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A series of crown ethers with single benzene, naphthalene, biphenyl and binaphthyl units are prepared by the intramolecular Okahara cyclization of appropriate symmetrical diols. The method is used to synthesize new crown ether compounds and to prepare previously-reported crown ethers in improved yields.

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Formation of crown ethers by a diol cyclization which involves an *in situ* monotosylation followed by intramolecular ring closure in the presence of a solid alkali hydroxide "template" was first reported by Okahara [1]. This method has proven to be a most efficient method for the preparation of unsubstituted and certain substituted crown ethers [2-7]. However, the synthesis of crown ethers which possess aromatic units by the Okahara method has not been reported.

A variety of crown ethers with aromatic units were first described in the pioneering publications of Pedersen [8,9]. Interest in these compounds continues because of their accessibility and the possibility for structural modification *via* substitution reactions on the aromatic rings. The published syntheses of these crown ethers consist of the reactions of dihydroxyaromatic compounds with appropriate glycol dichlorides or ditosylates in the presence of base.

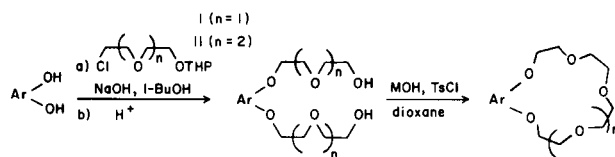
In this paper, we describe a valuable extension of the Okahara cyclization method to the preparation of several crown compounds which have single aromatic group units.









Results and Discussion.

Reactions of dihydroxyaromatic compounds such as catechol, 2,3-dihydroxynaphthalene, *o,o'*-biphenol and 1,1'-bi-2-naphthol with tetrahydropyranyl protected 2-(2'-chloroethoxy)ethanol (I) or 2-[2'-(2''-chloroethoxy)ethoxy]ethanol (II) in the presence of sodium hydroxide in 1-butanol produced the bis-tetrahydropyranyl ethers of diols III-X in good yields (65-90%). Acid-catalyzed deprotection gave the symmetrical diols III-X with two or three ethylenoxy units in each arm in overall yields of 55-79% (Table I).

Diols III-X were treated with *p*-toluenesulfonyl chloride and cesium, potassium or sodium hydroxide in dioxane to provide crown ethers XI-XVIII (Table II). The metal ion of the alkali hydroxide was varied to take advantage of the template effect in the cyclization [1]. For formation of the larger ring crown ethers XII, XIV, XVI and XVIII, cesium hydroxide was utilized. However, it was also demonstrated that the much less expensive potassium hydroxide could be employed for the synthesis of XII and XVIII without a

significant decrease in yield (Table II). Crown ethers with 15-crown-5 (XI, XIII) and 17-crown-5 (XV, XVII) rings were formed using sodium hydroxide.



Ar	n	Compound No.	m	Compound No.
	1	III	1	XI
	2	IV	3	XII
	1	V	1	XIII
	2	VI	3	XIV
	1	VII	1	XV
	2	VIII	3	XVI
	1	IX	1	XVII
	2	X	3	XVIII

Crown ethers XI-XIII, XVII and XVIII are known compounds which have been prepared by alternative procedures [9-11]. In all cases, the yields which we have obtained from the Okahara cyclization method surpass the best yields which have appeared in the literature. In the case of 2,3-naphtho-15-crown-5 (XIII) the yield enhancement from a reported 20% to the current 90% is particularly striking.

The aromatic unit influence upon cyclization yield is dependant upon the size of ring which is produced. Thus, for the formation of the smaller ring crown ethers, XI, XIII, XV and XVII, the cyclization yields of benzo-15-crown-5 (XI) and 2,3-naphtho-15-crown-5 (XIII) are very high (90-92%), whereas those for the 17-crown-5 compounds XV and XVII are much lower. Presumably this results from the non-planarity of the biphenyl and binaphthyl units

Table I
Analytical Data and Properties of Diols IV-VIII, X

Compound Number	Yield (%) [a]	Mp (°C)	Formula	IR, cm ⁻¹ (neat)	NMR, δ (deuteriochloroform)	Analyses		
						Calcd.	Found	
IV	79	oil	C ₁₈ H ₃₀ O ₈	3360 (OH) 1126 (C-O)	3.10-4.33 (m, 26H), 6.90 (s, 4H)	C H	57.74 8.07	57.49 8.24
V	57	55-56	C ₁₈ H ₂₄ O ₆	3380 (OH) 1120 (C-O)	3.30-4.40 (m, 18H), 6.98-7.75 (m, 6H)	C H	64.27 7.19	64.04 7.25
VI	61	oil	C ₂₂ H ₃₂ O ₈	3390 (OH) 1116 (C-O)	2.85-3.25 (m, 2H), 3.40-4.43 (m, 24H), 7.00-7.85 (m, 6H)	C H	62.25 7.60	61.98 7.47
VII	62	oil	C ₂₀ H ₂₆ O ₆	3420 (OH) 1128 (C-O)	3.00 (br s, 2H), 3.25-4.25 (m, 16H), 6.75-7.50 (m, 8H)	C H	66.28 7.23	66.10 7.18
VIII	55	oil	C ₂₄ H ₃₄ O ₈	3430 (OH) 1124 (C-O)	2.80 (br s, 2H) 3.35-3.90 (m, 20H), 4.00-4.35 (m, 2H), 6.83-7.50 (m, 8H)	C H	63.98 7.61	63.88 7.63
X	55	oil	C ₃₂ H ₃₈ O ₈	3430 (OH) 1122 (C-O)	2.65-4.30 (m, 26H), 7.00-8.10 (m, 12H)	C H	69.80 6.95	69.84 6.99

[a] Overall yield from reaction of the dihydroxyaromatic compound with the tetrahydropyranyl-protected chloroalcohol followed by acid-catalyzed removal of the tetrahydropyranyl group.

Table II
Analytical Data and Properties of Synthesized Crown Ethers IX-XVI

Compound Number	M of MOH	Yield (%)	Mp (°C)	Formula	IR, cm ⁻¹ (neat)	NMR, δ (deuteriochloroform)	Analyses		
							Calcd.	Found	
XI	sodium	92	77-78						
XII	cesium potassium	62 [a]	79-79.5	[a]	1128, 1097 (C-O) [c]	22.7 (s, 3H) [c], 3.35-4.30 (m, 24H), 6.87 (s, 4H), 7.42 (q, 4H)	C H	45.46 [c] 5.34	45.41 5.50
		70	oil	C ₂₅ H ₃₅ O ₁₀ CsS [c]					
		62 65 [b]							
XIII	sodium	90	114-116						
XIV	cesium	20 [a]	117-119	[a]	1118 (C-O)	3.50-4.55 (m, 24H), 7.10-7.85 (m, 6H)	C H	65.01 7.44	65.10 7.41
		75	63-64	C ₂₂ H ₃₀ O ₇					
XV	sodium	32	105-107		1134 (C-O)	3.35-4.60 (m, 16H), 6.80-7.65 (m, 8H)	C H	69.75 7.02	69.50 7.23
XVI	cesium	68	oil	C ₂₄ H ₃₂ O ₇	1126, 1113 (C-O)	3.35-4.20 (m, 24H), 6.80-7.50 (m, 8H)	C H	66.65 7.46	66.35 7.48
XVII	sodium	54	114-115						
		45 [d]	107-108.5	[c]					
			oil						
XVIII	cesium potassium	59	oil						
		48 [d]							

[a] Reference 9. [b] Reference 10. [c] For a 1:1 complex of XII with cesium tosylate, mp 159-160°. [d] Reference 11.

which interferes with the operation of the template effect. The similarity in yields for forming the larger ring crown ethers XII, XIV, XVI and XVIII suggests that the additional ethylenoxy units allow the template effect to operate even with non-planar aromatic units.

An obvious limitation of the synthetic method described

herein is for the formation of crown ethers with an aromatic unit and an even number of polyether oxygen atoms. This would require the use of unsymmetrical diols with a different number of ethylenoxy units in each arm. Preparation of such diols would be laborious and would markedly diminish the practicality of this approach.

EXPERIMENTAL

Melting points were taken with a Fisher-Johns melting point apparatus and are uncorrected. The ir and pmr spectra were obtained with a Nicolet MX-S spectrophotometer and a Varian EM 360A spectrometer, respectively. Elemental analysis was performed by Galbraith Laboratories, Inc. (Knoxville, Tennessee). A Sage Instruments model 314A syringe pump was used for slow additions of reagents.

The 2,3-dihydroxynaphthalene, *o,o'*-biphenol, 1,1'-bi-2-naphthol, 2-(2'-chloroethoxy)ethanol, 2-[2'-(2''-chloroethoxy)ethoxy]ethanol, dihydropyran, *p*-toluenesulfonyl chloride and cesium hydroxide were obtained from Aldrich Chemical Company and were used directly. Catechol was obtained from Crown Zellerbach Corporation and was recrystallized from ethyl ether before use. Reagent grade solvents were used as received. The tetrahydropyranyl ethers of 2-(2'-chloroethoxy)ethanol (I) [12], 1,2-bis(5-hydroxy-3-oxa-1-pentanoxy)benzene (III) [13], and 2,2'-bis(5-hydroxy-3-oxa-1-pentanoxy)-1,1'-binaphthalene (IX) [11] were prepared by literature procedures.

Tetrahydropyranyl Ether of 2-[2'-(2''-Chloroethoxy)ethoxy]ethanol (II).

Using the procedure which was reported for the preparation of I [12], except for the substitution of 2-[2'-(2''-chloroethoxy)ethoxy]ethanol for 2-(2'-chloroethoxy)ethanol, the title compound was obtained in 90% yield. The colorless liquid had bp 97-99° (0.35 torr); ir (neat): 1124 cm⁻¹ (C-O); nmr (deuteriochloroform): 1.40-1.90 (m, 6H), 3.40-4.10 (m, 14H), 4.58 (m, 1H).

Anal. Calcd. for C₁₁H₂₁ClO₄: C, 52.27; H, 8.37. Found: C, 52.24; H, 8.27.

Preparation of Diols.

The intermediate diols IV-VIII and X were obtained by modification of a literature method [12] to give the following general procedure. Nitrogen gas was bubbled through a solution of the dihydroxyaromatic compound (0.025 mole) in 1-butanol (75 ml) for 0.5 hour and sodium hydroxide (0.050 mole) was added in one portion. The mixture was brought to reflux under nitrogen and a solution of I or II (0.080 mole) in 1-butanol (38 ml) was added dropwise. Following completion of the addition, the reaction mixture was refluxed for 15 hours after which an additional amount of sodium hydroxide (0.018 mole) was added and refluxing was continued for an additional 15 hours. The solvent was evaporated *in vacuo* and dichloromethane was added to the residue. The insoluble salt was removed by filtration and the filtrate and washings were combined and evaporated *in vacuo* to give a crude product. Column chromatography (silica gel, ethyl acetate-petroleum ether, bp 30-60°) gave the pure bis-tetrahydropyranyl ether. The protected diol (0.020 mole) was dissol-

ved in 100 ml of dichloromethane-methanol (1:1, v/v) and 1 ml of concentrated hydrochloric acid was added. After the solution had been stirred for 1 hour at room temperature, 5 g of sodium bicarbonate was added. The mixture was filtered and the filtrate was evaporated *in vacuo* to produce the crude diol. The purified diol was obtained using a short chromatography column (alumina, ethyl acetate-methanol, 10:1).

Preparation of Crown Ethers.

The intramolecular cyclizations were conducted using the procedure reported by Okahara [3] for the synthesis of crown ethers without aromatic units. In the case of crown ether XII, a 1:1 complex of XII and cesium tosylate with mp 159-160° was isolated instead of the free ligand. The crown ether was separated by column chromatography on alumina with dichloromethane-ethyl acetate (1:1 v/v).

Acknowledgement.

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