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MACROCYCLIC POLYFUNCTIONAL LEWIS BASES—IX[1]

AZACROWN ETHERS

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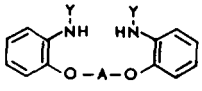
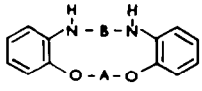
Abstract—Several new diazacrown ethers and one tetraazacrown ether have been obtained.

Up to date only a few diaza-analogues of crown ethers have been prepared. In particular this concerns the dibenzodiazacrowns-o-aminophenol derivatives of which only single examples are described.[2,3] According to Cram,[2] compounds of type **1** undergo alkylation with difficulty. Furthermore, removal of the protecting sulphonyl residue may not be performed easily. Hence only compound **3** has been described.[2] Direct alkylation of o-aminophenol using α,ω-dichlorethers led to a complex mixture of products.[3]

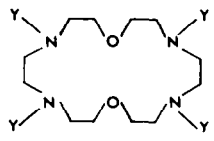
To obtain dibenzodiazacrown ethers we applied two methods. Alkylation of compounds of type **1** according to Cram[2] with ethylene bromide, 1,3-dibromopropane and 1,8-diiodo-3,6-dioxaoctane[4] in the presence of anhydrous sodium carbonate in dimethylformamide gave crude mixtures of tosyl derivatives which were converted into free amines using sodium naphthalenide in dimethoxyethane.[5] Owing to the low polarity of the dibenzodiazacrowns they were readily isolated from a mixture using column chromatography followed by crystallization. The diamines **2** may be directly alkylated under similar conditions. The macrocyclic compounds were isolated as above. Both methods are simple, but not very efficient. The last, one step synthesis gives usually inferior yields (see Table 1).



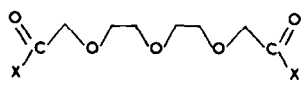
1: Y = p-$CH_3C_6H_4SO_2$
2: Y = H

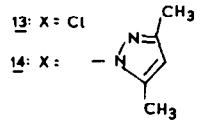


	A =	B =
3	$-CH_2CH_2OCH_2CH_2-$	$-CH_2CH_2OCH_2CH_2-$
4	$-CH_2CH_2-$	$-CH_2CH_2-$
5	$-CH_2CH_2-$	$-CH_2CH_2CH_2-$
6	$-CH_2CH_2CH_2-$	$-CH_2CH_2-$
7	$-CH_2CH_2CH_2-$	$-CH_2CH_2CH_2-$
8	$-CH_2CH_2OCH_2CH_2-$	$-CH_2CH_2-$
9	$-CH_2CH_2OCH_2CH_2-$	$-CH_2(CH_2OCH_2)_2CH_2-$
10	$-CH_2(CH_2OCH_2)_2CH_2-$	$-CH_2CH_2-$

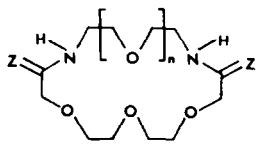


11: Y = p-$CH_3C_6H_4SO_2$
12: Y = H





13: X = Cl
14: X =



15: Z = O, n = 0
16: Z = H_2, n = 0
17: Z = O, n = 1
18: Z = H_2, n = 1

Tetra-azacrown ether **11** was obtained by alkylation of ditosylethylenediamine with dichloroethyl ether in DMF. Applying potassuim carbonate as a base, up to 40% yield of **11** was obtained, easily isolated due to its low solubility and good crystallizability. In the presence of sodium carbonate the yield of the desired product was lower than 10%. Since in the presence of soduim carbonate under similar conditions a fairly large amount of ditosyldiaza-9-crown-3 was obtained,[6] the reaction course may be strongly controlled by the template effect. We could not convert compound **11** into tetraazacrown **12** by the action of lithium aluminium hydride, Raney nickel and sodium naphthalenide. Only hydrolysis with concentrated sulphuric acid[7] gives the desired product.

In the cryptand synthesis described by Lehn,[8] one of the key substrates is tetraglycollic acid dichloride **13**. This compound was obtained in pure state by a

Table 1. Methods of preparation and properties of azacrown ethers

Compound	Yield % and method		M.p. °C	Formula and m.w.		M/e
4	3[a]	6[b]	209 - 211	$C_{16}H_{18}N_2O_2$	270.3	270
5	9[a]		188 - 190	$C_{17}H_{20}N_2O_2$	284.4	284
6	1[a]	7[b]	171 - 173	$C_{17}H_{20}N_2O_2$	284.4	284
7		3.5[b]	191 - 193	$C_{18}H_{22}N_2O_2$	298.4	298
8	8[a]		160 - 163	$C_{18}H_{22}N_2O_3$	314.4	314
9	12[a]		110 - 111	$C_{22}H_{30}N_2O_5$	402.5	402
10		8[b]	162 - 164	$C_{20}H_{26}N_2O_4$	358.4	358
12	25[c]		58 - 60	$C_{12}H_{28}N_4O_2$	260.3	260
16	60[d]		syrup	$C_{10}H_{22}N_2O_3$	218.3	218
18	90[d]		syrup	$C_{12}H_{26}N_2O_4$	262.3	262

[a] direct alkylation, [b] alkylation of ditosylderivative followed by reduction with sodium naphtalenide, [c] hydrolysis of tetratosylderivative with conc. sulphuric acid, [d] reduction of macrocyclid diamide with $LiAlH_4$.

four step synthesis from crude tetraglycollic acid.[8] Use of this compound in the synthesis of a macrocyclic diamide additionally requires application of twofold excess of diamine to neutralize hydrogen chloride liberated during the reaction. As we stated, tetraglycollic acid dimethylpyrazolide **14** may be successfully used for macrocycle synthesis. This compound was obtained in pure state by one step procedure from the crude tetraglycollic acid. Furthermore, the macrocyclic diamide synthesis does not require excess of diamine. The usefulness of compound **14** was demonstrated by synthesis of macrocyclic compounds **15** and **17**, which were simply liberated from linear by-products using ion-exchangers. Reduction of these compounds with lithium aluminium hydride gives diazacrowns **16** and **18**.

The protonation constants of compounds **12**, **16** and **18** and their susceptibility to form complexes have been described elsewhere.[9]

EXPERIMENTAL

Molecular weights and purities of macrocyclic compounds were determined by mass spectrometry on a Varian MAT 711 apparatus using FD technique. ^1H NMR spectra were taken at 60 MHz on a Tesla BS 467 spectrometer. MN Kieselgel 60 or MN Aluminiumoxid sauer (Macherey Nagel & Co) was used for column chromatography. Diamines **2** were synthesized as described.[10]

Dibenzodiaza-13-crown-4 **6**

To a soln of 1,3-bis(2′-aminophenoxy)propane dihydrochloride[10] (9 g, 27.2 mmol) in 50 ml dry pyridine, toluene-p-sulphonylchloride (11.4 g, 60 mmol) was added. The mixture was heated on a boiling water-bath for 1 h and cooled. The reaction mixture was diluted with water and the precipitate collected, washed with water, n-butanol and dried. Yield of the ditosyl-derivative is almost quantitative M.p. 228–230°. (Found C, 61.6; H, 5.22. Calc for $C_{29}H_{30}N_2O_6S_2$. C, 61.5; H, 5.30%).

A mixture of 2.83 g (5 mmol) of the ditosylderivative, 1.5 g Na_2CO_3, 0.5 ml (5.8 mmol) 1,2-dibromoethane and 7 ml DMF was boiled gently for 24 h. The solvent was evaporated under reduced pressure and the residue dissolved by heating in 20 ml xylene and filtered. The soln was again evaporated under reduced pressure to constant weight. An excess sodium naphthalenide soln, prepared from 2 g of naphthalene in 20 ml of dimethoxyethane[5] was added to the residue. After 2 h the solvent was removed and the residue was extracted three times with 30 ml portions of 1M HCl. The combined soln was treated with excess of NaOH pellets and the free amine was extracted with $CHCl_3$. The solvent was removed and the residue (1.4 g) was extracted with boiling CCl_4. The soln was applied to a short alumina column and the desired compound was eluted with CCl_4 and finally with ethylenedichloride. The colourless eluent was evaporated and the obtained crystals were washed with a small amount of ethyl ether. Yield 100 mg (7%). M.p. 171–173°.

Dibenzodiaza-21-crown-7 **9**

A mixture of (2.9 g, 8 mmol) 1,5-bis(2′-aminophenoxy)-3-oxa-pentane dihydrochloride,[10] 3 g anhydrous K_2CO_3, 1.6 ml (8.05 mmol) 1,8-diiodo-3,6-dioxaoctane[4] and 20 ml DMF was gently boiled for 10 h. After that the solvent was removed under vacuum and the residue was dissolved in a small amount of ethylene dichloride, applied on a short alumina column and chromatographed using the same solvent. The eluent was evaporated and the crystalline product was washed with ethyl ether. Yield 400 mg (12%). M.p. 110–112°.

Tetraaza-18-crown-6 **12**

Tetratosyl derivative **11**. A mixture of ditosylethylenediamine (1.85 g, 5 mmol), K_2CO_3 (1 g), dichloroethyl ether (0.66 ml) and DMF (2 ml) was heated at 170° (oil bath temp) for 5 h. Water was added to the cooled reaction mixture and the doughy product was kneaded several times with fresh water portions. The carefully separated residue was mixed with 10 ml of acetone. The precipitate was collected and washed with acetone. Yield 660–875 mg (30–40%). M.p. 242°. After recrystallization from boiling DMF it had m.p. 245°. (Found C, 54.8; H, 6.14. Calc for $C_{40}H_{52}N_4O_{10}S_4$ C, 54.8; H, 5.98%).

Tetraaza-18-crown-6. A soln of tetratosyl derivative **11** (1.75 g; 2 mmol) in 5 ml conc H_2SO_4 was heated at 100° for 3 days. The soln was then treated with excess NaOH pellets and the product extracted with $CHCl_3$. The organic layer was dried (Na_2SO_4) and evaporated. The residue was crystallized from heptane. Yield 130 mg (25%), m.p. 58–60°.

Tetraglycollic acid dimethylpyrazolide **14**

To an ice-cooled suspension of 3,5-dimethylpyrazole (2 g, 20.8 mmol) in 5 ml of dry pyridine 0-ethylphosphoric dichloride[11,12] (1.18 ml; 10 mmol) was added dropwise with stirring. The mixture was then warmed to 50° and cooled slowly to room temp. After 0.5 h 0.7 g of crude tetraglycollic acid[8] was added and the mixture was left for a day at room temp. The reaction mixture was then diluted with 50 ml of ice-water. The precipitate of diglycollic acid dimethylpyrazolide (m.p. 172–174°) which formed immediately was collected. The mother liquor was extracted with ethyl acetate and the organic layer was washed with 1 M HCl and then sat $NaHCO_3$ soln, and dried with $MgSO_4$. The solvent was removed under reduced pressure and to the residue a small amount of petroleum ether was added. The crystals were collected and recrystallized from ethyl acetate-petroleum ether or from benzene-petroleum ether. Yield 0.49 g, m.p. 64–65°. (Found C, 57.0; H, 6.80. Calc for $C_{18}H_{26}N_4O_5$ C, 57.1; H, 6.94%. H NMR ($CDCl_3$) δ[ppm]: 2.07 (C^3-CH_3, s, 6H); 2.42 (C^5-CH_3, s, 6H); 3.66 (OCH_2CH_2-, m, 8H); 4.46 (OCH_2CO, s, 4H) and 5.50 (C^4-H, s, 2H).

Macrocyclic diamide **15**

To a 100 ml portion of boiling benzene a soln of pyrazolide **14** (3.78 g, 10 mmol) in 40 ml of benzene and simultaneously a soln of ethylenediamine (0.66 ml, 11 mmol) dissolved in 40 ml of benzene were added dropwise during 2.5 h. After the addition was complete the boiling was continued for a further 4 h and the solvent was removed under vacuum. The dry residue was crystallized from THF. The crude product was dissolved in water and the solution was passed in turn through an Amberlite IR-120 (H^+) and an Amberlite IRA-410 (OH^-) column. The eluent was evaporated and the dry residue was again crystallized from THF. Yield 1.48 g (60%), m.p. 160–163°. (Found C, 49.1; H, 7.29%, *M/e* 246. Calc for $C_{10}H_{18}N_2O_5$ C, 48.8 H, 7.38%).

Macrocyclic diamide **17**

The diamide **17** was obtained analogously. It was crystallized from THF and dried in vacuum to remove water of crystallization. Yield 50%, m.p. 112–114°. (Found C, 49.5 and H, 7.15%. Calc for $C_{12}H_{22}N_2O_6$ C, 49.6 H, 7.65%). *M/e* = 290.

Diaza-15-crown-5 **16**

Compound **15** as reduced in THF with $LiAlH_4$ under conditions described in detail by Lehn[8] for 4 days using Soxhlet apparatus. The yield of a syrupy product was 60%.

Diaza-18-crown-6 **18**

Obtained in a similar way starting from compound **17**. Yield 90%.

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REFERENCES

[1]Part VIII: A. Horbaczewski and J. F. Biernat, *Inorg. Chim. Acta*, **74**, 131 (1983).
[2]S. A. G. Högberg and D. J. Cram, *J. Org. Chem.* **40**, 151 (1975).
[3]J. C. Lockhart, A. C. Robson, M. E. Thompson, D. Furtado, C. K. Kaura and A. R. Allen, *J. Chem. Soc. Perkin I*, 577 (1973).
[4]S. Kulstad and L. Å. Malmsten, *Acta Chem. Scand. B* **33**, 469 (1979).
[5]Ji. Sungchul, L. B. Gortler, A. Waring, A. Battisti, S. Bank and W. D. Clossen, *J. Am. Chem. Soc.* **89**, 5311 (1967).
[6]P. Vejmelka, Theses, Technical University, Aachen 1977.
[7]W. Rasshofer, W. Wehner and F. Vögtle, *Ann.* 916 (1976).
[8]B. Dietrich, J. M. Lehn, J. P. Sauvage and J. Blanzat, *Tetrahedron* **29**, 1629 (1973).
[9]E. Luboch, A. Cygan and J. F. Biernat, *Inorg. Chim. Acta*, **68**, 201 (1983).
[10]J. F. Biernat, E. Jereczek and A. Bujewski, *Pol. J. Chem.* **53**, 2351 (1979).
[11]G. Błotny and J. F. Biernat, *Ibid.* **53**, 689 (1979).
[12]E. Luboch and J. F. Biernat, *Ibid.* **55**, 2183 (1981).