

Caesium Salts in Crown Ether Synthesis. Preparation of Crown Ethers from Catechol, Resorcinol, Salicylic Acid, and 2,3-Dihydroxypyridine

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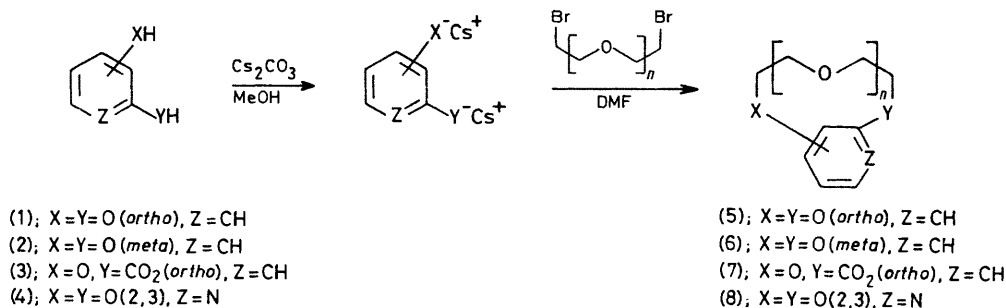
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Summary On treatment with caesium carbonate various dihydric phenols as well as salicylic acid are transformed into their dicaesium salts, which on reaction with dibromopolyethylene glycols afford crown ethers.

AROMATIC dicarboxylic acids as their caesium salts¹ react exceptionally cleanly with activated polyethylene glycols to form crown ethers.^{2,3} We have now found that the caesium salts of various phenolic compounds also are readily obtained and can be applied in crown ether synthesis following the general procedure exemplified in Scheme 1. Compounds of the types (5)–(8) have been

The yields compare well with those reported and no obvious advantage is offered by the caesium salt method in this case.

Similarly, the dicaesium salts of resorcinol (2) and salicylic acid (3) undergo this reaction to give the previously unreported crown ethers (6a–c) and (7a–c), respectively.† In these reactions, the yields of the products increase with the increase in the ring size, although this has not been established as a general rule. When the dipotassium salts of (3) were used instead of the dicaesium salts, the yields of (7a–c) were found to be 36, 12, and 54% respectively, as determined by ¹H n.m.r. spectroscopy.



SCHEME 1. $n = 3-5$.

prepared (Table) using, in these exploratory experiments, polyethylene glycol segments of tetra-, penta-, and hexaethylene glycols.

The dicaesium salt of catechol (1), when treated with the dibromides of the respective polyethylene glycols, gave compounds (5a–c) (Table), the first two of which were prepared by Pedersen, who used the disodium salt of (1).⁴

The products of these reactions were difficult to isolate and much material was lost; we have observed that reactions using caesium salts usually proceed more cleanly than those using other alkali metal salts.

The most sensitive compound examined so far is 2,3-dihydroxypyridine (4). The dicaesium salt of (4) is readily obtained but some decomposition occurs even

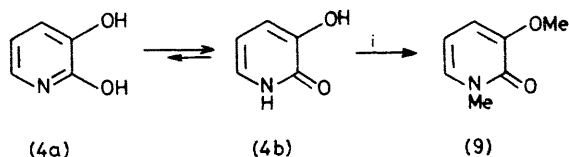
TABLE. Yields and properties of crown ethers.

Starting material	Product	Yield/% ^a	M.p./°C	Mol. weight		
				Theor.	Mass spectral	Osmometric
(1)	(5a; $n = 3$)	50 (62)	75.5–76.5	268·131	268·132	276
"	(5b; $n = 4$)	74 (60)	43–43·5	312·157	312·156	313
"	(5c; $n = 5$)	78	Oil	356·183	356·183	349
(2)	(6a; $n = 3$)	20	"	268·131	268·131	278
"	(6b; $n = 4$)	69	"	312·157	312·156	386 ^c
"	(6c; $n = 5$)	70	"	356·183	356·183	386
(3)	(7a; $n = 3$)	36	"	296·126	269·125	313
"	(7b; $n = 4$)	54	"	340·152	340·152	392 ^c
"	(7c; $n = 5$)	68	"	384 ^b	384 ^b	389
(4)	(8a; $n = 3$)	14	64·5–65·5	269·126	269·127	274
"	(8b; $n = 4$)	23	77–78·5	313·151	313·151	320
"	(8c; $n = 5$)	31	Oil	357·178	357·175	356

^a Isolated yields of pure product. Yields in parentheses are those reported in ref. 4. Spectral data are in agreement with the assigned structures. Osmometric mol. wts. indicate little contamination with oligomers. ^b Parent peak too weak for exact mass determination. ^c May contain small amounts of polyethylene glycols.

† Thus far we have not been able to obtain 1,4-bridged systems using hydroquinone as its dicaesium salt.

with rigid exclusion of oxygen. Reactions using this salt give the crown ethers (**8a—c**) in somewhat lower yields probably owing to the instability of the salt.† The assigned 2,3-disubstituted structures are not in accord with precedent derived from model reactions. The pyridone form (**4b**) is by far the most important tautomer of (**4**)⁵ and dialkylation would be expected to provide *N*,3-*O*-disubstituted structures. Indeed methylation of the dicaesium salt of (**4**) produces the known compound (**9**)⁶ (Scheme 2). The u.v. spectrum of (**4**) in EtOH shows



SCHEME 2. i, (1) Cs_2CO_3 —MeOH (2) MeI—DMF.

λ_{max} 241 (log ϵ 3.6) and 296 nm (log ϵ 3.9) and that of (**9**) shows λ_{max} 243 (log ϵ 3.7) and 296 nm (log ϵ 3.8) whereas, for example, (**8b**) [the u.v. spectra of (**8a**) and (**8c**) resemble closely that of (**8b**)] has λ_{max} 220 (log ϵ 3.9) and 275 nm (log ϵ 3.9), in close agreement with the values found for 2,6-dimethoxypyridine⁷ [λ_{max} (pH 8.6 buffer) 218 (log ϵ 3.8) and 279 nm (log ϵ 3.9)] and for a 2,6-dialkoxy-pyridine crown ether⁸ [λ_{max} (EtOH) 225 (log ϵ 4.4) and 277.5 nm (log ϵ 4.2)]. Moreover, the ¹H n.m.r. spectrum (CDCl_3)

of (**9**) [identical with that of (**4**)] shows 6-H at δ 6.90 ($J_{5,6}$ ca. 8, $J_{4,6}$ < 0.5 Hz) whereas that of (**8b**) [and of (**8a**) and (**8c**)] has the 6-H absorption at δ 7.72 ($J_{5,6}$ 5, $J_{4,6}$ 2 Hz). These data indicate 2,3-bridged pyridine structures for (**8a—c**).

All experiments were carried out under nitrogen. The dicaesium salts are prepared by adding 1 mmol of solid Cs_2CO_3 to 50 ml of a nitrogen-flushed methanolic solution of the phenol (1 mmol). Gas evolution occurs immediately.‡ Once the Cs_2CO_3 has dissolved, the methanol is removed under reduced pressure and 50 ml of dry dimethylformamide (DMF) is added; this is then removed under high vacuum along with the traces of remaining water and methanol. The dry precipitate is suspended in 50 ml of DMF and the dibromide of the appropriate polyethylene glycol (1 mmol) is added. The reaction mixture is kept at 65 °C for 4 days (most of the reactions are complete before the end of this period). The DMF is removed under high vacuum, the residue is dissolved in CH_2Cl_2 , and the organic layer is washed with NaCl solution followed by a 1% aqueous KOH solution. After drying over Na_2SO_4 and removal of the solvents, the crude product is purified either by chromatography over D.E.A.E. cellulose (cyclohexane) or by boiling with n-hexane followed by removal of insoluble material. The latter procedure is preferred. The compounds (**5a, b**) and (**8a, b**) could be recrystallized from n-hexane at -20 °C.§

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† The literature on heterocycle-containing crown ethers has recently been reviewed (G. R. Newkome, J. D. Sauer, J. M. Roper, and D. C. Hager, *Chem. Rev.*, 1977, **77**, 513). Examples of 2,6-dialkoxy-pyridine crown ethers have now been reported (G. R. Newkome, G. L. McClure, J. Broussard-Simpson, and F. Danesh-Koshboo, *J. Amer. Chem. Soc.*, 1975, **97**, 3232; ref. 8).

‡ Cs_2CO_3 is a remarkably strong base that deprotonates a wide variety of acidic organic compounds.

§ Professor D. N. Reinhoudt has kindly informed us of related experiments carried out at Shell Laboratories, Amsterdam.

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