Synthesis of New Alkyl- Alkenyloxy- and Hydroxy-substituted Diaza-crown Compounds

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New diaza-crown compounds with the macro ring nitrogen atoms situated in the 1,4-, 1,7- and 1,10-positions have been prepared. All of the new macrocycles contain alkyl groups on the nitrogen atoms and a functional group substituent in the form of either an allyloxymethyl, allyloxy or hydroxy group on one of the macro ring carbon atoms. A 1,4-diaza-crown attached to silica gel removes Hg(II) ions from an aqueous mixture of Hg(II), Cd(II) and Zn(II) ions.

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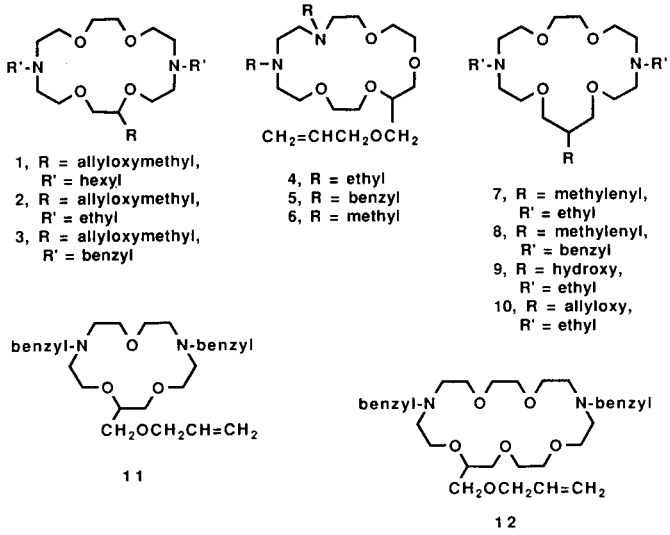
Introduction.

The aza-crown compounds have received considerable attention in recent years because of their ability to complex a variety of metal and organic cations and anions [2-6]. In general, preferential complexation results when the relative sizes of the cation and ligand cavities are matched. Often, changing the nature of the donor atoms in the macro ring has an even greater effect on complexation. The aza-crowns have complexation properties that are intermediate between those of the all oxygen crown ligands, which complex strongly with alkaline earth metal ions, and those of the all-nitrogen cyclams, which complex strongly with the heavy metal cations [7]. These complexation properties make the aza-crowns very interesting to researchers in diverse research areas. In addition, the aza-crowns are important intermediates for the synthesis of the cryptands and the nitrogen pivot lariat crown ethers [8-10]. They have important uses as synthetic receptors in molecular recognition processes, as catalysts in nucleophilic substitution and oxidation reactions [11,12] and in the design of chromogenic reagents which are sensitive to the alkali and alkaline earth cations [13]. In addition, they have anion complexation properties which are similar to those found in certain biological systems [14-16].

The recent permanent attachment of diaza-crowns to silica gel *via* a hydrocarbon-ether type linkage has made possible the design of systems capable of the selective and quantitative removal of cations from aqueous solutions [17-20]. For example, columns containing 2.3 grams of total material consisting of 10% (by weight) of *N,N'*-dihexyldiaza-18-crown-6 covalently bonded to silica gel were used to separate Hg(II) ions from Ag(I) ions. This application of selectively separating cations requires the design of new diaza-crowns with pendant functional groups which are capable of the further reactions required to attach the desired crown to silica gel [21,22]. A possible application for the silica gel-bound aza-crowns is to remove toxic heavy metal ions from waste solutions.

Our goal in this research was to find a convenient and high yield procedure, in as few steps as possible, to prepare the desired substituted diaza-crowns with different ring sizes and with the nitrogen atoms in varying ring positions. We also desired a functional group substituent so that later reactions to attach the crown to silica gel would be possible [21,23-25]. We have described five synthetic procedures to prepare allyloxymethyl-substituted diaza-18-crown-6 **1-3** [20]. Our best previous procedure required only five steps to the silica gel-bonded diaza-18-crown-6. We now report the synthesis of some allyloxymethyl-substituted diaza-18-crown-6 compounds with the nitrogen atoms in the 1,4-macro ring positions, **4-6**. Also included are four diaza-19-crown-6 compounds containing methylenyl, hydroxy or allyloxy substituents, **7-10**. Diaza-15-crown-5, **11**, and 21-crown-7, **12** compounds containing the allyloxymethyl substituent were also prepared so that these different sized diaza-crowns could be attached to silica gel. Compound **4** has been attached to silica gel in a manner similar to that reported [20] and this silica gel-bound crown separated Hg(II) ions from an equimolar mixture of Hg(II), Cd(II) and Zn(II) ions. A more detailed description of the selective separation properties of silica

Figure 1. Diaza-Crown Compounds

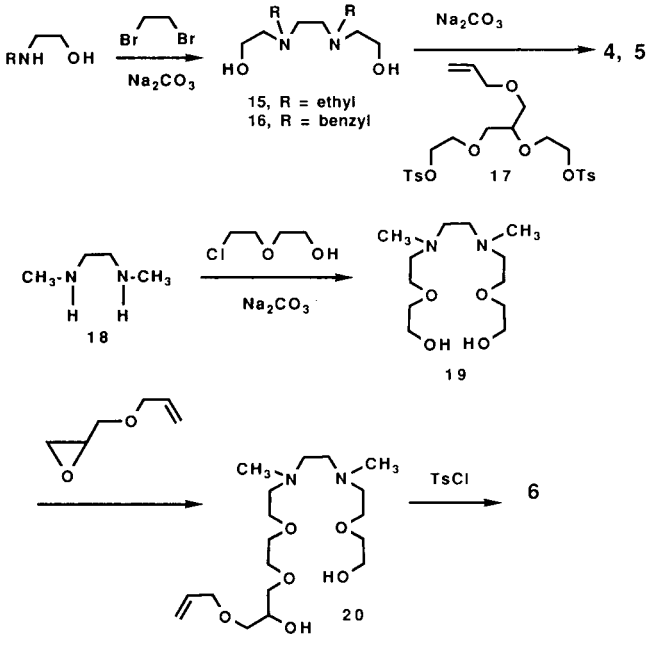


gel containing these new diaza-crowns will be published when the work is finished.

Results and Discussion.

The new macrocycles **4-6** were prepared by two synthetic procedures which are shown in Scheme I. In the first route, excess *N*-ethylethanolamine (**13**) or *N*-benzylethanolamine (**14**) was reacted with 1,2-dibromoethane in acetonitrile in the presence of potassium carbonate to give **15** or **16** in moderate yields. The lower yields could be due to elimination reactions of 1,2-dibromoethane. Ishidate and his co-workers prepared similar intermediate compounds from *N*-methylethanolamine and 1,2-dibromoethane [26]. The resulting diazadiols **15** and **16** were reacted with 4-allyloxymethyl-3,6-dioxa-1,8-octanediol ditosylate [20] in *t*-butyl alcohol in the presence of potassium *t*-butoxide to give crowns **4** and **5** in moderate yields. A major problem with this synthetic route is the difficulty of purification of the crown from various by-product impurities. Separation of the desired material from the undesirable by-products by column chromatography was difficult because the by-products could not be detected on alumina tlc plates using routine development methods such as iodine, permanganate ion or ultraviolet light. Differing amounts of the impurities were observed by nmr spectroscopy in the distillation fractions. In addition, the synthesis of ditosylate **17** requires three steps.

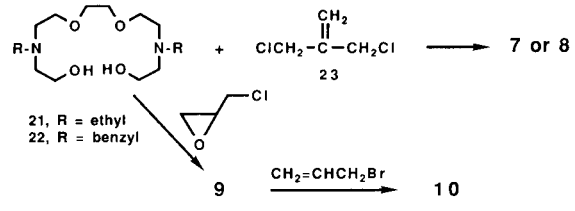
Scheme I. Preparation of Macrocycles 4-6



The second route in Scheme I is a more direct pathway to these compounds. *N,N'*-dimethylethylenediamine (**18**) and 2-(2-chloroethoxy)ethanol were reacted in toluene in the presence of sodium carbonate to produce 6,9-diazapentaethylene glycol **19**. This reaction is similar to that used by us to prepare the 3,12-diazapentaethylene glycol [20]. Diol **19** was readily converted to allyloxymethyl substituted diazahexaethylene glycol **20** on treatment with allyl glycidyl ether [20]. Diol **20** was readily ring closed using the Okahara ring closure reaction with tosyl chloride to give a good yield of macrocycle **6**. Thus, **6** was prepared in three steps from readily available starting materials.

Macrocycles **7** and **8** were prepared in two steps using 3-chloro-2-chloromethyl-1-propene (**23**), which was first used to prepare macrocycles by Tomoi and co-workers [27,28], as shown in Scheme II. Diazapentaethylene glycols **21** and **22** were prepared in high yield as reported [29] and then reacted with dihalide **23** to form **7** or **8** in excellent yields. Diol **21** was also reacted with epichlorohydrine to form hydroxy-substituted *N,N'*-diethyldiaza-19-crown-6 (**9**) in a moderate yield. Bartsch and his co-workers have used this reaction for the preparation of carbon-pivot lariat ethers without macro ring nitrogen atoms [30,31]. Macrocycle **9** was readily converted to allyloxy-substituted **10** upon treatment with allyl bromide. Each of compounds **7-10** has a functional group which will enable it to be attached to silica gel.

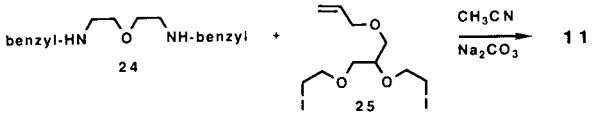
Scheme II. Preparation of Macrocycles 7-10



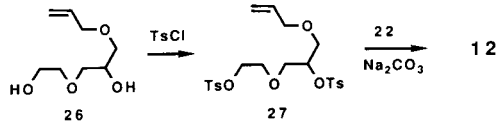
Diaza-18-crown-6 attached to silica gel has been used to separate various transition metal cations from other types of metal ions [17-20]. The silica gel attachment process used the reaction of allyloxymethyl-substituted diaza-18-crown-6 with trimethoxysilane followed by heating the resulting trimethoysilane-crown product on silica gel [17]. In order to prepare silica gel-bound diaza-15-crown-5 and diaza-21-crown-7, the allyloxymethyl-substituted *N,N'*-dibenzyl-15-crown-5 (**11**) and 21-crown-7 (**12**) compounds have been prepared as shown in Schemes III and IV. Crown **11** was prepared in a 70% yield from diamine **24** [32,33] and allyloxymethyl-substituted diiodide **25** [20] in acetonitrile in the presence of sodium carbonate (Scheme III). Macrocycle **12** was prepared in a moderate yield by reacting ditosylate **27** with diazapentaethylene glycol **22** in acetonitrile in the presence of sodium carbonate (Scheme IV). This reaction does not give easily separable products. First, two isomeric products, where the allyloxymethyl substituent is on carbon one (as shown) and on carbon two, were produced during the preparation of **26** [25]. Second, compound **27** has tosylate leaving groups in both primary and secondary carbon positions. The primary

tosylate is the most reactive with only a partial reaction taking place on the secondary carbon. Thus, the final reaction mixture contains both macrocycle **12** and open chain products so that the separation of **12** was difficult. It is also possible that **27** could undergo a base-catalyzed elimination reaction as was observed where allyloxymethylethylene glycol ditosylate was used in a ring closure reaction [20]. Ring closure reactions using alkyl-substituted ditosylates are best carried out using ditosylates with the alkyl group substituted on internal carbon atoms (like **25**).

Scheme III. Preparation of Macrocycle 11



Scheme IV. Preparation of Macrocycle 12



Allyloxymethyl-substituted macrocycles **4** and **12** were attached to silica gel by first reacting them with trimethoxysilane using a platinum catalyst [17] and then coating and heating the resulting crown-trimethoxysilane on 60-200 mesh silica gel. The **4**-silica gel material easily separated Hg(II) ions from an equimolar mixture of Hg(II), Cd(II) and Zn(II) ions. A more detailed description of specific metal ion separations by **4**-silica gel and **12**-silica gel will be published when the work is finished.

EXPERIMENTAL

The proton nuclear magnetic resonance (^{1}H nmr) spectra were obtained on a JEOL-FX-90Q or a Varian Gemini 200 spectrometer using deuteriochloroform. Elemental analyses were performed by MHW Laboratories, Phoenix, Arizona. Molecular weights were determined by the electron impact method on a Finnegan 8430 High Resolution Mass Spectrometer. Starting materials were purchased from Aldrich Chemical Co. when available. Starting diol **26** was prepared as reported [34]. Other starting materials and the macrocycles were prepared as follows:

1,8-Dihydroxy-3,6-diethyl-3,6-diazaoctane (**15**) (Scheme I).

A mixture of 35.6 g (0.4 mole) of **13**, 28.2 g (0.15 mole) of 1,2-dibromoethane and 30 g of anhydrous potassium carbonate was stirred in 200 ml of acetonitrile under reflux for 48 hours. The insoluble inorganic salts were filtered and the filtrate was evaporated under reduced pressure. The residue was distilled to give 28 g (34%) of **15**, bp 98-101°/0.1 mm; ^{1}H nmr: (δ) 1.05 (t, 6 H), 2.60 (m, 12 H), 3.60 (m, 4 H), 5.30 (s, 2 H). This material was used in the next step to prepare **4** without further purification.

1,8-Dihydroxy-3,6-dibenzyl-3,6-diazaoctane (**16**) (Scheme I).

Diol **16** was prepared as above for **15** from 60.5 g (0.4 mole) of **14** and 28.2 g (0.15 mole) of 1,2-dibromoethane to give 38 g (29%) of **16**, bp 205-207°/0.1 mm; ^{1}H nmr: (δ) 2.60 (m, 8 H), 3.45 (s, 4 H), 3.60 (m, 4 H), 5.60 (s, 2 H), 7.20 (m, 10 H). This material was used in the next step to prepare **5** without further purification.

11-Allyloxymethyl-1,4-diethyl-1,4-diaza-7,10,13,16-tetraoxacyclooctadecane (**4**) (Scheme I).

To a mixture of 1 g of potassium metal dissolved in 200 ml of *t*-butyl alcohol at 60°, was simultaneously added over a 2-hour period, 2.08 g (0.01 mole) of **15** and 5.28 g (0.01 mole) of **17** [20] each in 50 ml of dry dioxane. The mixture was refluxed for 16 hours, cooled, filtered and the solvent was evaporated under reduced pressure. The residue was chromatographed, first on neutral alumina (toluene/ethanol: 100/1), then on silica gel (ethanol) to give 0.82 g (21%) of **4** as an oil; ^{1}H nmr: (δ) 1.00 (t, 6 H), 2.60 (m, 12 H), 3.60 (m, 17 H), 4.00 (m, 2 H), 5.20 (m, 2 H), 5.90 (m, 1 H).

Anal. Calcd. for $C_{20}H_{40}N_2O_5$: C, 61.82; H, 10.38; mol. wt., 388.56. Found: C, 61.60; H, 10.17; mol. wt. 388.

11-Allyloxymethyl-1,4-dibenzyl-1,4-diaza-7,10,13,16-tetraoxacyclooctadecane (**5**) (Scheme I).

Macrocycle **5** was prepared as above for **4** from 3.28 g (0.01 mole) of **16** and 5.28 g (0.01 mole) of **17** to give 1.13 g (21%) of **5** as an oil; ^{1}H nmr: (δ) 2.70 (m, 8 H), 3.55 (m, 21 H), 4.00 (d, 2 H), 5.15 (m, 2 H), 5.90 (m, 1 H), 7.20 (s, 10 H).

Anal. Calcd. for $C_{30}H_{44}N_2O_5$: C, 70.28; H, 8.65; mol. wt., 512.62. Found: C, 70.17; H, 8.67; mol. wt., 512.

1,14-Dihydroxy-6,9-dimethyl-6,9-diaza-3,12-dioxatetradecane (**19**) (Scheme I).

A mixture of 17.6 g (0.2 mole) of **18**, 50 g (0.4 mole) of 2-(2-chloroethoxy)ethanol and 25 g of sodium carbonate was stirred in 250 ml of toluene under reflux for 3 days using a Dean-Stark apparatus to remove water. The insoluble inorganic salts were filtered and the filtrate was evaporated under reduced pressure. The residue was distilled twice to give 28 g (53%) of **19**, bp 134-137°/0.07 mm; ^{1}H nmr: (δ): 2.30 (s, 6 H), 2.65 (m, 8 H), 3.60 (m, 12 H), 5.30 (s, 2 H). Compound **19** was used without further purification to prepare **20**.

1,17-Dihydroxy-1-allyloxymethyl-9,12-dimethyl-9,12-diaza-3,6,15-trioxaheptadecane (**20**) (Scheme I).

Allyl glycidyl ether (4.1 g, 0.032 mole) was slowly dripped into 0.4 g (6.9 mmole) of pulverized potassium hydroxide dissolved in 28.5 g (0.108 mole) of **19** at 80° over a 2-hour period. The mixture was stirred overnight at room temperature. The mixture was then neutralized using 5% aqueous sulfuric acid. The water was removed by adding benzene and removing the benzene-water azeotrope. The residue was distilled twice to give 6 g (44%) of **20**, bp 198-203°/0.05 mm; ^{1}H nmr: (δ) 2.21 (s, 3 H), 2.23 (s, 3 H), 2.55 (m, 8 H), 3.50 (m, 19 H), 3.90 (m, 2 H), 5.20 (m, 2 H), 5.90 (m, 1 H). Compound **20** was not further purified but was used in the next step to prepare **6**.

11-Allyloxymethyl-1,4-dimethyl-1,4-diaza-7,10,13,16-tetraoxacyclooctadecane (**6**) (Scheme I).

Tosyl chloride (2.1 g, 0.011 mole) in 100 ml of dry dioxane was slowly added to a mixture of 3.79 g (0.01 mole) of **20** and 2.8 g (0.05 mole) of pulverized sodium hydroxide in 200 ml of dry dioxane. The resulting mixture was refluxed for 24 hours. The mixture was cooled, filtered and evaporated under reduced pressure. The residue was chromatographed on alumina (toluene/ethanol:

100/1) to give 2.23 g (62%) of **6** as an oil; ^{1}H nmr: (δ) 2.15 (s, 6 H), 2.50 (m, 8 H), 3.60 (m, 17 H), 4.0 (d, 2 H), 5.20 (m, 2 H), 5.90 (m, 1 H).

Anal. Calcd. for $C_{18}H_{36}N_2O_5$: C, 59.97; H, 10.07; mol. wt. 360.42. Found: C, 59.92; H, 9.89; mol. wt., 360.

15-Methylenyl-1,10-diethyl-1,10-diaza-4,7,13,17-tetraoxacyclononadecane (**7**) (Scheme II).

Mixtures of 5.84 g (0.02 mole) of **21** and 2.5 g (0.2 mole) of **23**, each in 100 ml of dioxane were simultaneously dripped into 35 ml of *t*-buty alcohol containing 2 g of dissolved potassium metal over a 3-hour period at 80°. The mixture was refluxed for 16 hours, filtered and evaporated under reduced pressure. The residue was chromatographed on neutral alumina (toluene/ethanol: 100/1) to give 4.6 g (67%) of **7** as an oil; ^{1}H nmr: (δ) 1.05 (t, 6 H), 2.60 (q, 4 H), 2.80 (m, 8 H), 3.60 (m, 12 H), 4.05 (s, 4 H), 5.15 (s, 2 H).

Anal. Calcd. for $C_{18}H_{36}N_2O_4$: C, 62.75; H, 10.53; mol. wt., 344.37. Found: C, 62.77; H, 10.66; mol. wt., 344.

15-Methylenyl-1,10-dibenzyl-1,10-diaza-4,7,13,17-tetraoxacyclononadecane (**8**) (Scheme II).

Macrocycle **8** was prepared as above for **7** from 8.32 g (0.02 mole) of **22** and 2.5 g (0.02 mole) of **23** to give 5.9 g (63%) of **8** as an oil; ^{1}H nmr: (δ) 2.90 (t, 8 H), 3.65 (t, 12 H), 3.75 (s, 4 H), 4.10 (s, 4 H), 5.25 (s, 2 H), 7.20 (m, 10 H).

Anal. Calcd. for $C_{28}H_{40}N_2O_4$: C, 71.76; H, 8.60. Found: C, 71.98; H, 8.62.

15-Hydroxy-1,10-diethyl-1,10-diaza-4,7,13,17-tetraoxacyclononadecane (**9**) (Scheme II).

Sodium hydride (0.05 mole) was suspended in 100 ml of THF under nitrogen. A solution of 5.84 g (0.02 mole) of **21** in 50 ml of THF was added dropwise followed by stirring at 40° for 30 minutes. Then, 1.85 g (0.024 mole) of 2-(chloromethyl)oxirane was added and the mixture was gradually heated and refluxed for 24 hours. The reaction mixture was cooled to 0°, 20 ml of ethanol was added and the mixture was neutralized with hydrochloric acid to *p*H 7. The mixture was extracted 3 times with chloroform. The chloroform solution was dried over anhydrous magnesium sulfate, filtered and evaporated. The residue was chromatographed on neutral alumina (toluene/ethanol:100/1) to give 2.1 g (31%) of **9** as an oil; ir: 3200-3500 (OH), 1200 (C-O-C) cm^{-1}; ^{1}H nmr: (δ) 1.00 (m, 6 H), 2.70 (m, 12 H), 3.60 (m, 17 H).

Anal. Calcd. for $C_{17}H_{36}N_2O_5$: C, 58.59; H, 10.41; mol. wt., 348.42. Found: C, 58.41; H, 10.26; mol. wt. 348.

15-Allyloxymethyl-1,10-diethyl-1,10-diaza-4,7,13,17-tetraoxacyclononadecane (**10**) (Scheme II).

A mixture of 1.5 g (4.4 mmoles) of **9**, 1.44 g (12 mmoles) of allyl bromide, 0.6 g (5.2 mmoles) of potassium *t*-butoxide and 50 ml of *t*-butyl alcohol was stirred at 60° for 1 hour. The mixture was filtered, the solvent and excess allyl bromide were evaporated under reduced pressure and the residue was chromatographed on neutral alumina (toluene/ethanol: 50/1) to give 1.2 g (81%) of **10** as an oil; ^{1}H nmr: (δ) 1.00 (t, 6 H), 2.60 (q, 4 H), 2.75 (m, 8 H), 3.60 (m, 17 H), 4.15 (m, 2 H), 5.20 (m, 2 H), 5.90 (m, 1 H).

Anal. Calcd. for $C_{20}H_{40}N_2O_5$: C, 61.82; H, 10.38; mol. wt., 388.45. Found: C, 61.87; H, 10.40; mol. wt., 388.

1-Allyloxymethyl-3-oxapentanediol-1,5-ditosylate (**27**) (Scheme IV).

Compound **26** [20] (19.6 g, 0.11 mole) was dissolved in pyridine at about -5°. Tosyl chloride (46.7 g, 0.22 mole) was also dissolved in pyridine and added very slowly to the cold, stirred diol solution. After 5 hours of stirring at -5°-0°, the solution was poured onto ice along with concentrated hydrochloric acid. The resulting oil was separated and the aqueous residue was extracted twice with methylene chloride. The oil was combined with the methylene chloride phases and the solution was dried over anhydrous magnesium sulfate. After filtration and evaporation, the residue was chromatographed on silica gel (methylene chloride) to obtain **27** in a 45% yield; ^{1}H nmr: (δ) 2.42 (s, 6 H), 3.6 (m, 6 H), 3.9 (m, 2 H), 4.1 (m, 2 H), 4.6 (m, 1 H), 5.2 (m, 2 H), 5.9 (m, 1 H), 7.4 (d, 4 H), 7.8 (d, 4 H). This material was used without further purification for the preparation of **12**.

11-Allyloxymethyl-1,7-dibenzyl-1,7-diaza-4,10,13-trioxacyclopentadecane (**11**) (Scheme III).

A mixture of 1.64 g (5 mmoles) of **24**, 2.32 g (5 mmoles) of **25**, 10 g of sodium carbonate, 0.1 g of sodium iodide and 300 ml of acetonitrile was stirred under reflux for 24 hours. The mixture was filtered, the solvent was evaporated under reduced pressure and the residue was chromatographed on alumina (toluene/ethanol: 50/1) to give 72% of **11**; ^{1}H nmr: (δ) 2.80 (m, 8 H), 3.60 (m, 25 H), 4.0 (m, 2 H), 5.20 (m, 2 H), 5.80 (m, 1 H), 7.30 (m, 10 H).

Anal. Calcd. for $C_{28}H_{40}N_2O_4$: C, 71.76; H, 8.60; mol. wt., 468.51. Found: C, 71.86; H, 8.41; mol. wt., 468.

14-Allyloxymethyl-1,10-dibenzyl-1,10-diaza-4,7,13,16,19-pentaoxacycloeicosane (**12**) (Scheme IV).

Potassium metal (0.585 g, 0.015 mole) was dissolved in 300 ml of *t*-butyl alcohol and 3.08 g (7.23 mmoles) of **22** was added. Compound **27** (3.5 g, 7.23 mmoles) in 100 ml of dioxane was slowly added to the mixture at 70°. The resulting mixture was refluxed for 24 hours and then filtered and evaporated under reduced pressure. The residue was chromatographed on neutral alumina (toluene/ethanol: 200/1) to obtain a 31% yield of **12** as an oil; ^{1}H nmr: (δ) 2.75 (m, 8 H), 3.60 (m, 17 H), 3.95 (d, 2 H), 5.15 (m, 2 H), 5.85 (m, 1 H), 7.25 (m, 10 H).

Anal. Calcd. for $C_{32}H_{48}N_2O_6$: C, 69.00; H, 8.69; mol. wt., 556.62. Found: C, 68.89; H, 8.55; mol. wt., 556.

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