is in the para-position relative to the macrocycle nitrogen atom.\(^{169}\)

Compound $\text{105}$ undergoes selective nitration, under mild conditions, of the 5-position of the benzene ring annelated to the macrocycle.\(^{147}\)

4′-Nitrobenzotriazacrown compound $\text{106}$ (see below, Section VII.2) is reduced with hydrogen in the presence of a palladium catalyst to form aniline derivative $\text{107}$.\(^{147}\) This product reacts with picryl chloride in the presence of potassium carbonate to afford benzotriazacrown compound $\text{105}$.\(^{147}\)

The formylation of benzocryptand $\text{88}$ has been carried out by the Vilsmeier reaction.\(^{149}\)

B is 4-pyrrolidinopyridine.
2. Benzoazacrown derivatives at the macrocycle nitrogen atom

The examples of synthesis of functional derivatives at the nitrogen atom refer to benzoaza-15-crown-5 ether $71$. This compound reacts with acyl chlorides with acylation of the secondary nitrogen atom. $^{136}$

$$
\begin{align*}
X = \text{Br (a, 95%), CO}_2\text{H (b, 59%).}
\end{align*}
$$

The amide bond in compound $108a$ was reduced with various reagents. This gave $N$-alkylbenzoaza-15-crown-5 ethers in good yields. $^{136}$

Attempts at alkylation of benzoazatriacrown compounds $109$ with CH$_2$CO$_2$H have failed. However, this reaction readily proceeds when ethyl bromoacetate is used as the alkylation agent. $^{147}$

VIII. Dibenzoazacrown compounds

1. Dibenzoazacrown derivatives

The dibenzoazacrown ethers described in the literature, in which the nitrogen atom of the macrocycle is conjugated with two benzene rings, have been synthesised by two routes. $^{170, 171}$

The first route involves the condensation of bisphenol $110$ with oligoethylene glycol derivatives under the action of bases. The reactions with oligoethylene glycol ditoluenesulfonates ($n = 2, 4$) were performed in the presence of potassium carbonate (with addition of catalytic amounts of KI in the case of dichlorides) in various solvents. The highest product yields were attained in cyclohexanone. $^{171}$ The addition of LiBr as the template salt in the synthesis of dibenzoaza-12-crown-4 ether increased the yield from 8% to 30%. The cyclisation of compound $110$ ($R^1 = \text{CHO, Ac}$) is accompanied by decylation giving rise to macrocycles $111$, which contain a secondary amino group. Subsequently, compound $111$ ($n = 3, R^2 = \text{Cl, R}^3 = \text{H}$) was acylated. The reaction of $111$ with formic acid and acetic anhydride furnished $N$-formylated and $N$-acylated dibenzoazacrown ethers in 60% and 76% yields, respectively.

The second route to dibenzoazomacrocyclic ethers consists of the intramolecular cyclisation of podand $112$ in the presence of potassium carbonate and copper(I) bromide under drastic conditions (Dowtherm, $220^\circ$ C). $^{171}$ Two products were isolated — compounds $113$ and $114$. The latter can also be synthesised from the NH-unsubstituted derivative $113$ by treatment with formic acid.

In some cases, podands containing two phenylene substituents are used as substrates in the synthesis of dibenzoazacrown ethers. Thus hydrogenation of nitroaldehyde $115$ over a platinum or a palladium catalyst gives dibenzoazacrown ether $116$ in 47% and 65% yield, respectively. $^{153}$

Examples of dibenzoazacrown compounds in which one nitrogen atom is conjugated with the benzene ring, while the second nitrogen atom is separated from the aromatic ring by a methylene bridge are reasonably assigned to the same Section. Compound $117$ was prepared by condensation of $N,N'$-ditosylamide $118$ with dibromomethane, induced by sodium n-butoxide in DMF. $^{172}$ Attempts at detosylation by treatment with concentrated H$_2$SO$_4$ failed.
The reaction of diamine 119 with carbon disulfide in pyridine using iodine as the catalyst resulted in the synthesis of dibenzazacrown compound 120, which is a thiourea derivative.173

![](image1)

**2. Dibenzodiaza- and dibenzotetraazacrown compounds**

The construction of the macrocycle in the dibenzazacrown compounds containing two or four nitrogen atoms conjugated with benzene rings is based most often on the condensation of two fragments. Only a few examples of the synthesis of dibenzotetraazacrown compounds from four fragments have been reported.

**a. Syntheses based on the condensation of two fragments**

The alkylation of diamines or \(N,N'\)-disubstituted analogues under the action of bases is a widely used method for the synthesis of dibenzazacrown compounds. The alkylation agents used include 2,3-dihaloalkanes and derivatives of oligoethylene glycols and theiraza analogues.143, 174–179

Dibenzazacrown compounds 121a–c have been prepared in good yields by the reaction of \(N,N'\)-derivatives of diamines 122a–c with dibromomethane in the presence of sodium n-butoxide.174 The tosyl groups present in compound 121c were removed by heating in concentrated \(H_2SO_4\) (yield 89%).

![image2]

The sodium hydride-induced condensation of diamine 123, tobenzyl ether 124 using dibromomethane and 1,2-dibromoethane as well as analogous \(O,O'\)-ditoluene sulfonates with longer alkylene chains as the alkylation agents,175

![image3]

Dibenzazacrown compounds 125 (Table 5) have been prepared in moderate yields by the alkylation of either the diamine as dihydrochloride (126a) or the \(N,N'\)-ditosyl derivative 126b with the corresponding dihalides under the action of alkali metal carbonates.178 In the latter case, the tosyl groups were removed after the reaction by treatment with sodium naphthalenide in dimethoxyethane.

![image4]

Dibenzodiaza- and dibenzotetraazacrown compounds 127 were prepared by the reaction of the \(N,N'\)-ditosyl derivative of diamine 128 with ditoluene sulfonates of propylene or butylene glycols on heating in DMF.177 Detosylation with concentrated \(H_2SO_4\) was successful only for compound 127 (\(n = 1, m = 4\)).

![image5]

The sodium hydride-induced condensation of diamine 129, containing \(N\)-acetyl protective groups, with the dichloride prepared from diethylene glycol affords dibenzodiaza-18-crown-6 compound 130.178

![image6]

Dinitrodibenzodiaza-30-crown-10 ether 131, with \(N\)-methyl substituents, has been obtained under similar conditions using appropriate reagents.179

![image7]

In an early study,143 dibenzodiaza-, triaza- and tetraaza-18-crown-6 compounds 132 were synthesised by condensation of \(N\)-tosyl- or \(N\)-mesyldiamines with appropriate ditoluene sulfonates. The reaction proceeds in the presence of potassium tert-butoxide in tert-butyl alcohol. The removal of the sulfonyl groups from the macrocycle nitrogen atoms is best accomplished by the heating of compounds 132 with an \(AcOH\) (glacial)–\(HBr\)–PhOH mixture (the yields of the NH derivatives were 30%–82%). Minor amounts of benzene ring bromination products were also isolated;
the bromine atoms were removed by treatment with hydrazine on a Pd catalyst.

Yet another method used rather widely to prepare dibenzo-
diazacrown compounds is acylation of the corresponding bridged bis(anilines) with dicarboxylic acid derivatives. Most often, this process is induced by bases and is carried out under high dilution conditions. Compounds 133 with \( m = 1 \) were used in \( \text{Pb}^{2+} \) extraction experiments and that with \( R^2 = \text{Bu} \) was also employed to study \( \text{Pb}^{2+} \) ion transport through plasticised cellulose triacetate membranes.

Dibenzodiazacrown compounds with different macrocycle sizes 133 have been obtained by the acylation of diamines 134 with oxalic and di- or triglycolic acid dichlorides (Scheme 7, Table 6). Compounds 133 with \( m = 1 \) were acylated with triglycolic acid dichloride under high dilution conditions, and the subsequent reduction of the resulting amides 136a, b was carried out with a solution of diborane in THF. The yields were reported only for \( R^1 = \text{H}, R^2 = \text{OBn} \): 136b, 43%; 135b, 88%.

Dibenzodiazacrown compounds 133a, b were employed in the preparation of benzoannelated cryptands 135a, b. The substrates 133a, b were acylated with triglycolic acid dichloride under high dilution conditions, and the subsequent reduction of the resulting amides 136a, b was carried out with a solution of diborane in THF. The yields were reported only for \( R^1 = \text{H}, R^2 = \text{OBn} \): 136b, 43%; 135b, 88%.

### Table 5. Synthesis of dibenzodiazacrown compounds 125.

<table>
<thead>
<tr>
<th>Compo-</th>
<th>X</th>
<th>Y</th>
<th>Z</th>
<th>Hal</th>
<th>Reaction conditions</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>und 126</td>
<td>(CH(_2))(_n)</td>
<td>(CH(_2))(_n)</td>
<td>Br</td>
<td>K(_2)CO(_3), DMF</td>
<td>1 – 9</td>
<td></td>
</tr>
<tr>
<td>a</td>
<td>(CH(_2))(_n)</td>
<td>(CH(_2))(_n)</td>
<td>I</td>
<td>K(_2)CO(_3), DMF</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>b</td>
<td>(CH(_2))(_n)</td>
<td>(CH(_2))(_n)</td>
<td>Br</td>
<td>Na(_2)CO(_3), DMF; 2) C(_6)H(_5)Na, DME</td>
<td>4 – 8</td>
<td></td>
</tr>
</tbody>
</table>

\( ^a \) DME is 1,2-dimethoxyethane.

### Table 6. Synthesis of dibenzodiazacrown compounds 133.

<table>
<thead>
<tr>
<th>( R^1 )</th>
<th>( R^2 )</th>
<th>( R^3 )</th>
<th>( m )</th>
<th>( n )</th>
<th>Step 1</th>
<th>Step 2</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>H</td>
<td>H</td>
<td>1</td>
<td>0</td>
<td>Py</td>
<td>benzene</td>
<td>54</td>
</tr>
<tr>
<td>H</td>
<td>H</td>
<td>H</td>
<td>1</td>
<td>0</td>
<td>Et(_3)N</td>
<td>toluene</td>
<td>61</td>
</tr>
<tr>
<td>H</td>
<td>H</td>
<td>H</td>
<td>1</td>
<td>1</td>
<td>Et(_3)N</td>
<td>toluene</td>
<td>88</td>
</tr>
<tr>
<td>H</td>
<td>H</td>
<td>H</td>
<td>1</td>
<td>1</td>
<td>Py</td>
<td>benzene</td>
<td>40</td>
</tr>
<tr>
<td>H</td>
<td>H</td>
<td>H</td>
<td>1</td>
<td>2</td>
<td>excess 134</td>
<td>benzene</td>
<td>88</td>
</tr>
<tr>
<td>H</td>
<td>Bu(_1)</td>
<td>H</td>
<td>1</td>
<td>1</td>
<td>Et(_3)N</td>
<td>toluene</td>
<td>63</td>
</tr>
<tr>
<td>H</td>
<td>OBn</td>
<td>H</td>
<td>0</td>
<td>2</td>
<td>Et(_3)N</td>
<td>THF</td>
<td>60</td>
</tr>
<tr>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>0</td>
<td>2</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>F</td>
<td>H</td>
<td>F</td>
<td>0</td>
<td>1</td>
<td>Py</td>
<td>CH(_2)Cl(_2)</td>
<td>40</td>
</tr>
</tbody>
</table>

Scheme 7
**Table 7. Synthesis of dibenzodithiadiazacrown compounds 139.**

<table>
<thead>
<tr>
<th>Compounds</th>
<th>X</th>
<th>Y</th>
<th>Reaction conditions</th>
<th>Yield (%)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>139 – 141</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a</td>
<td>OCH₂CH₂O</td>
<td>–</td>
<td>CH₂, O, S, NTs</td>
<td>a</td>
<td>50 – 87</td>
</tr>
<tr>
<td>b</td>
<td>O(CH₂)₂Z(CH₂)₂O</td>
<td>Z = O, S, NTs</td>
<td>CH₂, O, S, NTs</td>
<td>a</td>
<td>28 – 96</td>
</tr>
<tr>
<td>c</td>
<td>SCH₂CH₂S</td>
<td>–</td>
<td>CH₂, O, S</td>
<td>a</td>
<td>70 – 90</td>
</tr>
<tr>
<td>d</td>
<td>S(CH₃)₂Z(CH₂)₂S</td>
<td>Z = CH₂, O, S</td>
<td>CH₂, O, S, NTs</td>
<td>a</td>
<td>19 – 90</td>
</tr>
<tr>
<td>e</td>
<td>SCH₂(CH₂OCH₂)₂CH₂S</td>
<td>1 – 3</td>
<td>S</td>
<td>b</td>
<td>68 – 80</td>
</tr>
<tr>
<td>f</td>
<td>O(CH₂)₂O</td>
<td>3 – 5</td>
<td>CH₂, O, S, NTs</td>
<td>a</td>
<td>20 – 92</td>
</tr>
<tr>
<td>g</td>
<td>OCH₂CH(OAc)CH₂O</td>
<td>–</td>
<td>CH₂, O, S, NTs</td>
<td>a</td>
<td>18 – 95</td>
</tr>
</tbody>
</table>

*For compound 139g, X = OCH₂CH(OH)CH₂O.*
dicarboxylic acid dichlorides under similar conditions (see Table 7). The tosyl group from 139f (n = 5; Y = NTs) was removed by treatment with an AcOH–HBr–PhOH mixture (yield 71%). The macrocyclic 15-membered compounds 139a,c and 16–20-membered compounds 139b (Z = O, NTs; Y = CH2, O, NTs), 139f (n = 3–5; Y = S; n = 5; Y = CH2, O, NTs) and 139e were used in experiments on extraction and membrane transport of heavy and transition metal ions.192–194,197–199

The acylation of acetoxysubstituted aromatic diamine 140g with glutaric, diglycic, thiodiglycic and N-tosylminodiacetic acid dichlorides in the presence of pyridine in benzene gave 16-membered acetoxysubstituted crown lactams (see Table 7). The reduction of these products with diborane in dimethoxyethane to give macrocyclic diamines 139g is accompanied by elimination of the acetyl group.196 On attempted reduction in THF, only extremely stable complexes of compounds 139g with the solvent and, perhaps, with boron hydride were isolated.

Macrocyclic diamides 142, containing trifluoromethyl groups, have been prepared by acylation of diamines 143 with oxalyl chlorides.200

\[
\begin{align*}
\text{F}_3\text{C} &- \text{C} & & \text{H}_2\text{N} & & \text{H}_2\text{N} & & \text{C} & & \text{H}_2 \text{O} & & \text{CF}_3 \\
\text{O} & & \text{X} & & \text{O} & & \text{O} & & \text{Cl} & & \text{Cl} & & \text{Cl} \\
\end{align*}
\]

\( X = \text{CH}_2\text{CH}_2 (50\%), \text{(CH}_2\text{)}_2\text{S(CH}_2\text{)}_2 (79\%). \)

In the synthesis of compounds 144, diimidazolides 145 were used as acylating agents.178 The reaction takes place on heating of the reactants in pyridine, but the product yields are relatively low.

\[
\begin{align*}
\text{NH}_2 & & \text{H}_2\text{N} & & \text{Y} & & \text{Y} & & \text{NH} & & \text{NH} & & \text{O} & & \text{O} \\
\text{O} & & \text{O} & & \text{N} & & \text{N} & & \text{O} & & \text{O} & & \text{O} & & \text{O} & & \text{O} \\
\end{align*}
\]

\( X = (\text{CH}_2)_n, \text{CH}_2(\text{CH}_2\text{OCH}_2)_n\text{CH}_2 (n = 1, 2); Y = O, S, \text{NMe}. \)

\( \text{o-Phenylenediamine diamide 146 has been prepared by condensation of } \text{o-phenylenediamine with dichloride 147 at room temperature.}\)

\[
\begin{align*}
\text{NH}_2 & & \text{NH}_2 & & \text{Cl} & & \text{Cl} & & \text{O} & & \text{O} & & \text{Cl} & & \text{Cl} \\
\end{align*}
\]

\( \text{Macrocyclic derivatives of } N,N'-\text{diphenylthiourea 148 were obtained by the reaction of } \text{bis(}\text{anilines} 149 \text{ with carbon disulfide in pyridine in the presence of iodine as the catalyst.}\)

\( n = 0 (88\%), 1 (85\%). \)

Dibenzo[4,8-diaryl-9-ether 150 and its chloro derivative 151 are formed upon intramolecular alkylation of aromatic amines 152 and 153 in the presence of sodium carbonate. Amines 152, 153 were formed in a 10:1 ratio upon the reduction of nitro compound 154. Due to their low stability, they were not separated but used in the condensation as a mixture. The yields of products 150 and 151 are given in relation to the starting nitro compound 154.

Diamaonethiodiazacrown oxides 155a,b were synthesised from diamines 156a,b and oxalylidihydroxymoyl chloride in an aqueous solution of sodium carbonate at low temperature.203, 204 Dibenzo[diaza-12-crown-4 tetraoxide 155c was prepared from dioxime 156c in ethanol in the presence of sodium hydrogen carbonate.205

\[
\begin{align*}
\text{NH}_2 & & \text{H}_2\text{N} & & \text{X} & & \text{X} & & \text{Cl} & & \text{Cl} \\
\text{SO}_2 & & \text{Cl} & & \text{Cl} & & \text{Cl} & & \text{Cl} & & \text{Cl} \\
\end{align*}
\]

\( X = \text{CH}_2\text{C}_2 (a, 27\%), \text{CH}_2(\text{CH}_2\text{OCH}_2)_2\text{C}_2 (b, 63\%); \)

\( C(\equiv\text{NOH})C(\equiv\text{NOH}) (c, 65\%); \)

\( a\text{Na}_2\text{CO}_3, \text{H}_2\text{O}, \text{CH}_2\text{Cl}_2; (b) \text{NaHCO}_3, \text{EtOH}. \)

The macrocyclic dimines obtained by condensation of aliphatic diamines with the corresponding dialdehydes are important precursors of dibenzotetraazacrown compounds.206, 207 The reduction of dimines 157 yields dibenzotetraazacrown compounds 158 (Table 8).207–209 Schiff’s bases 157 (Y = O, S, NH) were synthesised in the presence of p-toluenesulphonic acid, which served as the catalyst.207
The reactions of diimines 157 \((n = 2; m = 1, 2; Y \text{ is none or CH}_2)\) with Grignard reagents have produced tetraazacrown compounds with alkyl substituents in the macrocycle 159,208,210

\[ \text{X} = \text{Ph} \]  
\[ \text{O} = \text{TsOH}, 62 \]  
\[ \text{LiAlH}_4, \text{THF} \]  
\[ 59\% \]  
\[ \text{NaBH}_4, \text{EtOH} \]  
\[ 71\% \]  
\[ \text{NaBH}_4, \text{MeOH} \]  
\[ 40\% \]

\( n = 2 – 5, R = \text{Et (87\% – 94\%); n} = 3, R = \text{Pr} (80\%), \text{Bu} (71\%).\)

An unusual procedure has been developed for the synthesis of symmetric dibenzotetraazacrown compounds 160.211 Dihydrofuran was used as the reagent; first, it was ozonised and then reduced with sodium cyanoborohydride to dialdehyde. The product was used, without isolation, in the reductive alkylation of 1,1'-dimethyl-\( \beta \)-phenylenediamine. The resulting diamine 161 was converted into dibenzotetraazacrown compound 160 using a similar reaction sequence. The yield of product 160 is given in relation to 1,1'-dimethyl-\( \beta \)-phenylenediamine.

![Chemical structures](image)

Dibenzodiaza- and tetraazacrown compounds 162 were prepared from diimines 163 and 2-alkyl-\( \beta \)-ethoxyacycloxins.208,212,213 The condensation products 164 thus formed, which contain C=C and C=N double bonds, were reduced with hydrogen over a Pd catalyst.208,212

![Chemical structures](image)

<table>
<thead>
<tr>
<th>Compounds 95</th>
<th>X</th>
<th>Catalyst</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>h</td>
<td>O(CH(_2))(_2)CHMe</td>
<td>Pd</td>
<td>30</td>
</tr>
<tr>
<td>i</td>
<td>O(CH(_2))(_3)</td>
<td>Pd</td>
<td>8</td>
</tr>
<tr>
<td>j</td>
<td>O(CH(_2))(_4)</td>
<td>Pd</td>
<td>64</td>
</tr>
<tr>
<td>k</td>
<td>O(CH(_2))(_2)CHMe</td>
<td>Pd</td>
<td>62</td>
</tr>
<tr>
<td>l</td>
<td>CH(_2)O(CH(_2))(_3)</td>
<td>Pd</td>
<td>23</td>
</tr>
<tr>
<td>m</td>
<td>O(CH(_2))(_2)OCHMe</td>
<td>Pd</td>
<td>58</td>
</tr>
<tr>
<td>n</td>
<td>O(CH(_2))(_3)</td>
<td>Pd</td>
<td>47</td>
</tr>
<tr>
<td>o</td>
<td>O(CH(_2))(_2)OCHMe</td>
<td>Pd</td>
<td>37</td>
</tr>
</tbody>
</table>

a. The major product is monomer 94i (35\%); b. Monomer 94m (7\%) was also formed.

Hydrogenation of aldehydes 165 containing an \( \beta \)-nitrophenyl-substituent has yielded a series of 16-, 18- and 20-membered dibenzodiazacrown compounds 95h – o.153 It is noteworthy that no formation of monomers (benzoazacrown compounds) was observed in the synthesis of 18- and 20-membered macrocycles 95h – j, o (see Section VI.3, the synthesis of compounds 94a – g).

![Chemical structures](image)

<table>
<thead>
<tr>
<th>X</th>
<th>R</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>O</td>
<td>H</td>
<td>37 86</td>
</tr>
<tr>
<td>O</td>
<td>Me</td>
<td>26 – 41 84</td>
</tr>
<tr>
<td>NH</td>
<td>Me</td>
<td>40 57</td>
</tr>
</tbody>
</table>

Thirteen- to sixteen-membered diimines 166 have been prepared from bis(phenols).214 First, bis(phenols) were treated with an ethanolic solution of potassium hydroxide and the resulting phenolates were made to react with dihalides or ditoluene sulfo-esters on heating in DMF.

![Chemical structures](image)

\( n = 0, 1; X = \text{Cl, Br, OTs; } Y = \text{(CH}_2\text{)}\(m\), m = 2 – 5; \text{CH}_3\text{C}(-\text{CH}_2\text{CH}_2\text{C}(-\text{CH}_2\text{O})\text{CH}_2\).}

b. Condensation of four fragments

Macroyclic dibenzotetramides 138a are formed as side products (yields < 5\%) in the reaction of \( \beta \)-phenylenediamine with di- and triglycolic acid chlorides in the presence of triethylamine under high dilution conditions in MeCN.144 The reaction gave benzodi-
lactam monomers (yield 30% for benzodilactam 74 with \( n = 1 \), see Section VI.1) or oligomers as the major products.

\[
\begin{array}{c}
\text{NH}_2 \text{NH}_2 + \text{ClO}_2 \text{ClO}_2 \rightarrow \text{Et}_3 \text{N, MeCN} \\
\text{NH} \text{NH} \text{O} \text{O} \text{Cl} \text{Cl} \\
\end{array}
\]

\( n = 1, 2. \)

Tetraaza[14]annulene 167 has been prepared by the condensation of \( o \)-phenylenediamine with propionaldehyde; the catalytic reduction of this product with hydrogen in the presence of Raney nickel gives dibenzocyclam 168.\(^{215}\)

\[
\begin{array}{c}
\text{NH}_2 + \text{CHO} \rightarrow \text{DMF} \\
\text{Ni-Ra, MeOH} \\
\text{NH} \text{NH} \\
\end{array}
\]

Dibenzodithiatetraazacrown compounds 169 were obtained in high yields by treatment of \( N, N' \)-diallyl-\( N, N' \)-ditosyl-\( o \)-phenylenediamines 170 with sulfur(II) chloride.\(^{216}\) In the case of substituted \( o \)-phenylenediamine 170 (\( R_1 = \text{Me} \)), this reaction gives a mixture of isomers.

\[
\begin{array}{c}
\text{Ts} \text{CsH}_2 \text{H}_2 \text{C} \text{HClO}_2 \text{ClO}_2 \text{S} \text{S} \text{S} \text{S} \rightarrow \text{Et}_3 \text{N, MeCN} \\
\text{NH} \text{NH} \text{O} \text{O} \text{O} \text{O} \text{O} \\
\end{array}
\]

\( R_1 = R_2 = \text{H}; R'_1 = \text{Me}; R'_2 = 4-\text{Me}, 5-\text{Me}. \)

IX. Functional derivatives of dibenzoazacrown compounds

1. Dibenzoazacrown derivatives at the benzene ring

The number of functional derivatives of dibenzoazacrown compounds at the benzene ring reported in the literature is relatively small. These compounds were mainly prepared during the dibenzoazacrown ring construction by condensation of reactants already containing the required substituents (see Section VIII.2). Some examples of the synthesis of functional derivatives of dibenzoazacrown compounds by electrophilic aromatic substitution have been reported.

For example, formylation of dibenzodiazacrown compound 171 by the Vilsmeier reagent gave dialdehyde 172 (yield 77%). The removal of the benzyl protective groups in the aryl substituents by hydrogenolysis gave rise to the desired product 173 (yield 97%).\(^{182}\)

\[
\begin{array}{c}
\text{POC}_3, \text{DMF} \\
\text{H}_2, \text{Pd/C, THF – MeOH} \\
\text{HO} \text{OH} \text{CHO} \\
\end{array}
\]

R = \( \text{CH}_2 \text{CO}_2 \text{Me} (171, 172, 173); \) R – R = \( \text{CH}_2(\text{CH}_2 \text{OCH}_2)_2 \text{CH}_2 \) (135b, 174, 175).

A similar formylation of benzoannelated cryptand 135b, followed by reductive elimination of the benzyl groups in compound 174, resulted in the formation of compound 175 in an overall yield of 71%.\(^{182}\) Macrocycles 173 and 175 were used to prepare crown-containing coumarins, which are fluorescent reagents for alkali and alkaline earth metal ions.

Dibenzoazacrown compounds easily enter into azo coupling with \( p \)-nitrophenyldiazonium chloride.\(^{169}\) Reduction of the dinitro derivative of \( N, N' \)-dimethyldibenzoazadiza-30-crown-10 compound 131 with hydrogen over a palladium catalyst gave diamine 176. This product reacts with methyl isothiocyanate to give a crown-containing thiourea derivative (yield 40% in relation to the starting compound 131).\(^{179}\)

2. Derivatives of dibenzoazacrown compounds at the macrocycle nitrogen atom

\( N \)-Substituted dibenzoazacrown compounds are often formed upon cyclisation or condensation of fragments (see Section
VIII.2. In addition, these compounds can be obtained by direct alkylation of pre-formed macrocycles; however, only a few such examples are known.

The reaction of compound 177 with dialkyl sulfate in methanol gave \( N,N' \)-dialkyl derivatives 121.\(^{175}\)

\[
\begin{align*}
\text{HN} & \quad \text{R}_{3} \text{SO}_{4}, \text{MeOH} \quad \text{HN} \\
& \quad \text{MeCN, K}_{2} \text{CO}_{3} \text{ or BDN} \\
\end{align*}
\]

\( R = \text{Me} (56\%); \text{Et} (62\%). \)

Derivatives 178 have been prepared in a similar way.\(^{181–183}\) Alkylation of dibenzodiazacrown compounds 133 with ethyl or methyl bromoacetate proceeds in the presence of potassium carbonate or 1,8-bis(dimethylamino)naphthalene (BDN). Compound 178 \((n = m = 1)\) has been used as an extractant for \( \text{Pb}^{2+} \) ions and in \( \text{Pb}^{2+} \) transport through plasticised membranes based on cellulose triacetate.\(^{181}\)

\[
\begin{align*}
\text{HN} & \quad \text{BrCH}_{2} \text{CO} \cdot \text{R}^{3} \\
& \quad \text{MeCN, K}_{2} \text{CO}_{3} \text{ or BDN} \\
\end{align*}
\]

\[
\begin{align*}
\text{HN} & \quad \text{O} \\
& \quad \text{CO} \\
\end{align*}
\]

\( R^{1} \quad R^{2} \quad R^{3} \quad m \quad n \quad \text{Yield (\%)} \)

<table>
<thead>
<tr>
<th>( R^{1} )</th>
<th>( R^{2} )</th>
<th>( R^{3} )</th>
<th>( m )</th>
<th>( n )</th>
<th>( \text{Yield (%)} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>H</td>
<td>Et</td>
<td>1</td>
<td>1</td>
<td>71</td>
</tr>
<tr>
<td>H</td>
<td>F</td>
<td>Et</td>
<td>0</td>
<td>2</td>
<td>54</td>
</tr>
<tr>
<td>O( \text{Bn} )</td>
<td>H</td>
<td>Me</td>
<td>0</td>
<td>2</td>
<td>91</td>
</tr>
</tbody>
</table>

X. Conclusion

The data presented in the review were classified according to the chemical type of the synthesised structures. To sum up, it is pertinent to present a brief systematisation of the data in terms of the synthetic methods used, as shown in Table 9. It can be seen that, despite the diversity of approaches, \([1 + 1]-\)condensation of two acyclic fragments still remains the key route to azacrown compounds. Nucleophilic aromatic substitution is widely used to prepare \( N \)-phenylaza- and \( N,N' \)-diphenyldiazacrown compounds, which is attributable to the ready availability of the starting compounds. The other methods for the synthesis of azacrown compounds are encountered much more rarely in relevant publications. Meanwhile, more and more publications deal with the synthesis of such compounds by \( C-N \) cross-coupling. Of the most recent publications on this topic, of special interest in our opinion are the studies on the synthesis of benzodi-acrown compounds started not long ago.\(^{151}\)

It should also be noted that the synthesis of functional derivatives of \( N \)-phenylaza- and \( N,N' \)-diphenyldiazacrown compounds is documented rather extensively. The number of known derivatives of annelated azacrown ethers is much smaller. The chemistry of benzoazacrown compounds has been poorly developed until recently because the synthesis of these compounds by condensation of two fragments is complicated and the podands needed for intramolecular condensation are difficult to obtain. We proposed a new methodology for the synthesis of functional derivatives of benzoazacrown ethers by the stepwise...
transformation of readily available oxygen-containing analogues, which appears a promising alternative to the existing approaches.

The review was written with the financial support of the Russian Foundation for Basic Research (Project No. 03-03-32177), the INTAS (Grant 2001-0267), the Russian Academy of Sciences and the RF Ministry of Science and Engineering.

References
