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NUCLEOPHILIC RING CLEAVAGE OF CROWN ETHERS, NOVEL METHOD FOR BUILDING UP CROWN ETHER RINGS

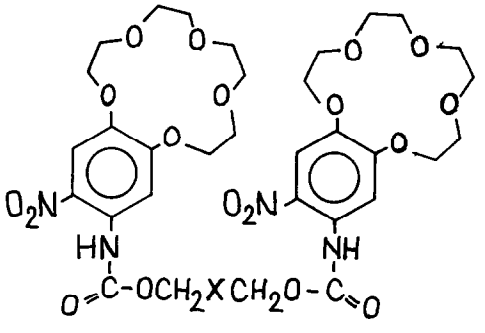
Béla Ágai[a], István Bitter[a], Zoltán Hell[a], Áron Szöllősy[b]
László Tőke[a*]

a: Technical University, Department of Organic Chemistry and Technology, Budapest, H-1111. Hungary

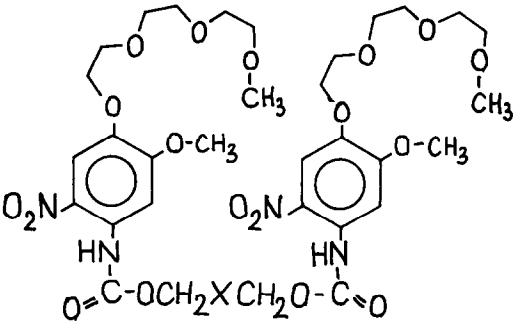
b: NMR Laboratory of the Institute of General and Analytical Chemistry, Budapest, H-1111.Hungary

Summary: The crown ether rings in 4-nitrobenzo-15-crown-5 and -18-crown-6 are cleaved by aqueous alkali affording long chain substituted pyrocatechols which proved to be good starting material for constructing crown ether rings other than the original one.

During the course of our synthetic work aiming at developing new potassium ionophores of bis-crown ether type (1)[1,2] we have investigated the role of the crown ether ring and the linkage as well in the selective complexation. Therefore we have synthesized the appropriate open chained derivatives (2) so that the effect of the linkage connecting the crown ether units could be studied separately[3].



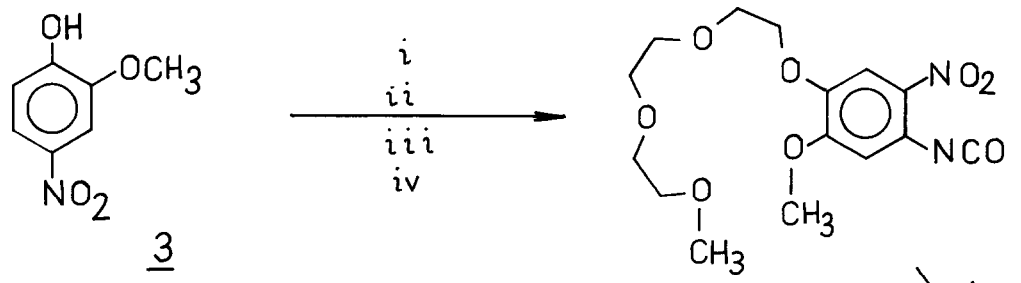
1



2

The easiest way of approaching compounds 2 was to start from 4-nitroguajacole(3, eq. 1).

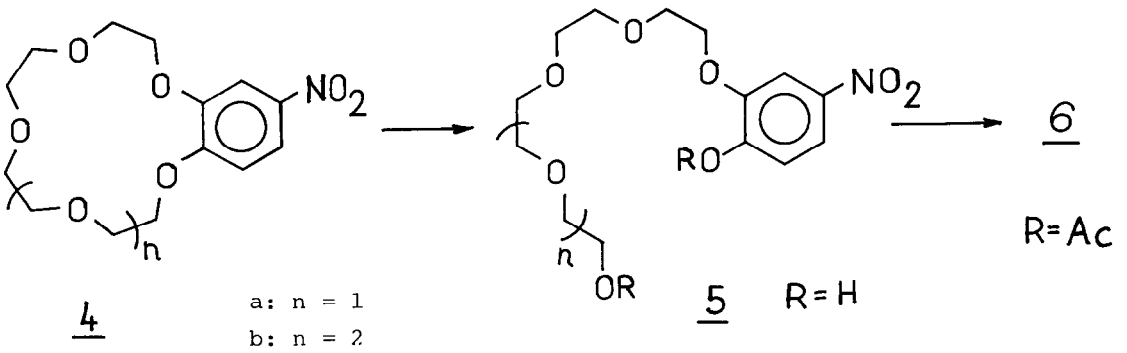
(1)



i: KOH, DMF, $Cl/CH_2CH_2O/_2CH_2CH_2OMe$
ii: H_2/Ra-Ni, Ac_2O
iii: HNO_3, KOH/EtOH
iv: $COCl_2$ in xylene
iz: $X/CH_2OH/_2$, Et_3N catalyst

The 4-nitro-quajacole is available by selective hydrolysis of 4-nitroveratrole[4]. The relatively easy nucleophilic replacement of the 1-MeO group in 4-nitroveratrole is due to the strong activation of the NO_2 group in position 4. This reaction gave us the idea to bring about similar hydrolytic C-O bond fission in the crown ether rings activated by NO_2 group, too[5] (eq.2).

(2)



We have observed much faster reaction with compounds 4a,b than that of 4-nitroveratrole (6 mmol substrate, 12 mmol KOH in 10 cm^3 water, 100°C). The enhanced rate of hydrolysis of crown ethers can be understood by assuming the increased electrophilic character of the aromatic C-1 carbon atom in the K^+ complex formed in the reaction.

t / h	Conversion[10]	
	4-nitroveratrole	4a
3	10%	38%
6	20%	50%

Although the site of the ring opening was anticipated the ^{1}H and ^{13}C nmr spectra of compounds 5a,b did not give enough evidence for the exact structure determination. The appearence of the acylation shifts of the H-6 and C-6 signals in the spectra of 6a,b diacetyl derivatives, however, unambigously proved that our expectation concerning the place of the nucleophilic attack was correct.

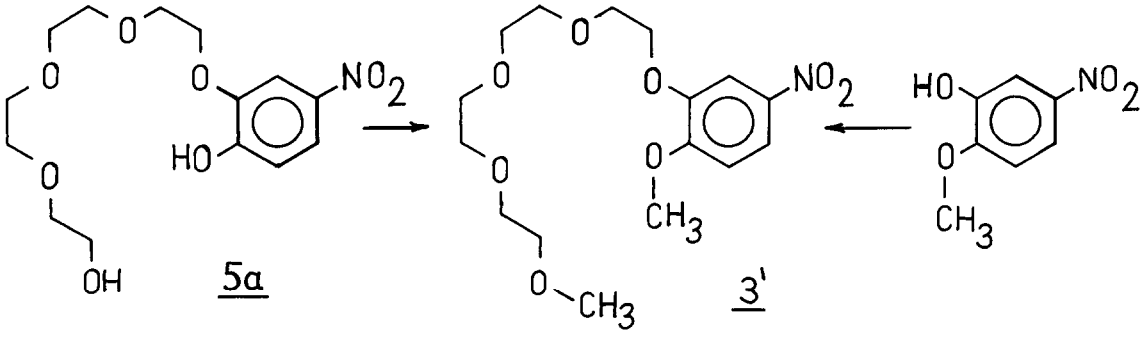
Solvent = $CDCL_3$ TMS = 0 ppm

Comp.	^{1}H nmr			^{13}C nmr						Δ ppm	
	H-3 *	H-5 *	H-6 *	C-1	C-2	C-3	C-4	C-5	C-6	H-6	C-6
4a	7.63d	7.81dd	6.84d	154.2	148.1	107.7	140.7	117.5	110.8	-	-
5a	7.67d	7.78dd	6.85d	153.7	145.4	118.1	139.5	114.4	107.4	0.29	15.4
6a	7.85d	7.80dd	7.14d	145.0	150.5	108.7	145.7	116.3	122.8		
5b	7.66d	7.78dd	6.84d	153.7	145.4	118.0	139.4	114.4	107.2	0.31	15.5
6b	7.83d	7.80dd	7.15d	144.9	150.4	108.6	145.6	116.1	122.7		

*Coupling constants of H-3 J_m = 2.5 Hz, H-6 J_o = 10 Hz

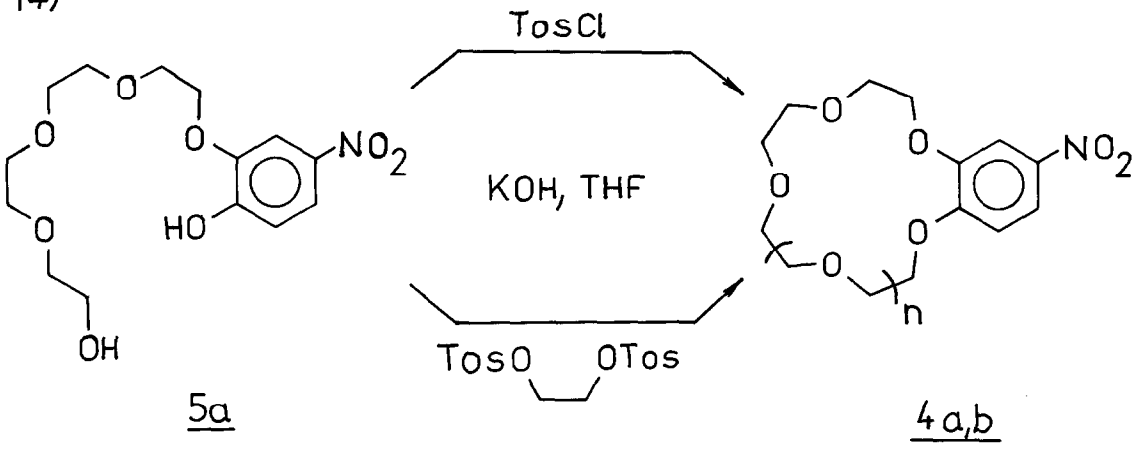
The structural assignement was supported by synthetic studies,too. Alkylating the di-potassium salt of 5a with MeI in DMF resulted in 3' (the regioisomer of 3) which was independently synthesized by the alkylation of 5-nitro-guajacole[7] with 1-chloro-3,6,9-trioxadecane according to equation 3 .

(3)



The ring opening of the 15-and 18-membered crown ethers may provide a novel important synthetic tool for the transformation of crowns of different size. Our preliminary results are promising because we succeeded in reclosing 5a to 4a and to 4b,respectively, using known methods (eg.4).

(4)



5a 4a,b

This method may have synthetic potential in the preparation of benzo-crown -crown ether not available by other routes owing to the very poor yields or expensive starting materials. Other nucleophiles (eg. amines, thio compounds, carbanions) are also expected to bring about ring cleavage(Preliminary studies with amines support this idea)resulting in precursors with hetero atom, other than oxygen, near to the aromatic ring. The auxiliary nitro group if it is necessary can be eliminated by known methods or utilized for versatile functionalizations.

References and notes

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4. D.F.Page, R.O.Clinton: J.Org.Chem. 27 218 (1962).
5. Compounds 3a,b have been prepared by nitration of benzo-15-crown-5 and benzo-18-crown-6 with 65 % HNO_3 in $CHCl_3$+AcOH mixture[6]. Compounds 4a,b and 5a,b are oils purified by preparative TLC (Kieselgel, benzol-MeOH 10:1). Yields are almost quantitative. Correct elemental analysis are available for every compounds. IR (neat): 4a: 1560, 1500 cm^{-1}, 4b:1560 1500 cm^{-1}, 5a: 1760, 1730, 1570, 1510 cm^{-1}, 5b:1760, 1730, 1580, 1520^{-1}
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10. Conversion was determined by UV spectrophotometry at 426 nm (phenolate), 328 nm (4a) in alkaline solution and at 336 nm in acidic solution (pH=1).

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