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SYNTHESIS OF NOVEL MACROCYCLIC ETHER-ESTER COMPOUNDS VIA THE INTRAMOLECULAR CYCLIZATION OF OLIGOETHYLENE GLYCOL MONOCARBOXYMETHYL ETHERS.

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Summary: By treating of the oligoethylene glycol monocarboxymethyl ethers with p-toluenesulfonyl chloride in the presence of alkali metal carbonates, novel macrocyclic polyether-monoester compounds were obtained in moderate yield.

Macrocyclic compounds such as crown ethers or cryptands, which possess complexing ability with various cations, have attracted special interest recently[1,2].

Indicative of the current interest in the synthesis of macrocyclic ether-ester compounds[3], a wide variety of polyether-diester compounds including ether-esters[4-10,12], thioether-esters[6,8,10,11] and ether-thiolesters[6,10] was prepared by Bradshaw, Izatt and Christensen by coupling of either dibasic acid salts and α,ω-dihalo compounds or dibasic acid chlorides and α,ω-dihydroxy compounds.

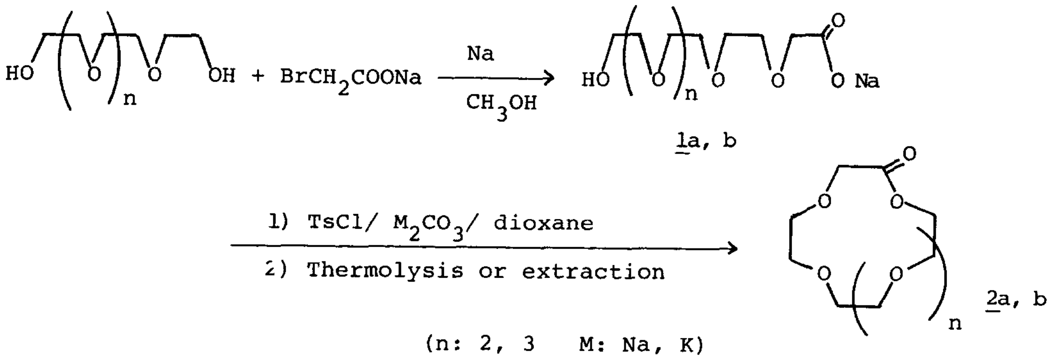
These new macrocyclic compounds with ester and oxyethylene units were found to have unique cation complexing properties which were opposite to those of typical crown ethers but comparable with those of some naturally occurring macrocyclic antibiotics[4].

Although the methods adopted by the above mentioned investigators[4-12] are very useful for the synthesis of macrocyclic polyether-di- and tetraester ligands, they cannot be applied to the preparation of macrocycles having one ester moiety in the molecule.

On the other hand, esters were prepared in high yield by the reaction of carboxylic acids and alcohols in the presence of aromatic sulfonyl chlorides[13]. The reaction was explained as proceeding *via* a mixed anhydride ($RCOOSO_2R'$) to the symmetrical anhydride (RCOOCOR), and by successive alcoholysis to the corresponding ester.

Recently, we have reported a new simple method for the preparation of various crown ethers[14] and N-substituted azacrown ethers[15] from α,ω-dihydroxy compounds such as oligoethylene glycols or polyoxyethylated amines *via* the *in situ* formation of their monotosylates.

In view of the analogy with the reaction of α,ω-dihydroxy compounds, intramolecular cyclization of oligoethylene glycol monocarboxymethyl ethers was attempted to obtain novel macrocyclic polyether-monoester compounds.



Thus, oligoethylene glycol monocarboxymethyl ethers (1a, b), which were prepared by the reaction of sodium bromoacetate with monosodium oligoethylene glycolates, were treated with equimolar amounts of p-toluenesulfonyl chloride in the presence of alkali metal carbonates whose metals are capable of acting as the template atom.

To a methanol solution containing 0.3 mol sodium methoxide, tetraethylene glycol (194g, 1 mol) was added. The solution was stirred for 15 min. at 40°C, and methanol was, then, evaporated *in vacuo*. The residue was diluted with three volumes of dioxane, and stirred with powdered sodium bromoacetate (48.3g, 0.3 mol) for 24 hr. at reflux temperature. From the viscous solution resulted, dioxane was distilled off, and the residue was submitted to extraction with toluene and/or vacuum distillation to remove excess tetraethylene glycol. The distillation residue was dissolved in isopropyl alcohol and sodium bromide was separated by filtration. After removal of solvent, crude sodium salt of carbomethoxy tetraethylene glycol (1a, 65.1g, 79.7%) was obtained from the filtrate as a viscous liquid. P-toluenesulfonyl chloride (8.4g, 44 mmol) was dissolved in dioxane and added to a suspension of 1a (10.1g, 37 mmol) in dioxane with stirring at room temperature. During the addition, powdered sodium carbonate was added in small portions to maintain the reaction mixture neutral, and totally 4.6g (43 mmol) of the carbonate was required. The reaction mixture was stirred further for 1 hr at 50°C, and then, insoluble solid was separated by filtration. Solvent was distilled off from the solution, and the macrocyclic polyether-monoester compound, 2-oxo-15-crown-5 (2a) was obtained, as a viscous liquid in the state of complex with Na^+. Similarly, starting from pentaethylene glycol, the complex of 2-oxo-18-crown-6 (2b) with Na^+ was also prepared in the same procedure.

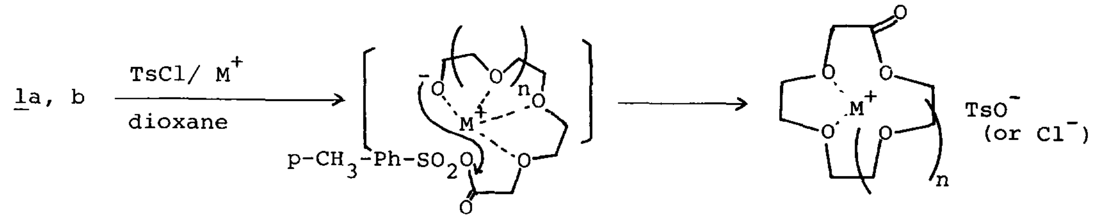
Both of these crude complexes showed one main peak in their GLC (10% Silicone SE-30 on Diasolid L, 2m, 210°C). The pure compounds were isolated from these complexes as slightly yellowish liquids by thermolysis using a Kugel-rohr apparatus under reduced pressure or extraction with n-hexane-benzene, followed by a column chromatography (alumina/benzene:MEK=4:1).

They were confirmed as the expected 2-oxo-1,4,7,10,13-pentaoxacyclopentadecane (2a) and 2-oxo-1,4,7,10,13,16-hexaoxacyclooctadecane (2b), respectively, based on their spectra and elementary analyses.

2a: Yield, 38%. Bp, 99-102°C/0.04 mmHg (Kugel-rohr). n_D^{20}, 1.4762. IR (neat, cm^{-1}); 2900s, 1765-1750s, 1460m, 1360m, 1290m, 1255m, 1200w, 1140s, 1045w, 1005w, 945m and 855w. Mass spectra, m/e (%); 234 (M^+, amplified), 103 (50), 102 (28), 87 (22), 86 (32), 73 (21), 58 (22), 45 (100), 44 (32), 43 (47) and 42 (32). NMR (CCl_4, δ); 3.50-3.80 (m, 14H), 4.12-4.28 (s+dd, 4H). Analysis for $C_{10}H_{18}O_6$; C%, 51.44 (51.27), H%, 7.90 (7.75). Saponification value; 240.4 (239.5).

2b: Yield, 42% (GLC 60%). Bp, 116-118°C/0.04 mmHg (Kugel- rohr). n_D^{20}, 1.4746. IR is almost the same as 2a. Mass spectra, m/e (%); 278 (M^+, amplified), 103 (54), 102 (27), 89 (30), 86 (30), 73 (24), 58 (27), 45 (100), 44 (28), 43 (50) and 42 (29). NMR (CCl_4, δ); 3.50- 3.70(m, 18H), 4.12-4.28 (s+m, 4H). Analysis for $C_{12}H_{22}O_7$; C%, 51.51 (51.79), H%, 8.10 (7.97). Saponification value; 208.0 (201.6).

The cyclization of oligoethylene glycol monocarboxymethyl ethers may proceed through the formation of their mixed anhydrides (3a, b).



3a, b

This new cyclization reaction not only offers a convenient route to macrocyclic polyether-monoester compounds, but also promises to afford the analogous macrocyclic polyether-polyesters, polyether-thiolesters, or polythioether-esters from the precursors with a hydroxy and a carboxy group at both ends of the molecule. Further work in this direction is under progress.

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