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CONVENIENT SYNTHESIS OF CROWN ETHERS CONTAINING A HYDRAZINE MOIETY

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Abstract: A new class of crown ethers containing a hydrazine moiety was synthesized in only 2, 3, or 4 steps starting from 1,2-diacetylhydrazine or 1,2-diethylhydrazine. Hydrazino-crown ethers with 2 or 4 nitrogen atoms in the ring were obtained by reacting the hydrazine derivatives with 1,11-diiodo-(or dichloro)-3,6,9-trioxaundecane, 4-allyloxymethyl-1,8-diiodo-3,6-dioxaoctane, 3-chloro-2-chloromethyl-1-propene, 1,10-dibenzyl-1,10-diaza-3,7-dioxadecane or diglycolyl dichloride (followed by reduction). The diazahydrazino-19-crown-6 compound formed a complex with methylammonium chloride.

The aza-crown compounds have received considerable interest in recent years because of their ability of complex a variety of metal and organic cations and anions.[1-8] Most aza-crown ethers have ethylene bridges between the nitrogen atoms. There have been a few aza-crowns with one carbon between nitrogen atoms in the form of the guanidinum, urea or thiourea moieties, which form complexes with cations, anions and amines.[9-11] Saturated crown ethers containing the hydrazine moiety (no atoms between nitrogen atoms) have not been reported. A few small ring hydrazine-containing compounds have been prepared including 1,4,5-oxadiazepine[12,13] and 1,5,6-oxadiazocyne[14] but these compounds have a small cavity. Some open-chain hydrazine compounds have the ability to complex metal ions.[15,16] We believe that crown ethers with hydrazine moieties built into the ring could have important complexing abilities. We have prepared aza-crown ethers where a hydrazine moiety has replaced one of the ring nitrogen atoms (compounds 1-6). A few convenient methods for the preparation of hydrazino-crown ethers with differing numbers of nitrogen atoms in the macroring and starting from hydrazine derivatives which are readily available are shown in Schemes 1 and 2.

Key intermediate **7** (Scheme 1) was prepared by first reacting 2.1 equivalents of N-[2-(2-chloroethoxy)ethyl]acetamide (**A**) with 1,2-diacetylhydrazine in DMF at 120°C in the presence of sodium carbonate. We have reported the use of the above mentioned acetamide **A** for the convenient synthesis of N-alkyl-substituted triaza- and tetraaza-crown compounds.[17] The reaction mixture was filtered, evaporated and the residue was chromatographed on silica gel using 2-propanol, then ethanol and methanol to give the tetraamide. The tetraamide product was reduced[18], followed by distillation to give **7** (55% overall); bp 115-117°/0.01mmHg. The same reaction sequence and conditions using 1,2-diethylhydrazine gave only a marginal yield of **7**.

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Compound 7 was reacted with B or C in acetonitrile[19] in the presence of sodium or potassium carbonate at reflux temperature to effect ring closure to form 1 and 2, respectively. The reaction mixture was filtered, evaporated and the residue was chromatographed[20] to give a 48% yield of crown 1[21] and a 50% yield of crown 2[21]. The NMR spectral signals are as follows: for 1, (δ) 0.90 (t, 6 H), 0.95 (t, 6 H), 2.55 (m, 16, H), 3.05 (s, 4 H), 3.55 (m, 8 H), 5.05 (s, 2 H); and for 2, (δ) 0.95 (t, 6 H), 1.00 (t, 6 H), 2.6 (m, 20 H), 3.55 (m, 17 H), 4.0 (m, 2 H), 5.2 (m, 2 H), 5.9 (m, 1 H).

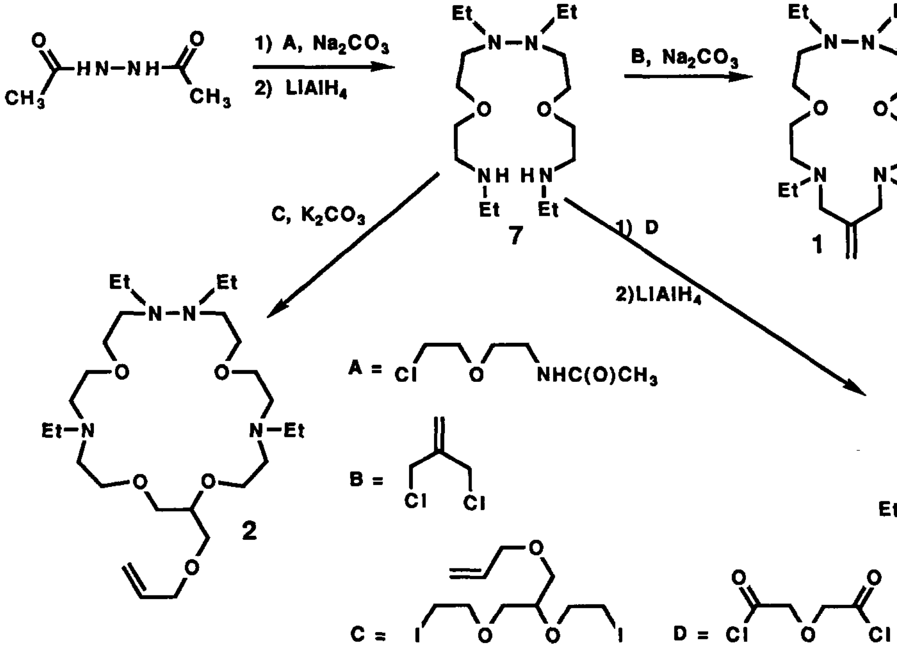
Compound 7 was also reacted with D[19] as follows. Each reactant in toluene was simultaneously added over a several hour period to toluene (well stirred) containing three equivalents of triethylamine at 5°C. The toluene solution was stirred for 24 hours at room temperature, filtered and evaporated. The residue was chromatographed[20] to give a 65% yield of the cyclic diamide. The cyclic diamide was reduced[18] and purified by chromatography[20] to give a 71% yield of 3[21] as an oil; NMR (δ): 0.95 (t, 6 H), 1.00 (t, 6 H), 2.6 (m, 20 H), 3.55 (m, 12 H).

The starting 1,2-diacethylhydrazine was also condensed with 1,11-dichloro-3,6,9-trioxaundecane in DMF[19] at 130°C in the presence of sodium carbonate (see Scheme 2). The solution was stirred for 48 h, filtered and evaporated. The residue was chromatographed[20] to give two cycloaddition products, a 13-membered ring from a 1:1 cyclocondensation and a 26-membered ring from a 2:2 cyclocondensation. These products were separately reduced[18] followed by purification by chromatography[20] to give crown 4[21] (35% overall); NMR (δ): 0.95 (t, 6 H), 2.45 (q, 4 H), 2.65 (t, 4 H), 3.65 (m, 12 H), and crown 5[21] (8% overall). Crown 4 was also synthesized in one step by reacting 1,2-diethylhydrazine dihydrochloride with 1,11-diiodo-3,6,9-trioxaundecane in acetonitrile or ethanol[19] in the presence of sodium carbonate at reflux temperature. The reaction mixture was purified as above to give a 41% or 36% yield of crown 4. No crown 5 was observed in this reaction because of the sodium ion template effect. 1,2-Diethylhydrazine dihydrochloride was also reacted with chloroacetyl chloride in a mixture of chloroform and water as follows (Scheme 2). To 1 equivalent of 1,2-diethylhydrazine in water were dropped simultaneously at 0°C, 3 equivalents of chloroacetyl chloride in chloroform and an aqueous solution of 3 equivalents of potassium carbonate. The mixture was vigorously stirred during the addition process. After 3 h, the chloroform layer was separated, washed twice with water, dried over anhydrous magnesium sulfate and evaporated. The residue was crystallized from 2-propanol to yield 78% of compound 8, m.p. 66°C. This diamide was condensed at reflux temperature with compound H[19] in acetonitrile in the presence of sodium carbonate over a 24-h period. The reaction mixture was filtered and evaporated and the crude product was purified by chromatography[20] and then was reduced[18] to give crown 6[21] (45%), NMR (δ): 1.00 (t, 6 H), 2.70 (m, 12 H), 3.00 (m, 4 H), 3.55 (m, 8 H), 3.60 (s, 4 H), 7.30 (m, 10 H).

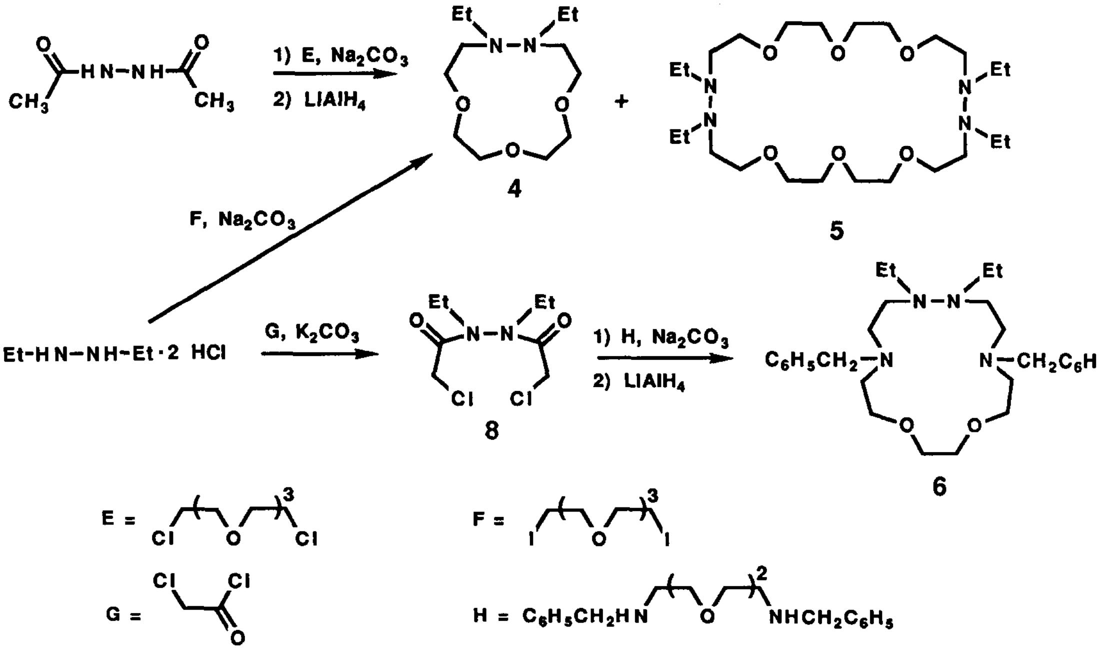
This work reports only the synthetic pathway to form hydrazino-crowns with ethyl substituents on the hydrazine nitrogen atoms. Hydrazino-crown compounds with benzyl substituents have also been prepared and other synthetic pathways for the formation of these crowns are being investigated.

A study of the complexation of these hydrazino-crowns has been started. Although the complexation work is not complete, it has been found that crown 3 forms a complex with alkylammonium salts. The log K and ΔH values in methanol-water (9/1) solvent mixture for the interaction of 3 with methylammonium chloride are 1.52 ± 0.04 and -23.7 ± 3.5, respectively, as

Scheme 1. Preparation of Compounds 1-3.



Scheme 2. Preparation of Compounds 4-6



determined by a calorimetric technique.[22] The comparable log K and ΔH values for triaza-18-crown-6 (compound 3 with an N-benzyl-substituted nitrogen atom replacing the hydrazine moiety) are 4.15 ± 0.01 and -33.3 ± 0.3, respectively. It is evident from these data that compound 3 forms a weaker complex with alkylammonium salts than does the comparable triaza-18-crown-6. Triaza-18-crown-6 has the three nitrogen atoms evenly spaced around the macroring for an optimum fit for the three hydrogens of the ammonium cation.[23] The hydrazine moiety interferes with this optimum hydrogen bonding arrangement. One ammonium hydrogen would bond well to one hydrazine nitrogen atom and the amino nitrogen atom on the same side but the other amino nitrogen would not be in a symmetrical position to receive the third hydrogen bond. This would reduce the interaction of 3 with an alkylammonium cation. It is also possible that the two neighboring ethyl substituents on the hydrazine nitrogen atoms hinder the approach of the ammonium hydrogen, thereby reducing the ability of either hydrazine nitrogen to accept a hydrogen bond. More complete results of this study on the complexation of these compounds with both alkylammonium and metal cations will be reported when the study is finished.

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18. Reduction was by lithium aluminum hydride in THF at 0-5°C using one equivalent of the hydride per amide group. After the amide was added, the mixture was refluxed for 24 h, cooled and water, 10% aqueous sodium hydroxide and water were added. The resulting mixture was filtered, the residue was washed with THF and the combined THF mixtures were evaporated.
19. Equimolar amounts of each reactant was used.
20. Chromatography was on neutral alumina using toluene/ethanol:100/1 as eluant.
21. Satisfactory elemental analyses, molecular weights by MS, and IR spectra were obtained.
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