(t, J = 8.0 Hz, 3 H, CH_3), 3.15 (s, 6 H, NCH_3), 4.09 (q, J = 8.0 Hz, 2 H, CH_2), 4.13 (q, J = 8.0 Hz, 2 H, CH_2), 6.05 (s, 2 H, H_c and H_d), 6.80 (s, 2 H, NH), 7.79 (broad s, 1 H, H_a).

Anal. Calcd for $C_{20}H_{31}N_5O_8$: C, 51.16; H, 6.66; N, 14.92. Found: C, 51.30; H, 6.57; N, 14.88.

Registry No.—**1a**, 696-68-4; **1b**, 2175-90-8; **2a**, 6830-78-0; **2b**, 1671-87-0; **3**, 54384-98-4; **4a**, 54384-99-5; **4b**, 54385-00-1; **6**, 32683-51-5; **7a**, 54385-01-2; **8**, 1972-28-7; **9**, 54385-02-3; **10**, 54385-03-4.

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The Oxetane Function Spiro to Polyoxaaza Macroheterocycles

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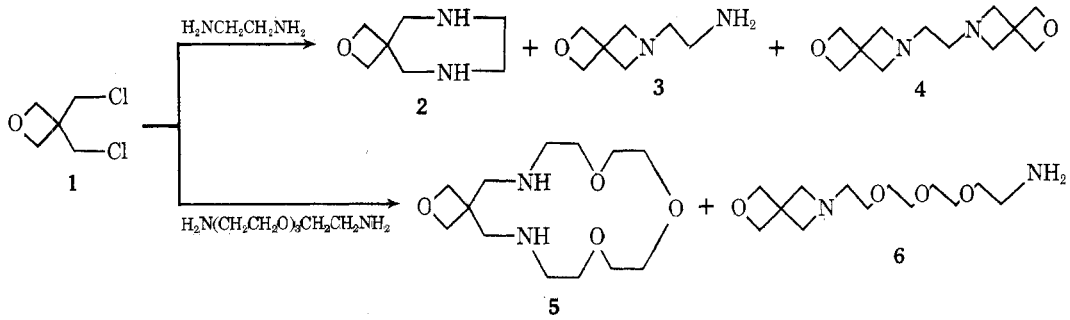
Base-induced condensation of oxaazadiols with 3,3-bis(chloromethyl)oxetane gives macrocyclic aza polyethers bearing one or two spirooxetane rings. Thermolysis of appropriately constituted oxaaza macrocycles is shown to give novel polycyclic structures, as does condensation with bis(acid chloride). Ring closure of α,ω-diamines with 3,3-bis(chloromethyl)oxetane leads to polyoxaaza macrocycles in low yield.

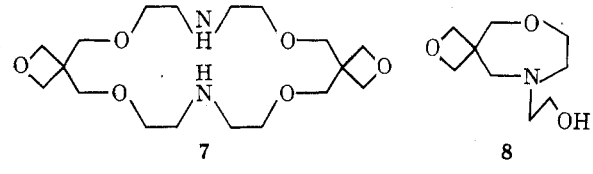
The previous paper[1] in this series described the one-step synthesis of macrocyclic polyethers and polysulfides bearing one or two spirooxetane substituents. This paper presents syntheses of a number of related polyoxaaza macrocycles and some chemistry of the imine group in such rings.

Synthesis from α,ω-Diamines. Alkylation of α,ω-diamines with dihalides does not usually lead to good yields of diaza macrocycles,[2] and reaction of 3,3-bis(chloromethyl)oxetane (1) with primary α,ω-diamines has been found to give several types of products. Ethylenediamine with **1** gave volatile products resulting from monoalkylation of both nitrogen atoms (i.e., **2**) and from dialkylation (i.e., **3** and **4**) along with low polymers. A similar result was observed starting from **1** and 3,6,9-trioxaundecane-1,11-diamine, since both macrocycle **5** and azetidine **6** were formed. The distillation cut which contained **5** and **6** in roughly equal amounts was separated by taking advantage of the superior ability of **5** to form complexes. The crystalline complex, **5** · NaSCN, was precipitated while **6** remained in solution.



Synthesis from α,ω-Diols. Three α,ω-diols having aza nitrogen were condensed with **1** or with 3,3-bis(bromomethyl)oxetane. Attempts to selectively benzoylate the amine function in these diols under mild conditions gave little derivatization, a result indicative of rather low nucleophilicity of the amine centers. The condensations were therefore carried out with the dipotassium salts of the diols containing unmasked imine groups. Alkylation on nitrogen appeared to be a minor side reaction, and the results are roughly comparable to those obtained with the polyethylene glycols.[1]

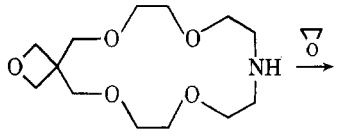
In the presence of 2 equiv of potassium *tert*-butoxide and in *tert*-butyl alcohol as solvent, diethanolamine condensed with **1** to give dispiro macrocycle **7** in 17% yield along with 1% of N-alkylated product (**8**). The effect of nitrogen in the macrocyclic polyether on complex formation is indicated by the fact that **7** readily displaced water from cupric acetate hydrate to form **7** · $Cu(OAc)_2$.



3,9-Dioxa-6-azaundecane-1,11-diol (**9**) was obtained by the following sequence of reactions. Interestingly, the three-stranded compound **10** was the only acyclic polyether encountered in this study which gave a crystalline complex, namely **10** · NaSCN.

$$HO(CH_2CH_2O)_2H \xrightarrow{SOCl_2} Cl(CH_2CH_2O)_2H \xrightarrow{NH_3}$$
$$H_2N(CH_2CH_2O)_2H + HN(CH_2CH_2OCH_2CH_2OH)_2 +$$
11 9
$$N(CH_2CH_2OCH_2CH_2OH)_3$$
10

Condensation of the dipotassium salt of **9** with **1** gave macrocycle **12** in 67% yield. A 1:1 complex of **12** with NaSCN was easily prepared. The presence of a secondary amine function in **12** which can be derivatized was shown by its reaction with excess ethylene oxide to form **13.**



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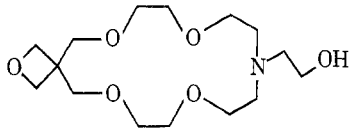
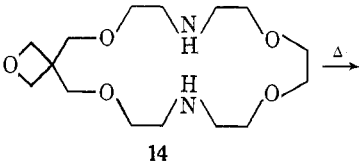


13

Finally, the dipotassium salt of 6,9-dioxa-3,12-diazatetradecane-1,14-diol[2] was condensed with **1** to form macrocycle **14** in 71% crude yield. Purification of **14** was best effected by crystallization as the 1:1 complex with sodium thiocyanate or sodium iodide. Attempted fractional distillation of crude **14** necessitated temperatures near 200°, high enough for intramolecular attack of nitrogen on the oxetane ring to occur.[3] As a result, the distillate proved to be largely the bicyclic compound **15.** This product formed a relatively insoluble 1:1 complex with sodium thiocyanate, and mixtures of **14** · NaSCN with **15** · NaSCN could be separated by fractional crystallization from acetone.



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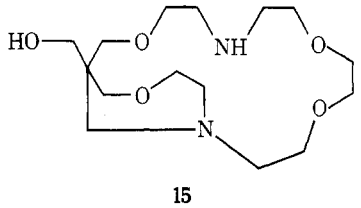
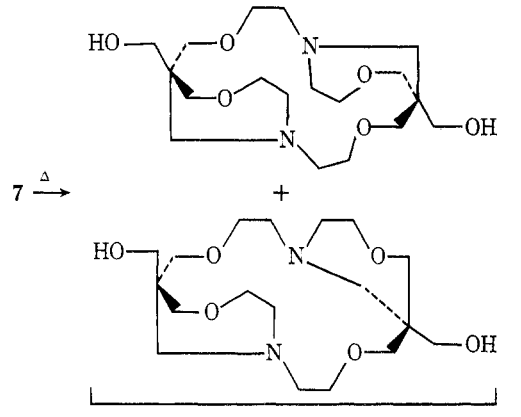


15

Further Reactions of the Oxetane and the Amine Functions. Since both amine groups in **7** are in position to close a seven-membered ring by intramolecular attack on an oxetane ring, thermolysis of neat **7** was undertaken. Little reaction occurred at 210°, but at 230° the rearrangement proceeded to give two isomers of **16,** presumably those represented below. Although no complexes of **16** have yet been prepared, the unusual cavity with both bridgehead carbon and nitrogen atoms is expected to yield interesting results.[4]

Thermolysis of **12** at 230° led mainly to recovered starting material, a result ascribable to steric crowding associated with closure of a ten-membered ring. Thus, although **7** underwent intramolecular ring closure to **16** even in the presence of a large excess of ammonia, **12** reacted with ammonia to form **17.**



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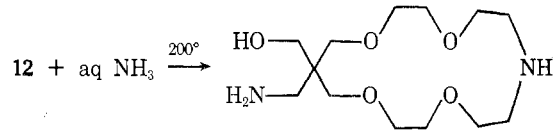
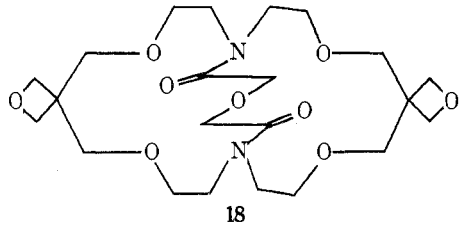
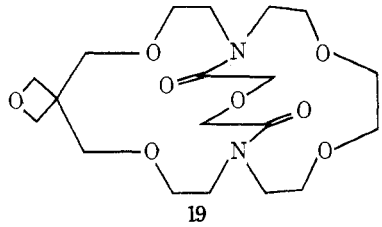


17

By means of the general technique used on related compounds by Simmons and Park[5] and Lehn and Montavan,[6] the diamines **7** and **14** were bridged with diglycolyl dichloride to give **18** and **19,** the first examples of cage polyethers bearing the oxetane function. Presumably the amide groups could be reduced to amine with diborane to provide strongly complexing ligands.



18



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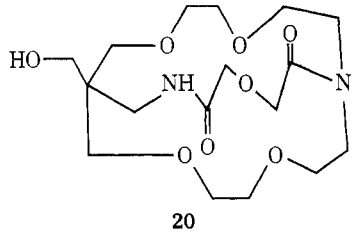
Diglycolyl dichloride was also treated with **17** to form the diamide **20,** in this case a cage polyether with one carbon and one nitrogen as bridgehead atoms.



20

Experimental Section[7]

2-Oxa-6,9-diazaspiro[3.6]decane (2), *N*-(2-Aminoethyl)-2-oxa-6-aza- spiro[3.3]heptane (3), and 1,2-Bis[*N*-(2-oxa-6-aza-spiro[3.3]heptyl)]ethane (4). A mixture of 15.5 g (0.10 mol) of 3,3-bis(chloromethyl)oxetane, 6.0 g (0.10 mol) of ethylenediamine, 300 ml of 1-propanol, and 31.8 g (0.30 mol) of anhydrous sodium carbonate was refluxed under nitrogen for 2 weeks. The mixture was then filtered and distilled to give 1.5 g (10%) of **3,** bp 45–47° (0.1 mm), and 0.7 g (5%) of **2,** bp 60° (0.1 mm).

For **3**: ir 2.97, 3.03, and 6.25 (NH_2), 3.40, 3.48, and 3.56 (saturated CH), 10.30, and 10.60 μ (oxetane); ^1H NMR (acetone-d_6) 4.60 (s, 2 H, oxetane), 3.30 (s, 2 H, azetidine), 1.83 ppm (broad, NH shifted by addition of D_2O), with rough triplets of AA'BB' at 197 (hidden), 190, 183, and 160, 153, 146 Hz (1 H each); mass spectrum *m/e* 142 (M^+), 112.0779 ($M^+ - CH_2NH_2$ and not $M^+ - CH_2O$), 82 ($M^+ - CH_2NH_2 - CH_2O$).

Anal. Calcd for $C_7H_{14}N_2O$: C, 59.13; H, 9.92; N, 19.70. Found: C, 59.25; H, 9.94; N, 19.82.

Compound **2** crystallized and was triturated with a small amount of ether, then ether–petroleum ether to give 0.2 g of deliquescent and somewhat impure **2**: mp 54–55°; ir (Nujol) 3.08 (NH), 10.47 μ (oxetane); ^1H NMR (acetone-d_6) δ 4.27 (s, 2 H, oxetane), 3.12 (s, 2 H, CCH_2N), 2.76 (s, 2 H, NCH_2CH_2N), 2.63 ppm (s, 1 H, NH shifted downfield with D_2O); mass spectrum *m/e* 142 (M^+), 141 ($M^+ - H$), 112.1008 ($M^+ - CH_2O$ and not $M^+ - CH_2NH_2$). Trimethylsilylation gave *m/e* 286 [M^+ for addition of two $(CH_3)_3Si$ groups], 273 ($M^+ - CH_3$), 256 ($M^+ - CH_2O$).

Anal. Calcd for $C_7H_{14}N_2O$: C, 59.13; H, 9.92; N, 19.70. Found: C, 59.76; H, 10.34; N, 18.92.

Sublimation of **4** from the distillation residue at 100° (0.3 mm) gave 0.9 g, mp 90–95°. Resublimation at 75° (0.03 mm) gave 0.64 g (6%) of **4**: mp 95–99°; ir (Nujol) 10.36 and 10.65 μ (oxetane); ^1H NMR (acetone-d_6) 4.60 (s, 2 H, oxetane), 3.25 (s, 2 H, azetidine), 2.26 ppm (s, 1 H, NCH_2CH_2N); mass spectrum *m/e* 224 (M^+), 194 ($M^+ - CH_2O$), 172, 126, 112, 82.

Anal. Calcd for $C_{12}H_{20}N_2O_2$: C, 64.25; H, 8.99; N, 12.49. Found: C, 63.83; H, 9.01; N, 12.41.

2,9,12,15-Tetraoxa-6,18-diazaspiro[3.15]nonadecane (5) and *N*-(11-Amino-3,6,9-trioxa-1-undecyl)-2-oxa-6-azaspiro[3.3]-heptane (6). A mixture of 15.5 g (0.10 mol) of 3,3-bis(chloromethyl)oxetane, 19.2 g (0.10 mol) of 3,6,9-trioxaundecane-1,11-diamine, 38.7 g (0.30 mol) of diisopropylethylamine, and 500 ml of 1-propanol was refluxed under nitrogen for 3 days. The mixture was cooled, treated with 21.2 g (0.20 mol) of anhydrous sodium carbonate, and refluxed for an additional 5 hr. The reaction mixture was then filtered and distilled in a molecular still to give 4.6 g (17%) of an approximately equimolar mixture of isomers **5** and **6**: bp 108–110° (0.1 μ); ir 2.98 (sh) and 3.02 (NH), 6.26 (NH_2, relatively weak), 8.9 (broad, COC), 10.28, and 10.61 μ (oxetane ring); NMR indicated a mixture of oxetanes for which assignments could be made as described below.

Anal. Calcd for $C_{13}H_{26}N_2O_4$: C, 56.91; H, 9.55; N, 10.21; mol wt, 274. Found: C, 56.88; H, 9.23; N, 9.93; mol wt, 274 (field ionization mass spectrum).

The mixture of **5** and **6** was separated by formation of the crystalline complex of **5** with NaSCN. A solution of 1.2 g (0.0044 mol) of the mixture and 0.32 g (0.004 mol) of NaSCN in 10 ml of acetone was evaporated to ca. 5 ml, 5 ml of ether was added, and the mixture was allowed to stand overnight. The supernatant liquid was decanted and the solid was recrystallized from acetone–ether, then from acetone to give the 1:1 complex as large, colorless cubes: mp 154.5–155.5°; ir (Nujol) 3.08 (NH), 4.85 (SCN), 8.8–9.5 (COC), 10.21, and 10.60 μ (oxetane); ^1H NMR (acetone-d_6) 4.43 (s, 2 H, oxetane CH_2), 3.67 (s, 4 H, OCH_2CH_2O), 3.12 (s, 2 H, CCH_2N), and 2.43 ppm (broad, 1 H, NH) with rough triplets of an AA'BB' pattern at 225, 220.5 (hidden), 216 (2 H, NCH_2CH_2O) and 177, 172.5, 168 Hz (2 H, NCH_2CH_2O).

Anal. Calcd for $C_{14}H_{26}N_3NaO_4S$: C, 47.31; H, 7.37; N, 11.82; Na, 6.47. Found: C, 47.49; H, 7.21; N, 11.62; Na, 7.33.

The mother liquor from complex formation was evaporated to a viscous residue and the residue was extracted with 50 ml of benzene. Evaporation of the benzene gave a residue which was extracted with 50 ml of petroleum ether. Evaporation of the petroleum ether gave an oil, nearly pure **6**: ^1H NMR (acetone-d_6) 4.60 (s, 2 H, oxetane), 3.57 and 3.54 (both s, combined area 6 H, $NCH_2CH_2O-CH_2CH_2OCH_2CH_2$), and 3.31 ppm (s, 2 H, azetidine) with rough triplets of an AA'BB' pattern hidden near 200 Hz and at 155.5, 150, and 144 Hz; NH_2 resonance uncertain owing to impurity peaks.

Subtraction of the above spectrum from that of the original mixture leaves for uncomplexed **5** ^1H NMR 4.30 (s, 2 H, oxetane), 3.55 (s, 4 H, OCH_2CH_2O), and 2.93 ppm (s, 2 H, CCH_2N) with AA'BB' triplets hidden near 210 and at 169, 164, and 159 Hz.

2,6,12,16,19,25-Hexaoxa-9,22-diazadispiro[3.9.3.9]hexacosane (7) and *N*-(2-Hydroxyethyl)-2,6-dioxa-9-azaspiro[3.6]decane (8). A solution of 105.0 g (1.0 mol) of diethanolamine, 155.0 g (1.0 mol) of 3,3-bis(chloromethyl)oxetane, and 233 g (2.08 mol) of potassium *tert*-butoxide in 2.5 l. of *tert*-butyl alcohol was refluxed and stirred under N_2 for 2 days. The addition of oxetane, glycol, and butoxide was repeated, and reaction was continued for 4 days. Filtration and evaporation of the filtrate to 60° (0.5 mm) gave a semisolid residue which was kept at 90° and extracted continuously with heptane for 3 days. Removal of heptane from the extract and recrystallization from ether gave 63.6 g (17%) of **7**, mp 118.5–119°. An analytical sample was recrystallized from tetrahydrofuran: mp 118.5–119°; ir (Nujol) 3.04 (NH), 8.6–9.5 (COC), 10.07, 10.29, 10.52, and 10.75 μ (oxetane); NMR [$(CD_3)_2CO$] 4.36 (s, 1, oxetane CH_2), 3.68 (s, 2, along with underlying OCH_2CH_2N, CCH_2O), 2.30 ppm (very broad NH) with AA'BB' branches at 221 (hidden), 216.5, and 211 (OCH_2CH_2N) and 172, 166.5, and 162 Hz (OCH_2CH_2N).

Anal. Calcd for $C_{18}H_{34}N_2O_6$: C, 57.73; H, 9.15; N, 7.48; mol wt, 374.5. Found: C, 57.62; H, 8.86; N, 7.61; mol wt, 398 (ebullioscopic, PhH).

Distillation of the ether filtrate afforded, in addition to considerable viscous residue, 4.9 g (1.3%) of **8**: bp 108–114° (0.25 mm); ir 2.92 (OH), 3.42 and 3.49 (saturate CH), 8.5–9.5 (COC, COH), and 10.4 μ (oxetane); NMR [$(CD_3)_2CO$] 4.37 (s, 4, oxetane CH_2), 3.97 (s, 2, CCH_2O), 3.07 (s, 2, CCH_2N), with multiplets at 3.7–3.4 (5, OCH_2CH_2N + OH) and 2.8–2.55 ppm (4, OCH_2CH_2N).

Anal. Calcd for $C_9H_{17}NO_3$: C, 57.73; H, 9.15; N, 7.48. Found: C, 57.42; H, 9.27; N, 7.38.

The 1:1 complex of **7** with cupric acetate was obtained as follows. Solutions of 0.20 g (0.001 mol) of $Cu(OAc)_2 \cdot H_2O$ in 15 ml of warm absolute ethanol and 0.36 g (0.001 mol) of diamine **7** in 10 ml of ethanol were mixed to give deepening of blue color, but no precipitate. Most of the solvent was removed and 25 ml of ether was added. The precipitate was triturated thoroughly and filtered to give 0.52 g (93%) of violet 1:1 complex, mp 156–158° dec, recrystallized from tetrahydrofuran–ether for analysis: mp 159–160.5° dec; ir (Nujol) 3.08 and 3.16 (NH), 6.21 and 6.29 (CO_2^-), broad 8.6–9.5 (COC), and 10.24, 10.77 μ (oxetane); ^1H NMR signals greatly broadened by paramagnetic Cu^{2+}.

Anal. Calcd for $C_{22}H_{40}CuN_2O_{10}$: C, 47.51; H, 7.25; N, 5.04; Cu, 11.43. Found: C, 47.64; H, 7.59; N, 4.95; Cu, 11.51.

5-Chloro-3-oxapentan-1-ol and Its Reaction with Ammonia. A mixture of 1696 g (16.0 mol) of diethylene glycol and 632 g (8.0 mol) of pyridine was cooled at 0° and stirred while 952 g (8.0 mol) of thionyl chloride was added at a rate sufficient to maintain the temperature near 20°. When all the thionyl chloride had been added (3.5 hr), the temperature was raised to about 80°, at which point noticeable SO_2 evolution occurred. After 3 hr at 80°, the mixture stood over the weekend. It was then heated slowly to 125° and held at 125° until gas evolution had nearly ceased (3 hr). The mixture was distilled and the fraction of bp 60–110° (5 mm) was redistilled through a spinning band column to afford 453 g (45%) of 5-chloro-3-oxapentan-1-ol: bp 75–76° (5 mm); $n^{22}D$ 1.4519;[8] ir 2.92 (OH), 8.8–9.5 (COC), 13.4 μ (CCl).

A mixture of 110 g (0.88 mol) of the chloropentanol, 100 g of NH_3, and 500 ml of absolute alcohol was heated at 120° for 15 hr under autogenous pressure. The reaction mixture was refluxed with 150 g of anhydrous sodium carbonate for 4 hr and filtered, and the filtrate was distilled. There was thus obtained 40.6 g (44%) of **11**, bp 98–99° (5 mm), $n^{24}D$ 1.4588, and 21.6 g (25%) of **9**, bp 128° (20 μ), $n^{27}D$ 1.4717.

For **11**: ir 2.99 and 3.05 (NH_2), 3.1 (broad sh, H-bonded OH, NH_2), 6.25 (NH_2), and 8.92 and 9.33 μ (C–O); ^1H NMR 4.17 (s, partial exchange with acetone-d_6, OH), 3.56 (s atop broad multiplet, OCH_2CH_2O), 3.2–3.8 (multiplet, OCH_2CH_2N), 1.90 ppm (broad s, partial exchange with acetone-d_6, NH_2).

Anal. Calcd for $C_4H_{11}NO_2$: C, 45.69; H, 10.55; N, 13.33. Found: C, 45.75, 45.35; H, 10.05, 10.24; N, 12.41.

For **9**: ir 3.0–3.05 (broad, NH, H-bonded OH), 8.95 and 9.38 μ (C–O); ^1H NMR 3.93 (s, 3 H, OH + NH), 3.4–3.7 ppm (multiplet, 12 H, $OCH_2CH_2OCH_2$), with one branch of an AA'BB' pattern at 172, 167, and 162 Hz (4 H, CH_2N), addition of D_2O changed only the δ 3.93 peak to 4.07.

Anal. Calcd for $C_8H_{19}NO_4$: C, 49.72; H, 9.91; N, 7.25. Found: C, 49.96; H, 9.62; N, 7.60.

Scale-up of the synthesis gave an improved yield of **9**. A mixture of 450 g (3.6 mol) of 5-chloro-3-oxapentan-1-ol, 400 g of ammonia, and 2 l. of absolute ethanol was heated at 125° for 15 hr under autogenous pressure in a 3-gal autoclave. The dark reaction mixture was refluxed for 4 hr with 600 g of anhydrous Na_2CO_3, filtered, and distilled to give 164.3 g (43%) of **11**, bp 60–65° (0.2 mm), and 145.3 g (42%) of **9**, bp 140–145° (15 μ).

Diol **9** was also obtained by alkylation of by-product **11** as follows. A solution of 52.5 g (0.50 mol) of **11** and 74.7 g (0.60 mol) of 5-chloro-3-oxapentan-1-ol in 200 ml of 1-butanol was heated at

100° for 4 days. The mixture was then refluxed for 1.5 hr with 100 g of anhydrous Na_2CO_3, filtered, and distilled to give 39.3 g (41%) of **9**, $n^{22.5}D$ 1.4743, and 15.4 g (11%) of **10**, bp 174–176° (4 μ), $n^{22.5}D$ 1.4820. For **10**, ir and NMR fit the assigned structure.

Anal. Calcd for $C_{12}H_{27}NO_6$: C, 51.23; H, 9.67; N, 4.98. Found: C, 51.26; H, 9.13; N, 5.37.

A stable, crystalline complex was obtained from the acyclic compound **10** and NaSCN. Reaction of 0.50 g (0.0062 mol) of NaSCN and 1.74 g (0.0062 mol) of **10** in acetone led to 2.14 g (95%) of the 1:1 complex. Recrystallization from acetone gave an analytical sample: mp 104–105°; ir (Nujol) 2.93 (OH), 3.15 (NH), 4.79 (SCN), 8.5–9.5 μ (COC, COH). The ^1H NMR spectrum was similar to that of the uncomplexed amine.

Anal. Calcd for $C_{13}H_{27}N_2NaO_6S$: C, 43.08; H, 7.51; N, 7.73; Na, 6.34. Found: C, 43.62; H, 7.28; N, 7.74; Na, 5.7.

2,6,9,15,18-Pentaoxa-12-azaspiro[3.15]nonadecane (12). An attempt to N-benzoylate **9** with benzoic acid–dicyclohexylcarbodiimide in glyme led instead to 73% of *N*-benzoyl-*N,N'*-dicyclohexylurea. Similarly, the mixed anhydride PhCOOCOO-*i*-Bu with **9** did not give the *N*-benzoyl derivative. In view of the rather low reactivity of the N atom in **9** as a nucleophile, condensation with bis(chloromethyl)oxetane was attempted directly.

A solution of 62.0 g (0.40 mol) of bis(chloromethyl)oxetane, 94.0 g (0.84 mol) of potassium *tert*-butoxide, and 77.2 g (0.40 mol) of **9** in 1 l. of *tert*-butyl alcohol was refluxed and stirred under N_2 for 6 days. Filtration and evaporation of the reaction mixture to 50° (0.5 mm) gave a residue which crystallized on cooling. The crude **12** was kept molten at ~90° and extracted continuously with heptane for 1 day. The cooled extract was filtered, and the solid so isolated was recrystallized from ether to give 74.2 g (67%) of **12**, mp 79–81°. An analytical sample, mp 80–81°, was recrystallized from ether: ir (Nujol) 3.01 (NH), 8.6–9.1 (COC), 10.22, and 10.74 μ (oxetane); NMR [$(CD_3)_2CO$] 4.32 (s, 4, oxetane CH_2), 3.65 (s, 4, CCH_2O), 3.57 (s, 12 with underlying OCH_2CH_2N, OCH_2CH_2), and 2.32 ppm (broad s, 1, NH) with OCH_2CH_2N appearing as AA'BB' at 214 (hidden), 209, and 204 (OCH_2) and 162, 157, and 152 Hz (4, CH_2N). Addition of D_2O moved the NH resonance downfield.

Anal. Calcd for $C_{13}H_{25}NO_5$: C, 56.71; H, 9.15; N, 5.09; mol wt, 275. Found: C, 56.61; H, 8.88; N, 5.04; mol wt, 272 (cryoscopic, PhH).

A 1:1 complex of **12** with NaSCN was prepared in acetone, crystallized by concentration and addition of a small amount of ether, and isolated in 93% yield, mp 113–114°. A recrystallized sample had mp 113–114°; ir (Nujol) 3.03 (NH), 4.86 (SCN), 8.7–9.5 (COC), 10.36, 10.57, and 10.75 μ (oxetane); NMR [$(CD_3)_2CO$] 4.43 (s, 4, oxetane CH_2), 3.98 (s, 4, CCH_2O), and 3.73 ppm (s, 12 with nearby OCH_2CH_2N, OCH_2CH_2O), with OCH_2CH_2N appearing as AA'BB' at 221, 216.5, and 211.5 (OCH_2) and 174.5, 169.5, and 165 Hz (4, CH_2N).

Anal. Calcd for $C_{14}H_{25}N_2NaO_5S$: C, 47.18; H, 7.07; N, 7.86; Na, 6.45. Found: C, 47.41; H, 7.14; N, 8.16; Na, 6.06.

Reaction of 12 with Ethylene Oxide. A mixture of 27.5 g (0.10 mol) of **12**, 10 g (0.23 mol) of ethylene oxide, and 200 ml of methanol was heated in a bomb tube at 100° for 6 hr autogenous pressure. Solvent was evaporated, and the product was volatilized in a very short-path still at about 190° (~20 μ), giving 27.6 g (87%) of *N*-(2-hydroxyethyl)-2,6,9,15,18-pentaoxa-12-azaspiro[3.15]nonadecane (**13**) as a nearly colorless oil: ir (2.90 (OH), 8.7–9.5 (COC, COH), 10.23, and 10.80 μ (oxetane); NMR [$(CD_3)_2CO$] 4.29 (s, 4, oxetane CH_2), 3.74 (s, 4, CCH_2O), 3.6–3.3 (m, 15, OCH_2CH_2O + OH + OCH_2CH_2N), 2.85–2.5 ppm (m, 6, CH_2N).

Anal. Calcd for $C_{15}H_{29}NO_6$: C, 56.41; H, 9.15; N, 4.39. Found: C, 56.43; H, 8.80; N, 4.54.

The complex of **13** with NaSCN could not be induced to crystallize.

2,6,12,15,21-Pentaoxa-9,18-diazaspiro[3.18]docosane (14) and 15-Hydroxymethyl-4,7,13,17-tetraoxa-1,10-diazabicyclo[13.4.1]eicosane (15). A solution of 202 g (0.855 mol) of 6,9-dioxa-3,12-diazatetradecane-1,14-diol, 132.8 g (0.855 mol) of 3,3-bis(chloromethyl)oxetane, and 191.5 g (1.71 mol) of potassium *tert*-butoxide in 2.35 l. of *tert*-butyl alcohol was stirred and refluxed under N_2 for 5 days, cooled, and filtered. The filtrate was concentrated to 50° (0.5 mm) and the residual oil was extracted continuously with pentane for 4 days. Concentration of the extracts gave 198.4 g (71%) of crude **14** as a thick yellow oil. This product could not be purified by distillation (see below), but NMR and ir indicated it to be **14**. The structure was confirmed by isolation of the 1:1 complex of **14** with NaSCN in high yield as follows.

A solution in acetone (15 ml) of 3.18 g (0.01 mol) of crude **14** and 0.81 g (0.01 mol) of NaSCN was evaporated to a volume of 10 ml and 5 ml of ether was added. The cloudy solution was seeded with previously prepared complex and on standing gave 3.20 g (80%) of 1:1 complex, mp 147–150°. Recrystallization from a small amount of acetone gave 2.63 g of complex, mp 151–153.5°, shown by mixture melting point to be the same as authentic complex. An analytical sample of similarly prepared complex had mp 151–153°; ir (Nujol) 2.97 and 3.04 (NH), 4.82 (SCN), 8.5–9.5 (COC), 10.03, 10.48, and 10.53 μ (oxetane); NMR [$(CD_3)_2CO$] 4.36 (s, 2, oxetane CH_2), 3.90 (s, 2, CCH_2O), 3.75–3.5 with major singlet at 3.64 for OCH_2CH_2O (m, 6, OCH_2), and 2.23 ppm (broad, 1, NH), with one branch of A_2B_2 at 173.5, 168, and 164 Hz (4, NCH_2).

Anal. Calcd for $C_{16}H_{30}N_3NaO_5S$: C, 48.11; H, 7.57; N, 10.52; Na, 5.75. Found: C, 47.76; H, 7.57; N, 10.60; Na, 5.65.

A 1:1 complex of **14** with NaI was similarly obtained as hygroscopic crystals: mp 143–145°; ir (Nujol) 3.09 (NH), 8.5–9.5 (COC), 10.07, and 10.57 μ (oxetane); NMR [$(CD_3)_2CO$] 4.38 (s, 2, oxetane CH_2), 3.95 (s, 2, CCH_2O), 3.7–3.55 with major singlet at 3.67 (m, 6, OCH_2), 3.0–2.7 (m, 2, NCH_2), and 1.83 ppm (s shifted downfield by D_2O, 1, NH).

Anal. Calcd for $C_{15}H_{30}N_2NaO_5I$: C, 38.47; H, 6.46; N, 5.98; I, 27.10. Found: C, 38.36; H, 6.37; N, 5.77; I, 26.90.

Another preparation of **14** gave a similar yield of crude product, which was distilled through a Vigreux column. Fractions taken at ~160 (0.3 μ) to 180° (1.0 μ) were 65.7 g (21%) of mixtures of **14** and **15**. Product distilled at 180–185° (1.0 μ) was 85.1 g (27%) of the exceptionally viscous **15**, formed by intramolecular attack of NH on the oxetane ring: ir 2.92, 3.00, and 3.12 (OH, NH), 3.37 (sh), and 3.46 (saturate CH), 8.5–9.5 μ (COC, COH); NMR [$(CD_3)_2CO$] 3.8–3.1 (m, 2, OCH_2 + OH + NH) and 2.8–2.5 ppm (m, 1, NCH_2).

Anal. Calcd for $C_{15}H_{30}N_2O_5$: C, 56.58; H, 9.50; N, 8.80. Found: C, 56.75; H, 9.74; N, 8.57.

The 1:1 complex was prepared in acetone from 3.18 g (0.01 mol) of **15** and 0.81 g (0.01 mol) of NaSCN, 3.57 g (90%), mp 163–164°. An analytical sample was obtained from acetone–ether: mp 164–165°; ir (Nujol) 2.95 (OH), 3.02 (NH), 4.83 and 4.92 (SCN), 8.6–9.6 μ (COC, COH); NMR [$(CD_3)_2CO$] 3.7–3.15 (m, 19, OCH_2 + OH) and 2.7–2.3 ppm (m, 11, NCH_2 + NH).

Anal. Calcd for $C_{16}H_{30}N_3NaO_5S$: C, 48.11; H, 7.57; N, 10.52; Na, 5.75. Found: C, 47.84; H, 7.67; N, 10.38; Na, 5.68.

Isomers of 6,16-Bis(hydroxymethyl)-4,8,14,18-tetraoxa-1,11-diazatricyclo[14.4.1.1^{6,11}]docosane (16). Thermolysis of neat **7** at 205–210° under nitrogen for 8 hr gave recovered **7**. At 225–230° for 24 hr, 4.0 g (0.0107 mol) of **7** formed a viscous product which gave 2.7 g of isomers of **16**, mp ~155–170°, when triturated with 30 ml of benzene. Two recrystallizations from benzene gave 1.3 g of needles, isomer A, mp 177.5–177°. A second crop, 0.2 g, mp 173–176°, raised the yield to 1.5 g (38%). An analytical sample was obtained from acetone: mp 177.5–178.5°; ir (Nujol) 2.90 (OH), 8.5–9.6 μ (COC, COH); NMR [$(CD_3)_2SO$] 4.2–1.6 ppm (complex multiplet). A broad band at 4.2 ppm (OH) was shifted upfield by addition of D_2O, leaving none in the region for oxetane ring. Mass spectrum *m/e* for silylation product 518 (disilylated M^+), 503 (disilylated $M^+ - CH_3$). Mass measurement on parent gave *m/e* 518.3190 for $C_{24}H_{50}O_6N_2Si_2$ (calcd, 518.3204).

Anal. Calcd for $C_{18}H_{34}N_2O_6$: C, 57.73; H, 9.15; N, 7.48. Found: C, 58.00; H, 9.02; N, 7.44.

The filtrate from isomer A contained some lower melting isomer B, which could not be isolated by crystallization from ether or benzene.

An attempt to obtain intermolecular addition to the oxetane rings with ammonia was carried out below 210°, but in water solution. In the polar solvent, reaction proceeded at only 200° to give the two isomers of **16** rather than ammonia adducts. In this case, isomer B was isolated as follows.

A mixture of 8.2 g (0.022 mol) of **7** and 100 ml of concentrated NH_4OH was heated at 200° for 17 hr under autogenous pressure. The clear reaction mixture was evaporated to a solid residue, which was heated with 25 ml of acetone and cooled to give 2.75 g of isomer A, mp 173–177°. A second crop, 1.68 g, mp 125–135°, was mainly isomer B. A third crop, 0.34 g, mp 171–176°, raised the yield of isomer A to 3.09 g (38%). The second crop was recrystallized from methanol–acetone to give 1.21 g (15%) of isomer B, mp 126–128°. An analytical sample was obtained from acetone with a little methanol added, as large cubes: mp 127.5–129°; ir (Nujol) 2.91 (OH) and 8.5–9.5 μ (COC, COH) with no isomer A detectable; NMR [$(CD_3)_2SO$] 4.3–2.1 ppm (complex multiplet different from that for isomer A). A broad band at 4.3 ppm (OH) was shifted upfield by D_2O, leaving none in the region for oxetane ring. Mass

spectrum *m/e* for silylated derivative 518 (disilylated M^+); the spectrum is nearly identical with that of isomer A.

Anal. Calcd for $C_{18}H_{34}N_2O_6$: C, 57.73; H, 9.15; N, 7.48. Found: C, 57.50; H, 8.80; N, 7.76.

15-Aminomethyl-15-hydroxymethyl-1,4,10,13-tetraoxa-7-azacyclohexadecane (17). After neat **12** was heated under nitrogen at 220–230° for 20 hr, 81% of the starting material was recovered. Ammonia can therefore attack **12** to form an adduct.

A mixture of 27.5 g (0.01 mol) of **12** and 200 ml of concentrated NH_4OH was heated at 200° for 20 hr under autogenous pressure. Evaporation of the reaction mixture gave 28.8 g of viscous residue. Attempts to crystallize 1.4 g of the crude product failed, so the remainder was distilled in a molecular still to give 15.2 g (52%) of **17**: bp 105° (1 μ); mp 52–56°; ir (neat) 2.95 (sh), 3.03 and 3.14 (OH, NH, NH_2), 3.50 (saturated CH), 6.24 (NH_2), and broad 8.6–9.6 μ (COC, COH); NMR [$(CD_3)_2CO$] 3.7–3.5 (m, 18, OCH_2), 3.18 (broad s, 3, with partial exchange into $(CD_3)_2CO$, OH, and NH_2), 2.65–2.9 (m, 6, NCH_2), and 1.30 ppm (broad s, 1, NH). D_2O shifted the 3.18 ppm peak downfield. Mass spectrum *m/e* for silylated derivative 508 (trisilylated M^+), 493 (trisilylated $M^+ - CH_3$), 436 (disilylated M^+), and 421 (disilylated $M^+ - CH_3$). Mass measurement of trisilylated parent gave *m/e* 508.3181 (calcd for $C_{22}H_{52}O_5N_2Si_3$, 508.3181).

Anal. Calcd for $C_{13}H_{28}N_2O_5$: C, 53.40; H, 9.65; N, 9.58. Found: C, 53.73; H, 10.04; N, 9.95.

Dispiro[oxetane-3,6′-21′,25′-diketo-4′,8′,14′,18′,23′-pentaoxa-1′,11′-diazabicyclo[9.9.5]pentacosane-16′,3″-oxetane] (18). Solutions of 37.5 g (0.10 mol) of **7** in 200 ml of purified CH_2Cl_2 and 17.1 g (0.10 mol) of diglycolyl dichloride in 200 ml of dry benzene were added simultaneously and with vigorous stirring to a mixture of 50 ml of triethylamine and 1 l. of dry benzene. After the addition was completed (4 hr), the mixture was filtered and the filtrate was evaporated to give 32.3 g of solid. Extraction of the filter cake with hot benzene gave another 1 g of solid. Recrystallization of the crude product from acetone gave 20.5 g (43%) of **18**, mp 188–191°. An analytical sample, mp 190–192°, was obtained from acetone: ir (Nujol) 5.97 and 6.02 (amide CO), 8.6–9.4 (COC), 10.15, 10.33, and 10.51 μ (oxetane); ^1H NMR [$(CD_3)_2SO$] 4.5–4.0 (m, 4) and 3.8–3.2 ppm (m, 5).

Anal. Calcd for $C_{22}H_{36}N_2O_9$: C, 55.92; H, 7.68; N, 5.93; mol wt, 473. Found: C, 55.82; H, 7.74; N, 6.16; mol wt, 467 (ebullioscopic, PhH).

Spiro[20,24-diketo-4,8,14,17,22-pentaoxa-1,11-diazabicyclo-[9.8.5]tetracosane-6,3′-oxetane] (19). Solutions of 31.8 g (~0.10 mol) of crude **14** in 200 ml of dry benzene and 17.1 g (0.10 mol) of diglycolyl dichloride in 210 ml of dry benzene were added dropwise and simultaneously to a vigorously stirred mixture of 50 ml of triethylamine and 1 l. of dry benzene. After addition was completed (3.5 hr), stirring was continued for an additional 15 min, the mixture was filtered, and the filtrate was evaporated to give 26.3 g of viscous residue. Crystallization from acetone gave 12.3 g (30%) of **19**, mp 178–181°. An analytical sample was obtained from acetone: mp 180.5–182°; ir (Nujol) 6.03 (C=O), 8.6–9.6 (COC), 10.27, and 10.78 μ (oxetane); ^1H NMR [$(CD_3)_2SO$] 4.3–4.0 (m, 1) and 3.7–3.2 (m, 2).

Anal. Calcd for $C_{19}H_{32}N_2O_8$: C, 54.79; H, 7.75; N, 6.73; mol wt, 416. Found: C, 54.88; H, 7.92; N, 6.50; mol wt, 417 (ebullioscopic, PhH).

2,6-Diketo-9-hydroxymethyl-4,11,14,19,22-pentaoxa-1,7-diazabicyclo[7.7.7]tricosane (20). A solution of 12.4 g (0.0425 mol) of diamine **17** diluted to 150 ml with purified methylene chloride and a solution of 7.3 g (0.0425 mol) of diglycolyl dichloride diluted to 150 ml with dry benzene were added simultaneously to a vigorously stirred mixture of 2 l. of dry benzene and 25 ml of triethylamine. Addition required 2.75 hr. The mixture was stirred for another 0.5 hr and filtered, and the solid was rinsed with benzene. Evaporation of the filtrate and rinsings gave a solid residue which was extracted with 2 × 500 ml of hot acetone. Evaporation of acetone gave 8.7 g of crude **20**. Another 0.9 g of crude **20** was obtained by extraction of the benzene-insoluble solid with cold acetone. Recrystallization of the crude product from 1:1 methanol–acetone gave 5.8 g (35%) of **20**, mp 182–185°. An analytical sample was recrystallized from methanol, then from methanol–acetone: mp 186–187.5°; ir (Nujol) 2.94 and 3.02 (OH and NH), 5.99 and 6.07 (C=O), 6.52 (amide II), and broad 8.7–9.4 μ (COC, COH); mass spectrum *m/e* (silylated derivative) 462 (monosilylated M^+). Mass measured at *m/e* 462.2415 corresponds to $C_{20}H_{38}O_8N_2Si$ (calcd, 462.2395) with no higher mass peaks observed. A model of this compound is very compact and suggests that silylation at the amide group may be hindered.

Anal. Calcd for $C_{17}H_{30}N_2O_8$: C, 52.30; H, 7.74; N, 7.18. Found: C, 52.48; H, 7.98; N, 7.13.

Registry No.—**1**, 78-71-7; **2**, 54384-39-3; **3**, 54384-40-6; **4**, 54384-41-7; **5**, 54384-42-8; **5** NaSCN, 54384-43-9; **6**, 54384-44-0; **7**, 54384-45-1; **7** $Cu(OAc)_2$, 54484-53-6; **8**, 54384-46-2; **9**, 54384-47-3; **10**, 54384-48-4; **10** NaSCN, 54384-49-5; **11**, 929-06-6; **12**, 54384-50-8; **12** NaSCN, 54384-51-9; **13**, 54384-52-0; **14**, 54384-53-1; **14** NaSCN, 54384-54-2; **14** NaI, 54384-55-3; **15**, 54384-56-4; **15** NaSCN, 54384-57-5; **16** isomer A-B, 54384-62-2; **16** isomer B-A, 54423-05-1; **17**, 54384-58-6; **18**, 54384-59-7; **19**, 54384-60-0; **20**, 54384-61-1; ethylenediamine, 107-15-3; 3,6,9-trioxaundecane-1,11-diamine, 929-75-9; diethanolamine, 111-42-2; 5-chloro-3-oxapentan-1-ol, 628-89-7; diethylene glycol, 111-46-6; ethylene oxide, 75-21-8; 6,9-dioxa-3,12-diazatetradecane-1,14-diol, 50977-92-9; diglycolyl dichloride, 21062-20-4.

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