

Improved Synthesis of 3 α ,5 α -Cyclosteroids

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Derivatives of 6 β -hydroxy-3 α ,5 α -cyclocholestane (*i*-cholesterol) are formed in the solvolysis reactions of cholesteryl tosylate.¹ The mechanism of their formation was discussed by Winstein² as one of the first examples of neighboring group participation. They were used in limited cases in synthetic applications, *i.e.*, in ecdysone synthesis,³ in 19-methyl oxidation by lead tetraacetate,⁴ and in a number of cases, for the protection of 3 β -hydroxy-5-ene functionality common in many sterols.⁵

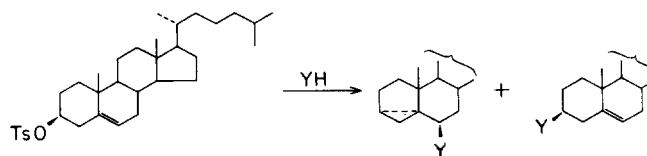
We were interested in synthesizing 3 α ,5 α -cyclosteroidal derivatives with different 6 β functionalities for possible future use in remote functionalizations closely related to the classical Breslow type reactions.⁶ We now wish to report the results of the solvolysis reactions of cholesteryl tosylate in a number of solvents.

Ethanol and 2-propanol solvolyses in the presence of solid base resulted in the formation of 3 α ,5 α -cyclo derivatives as expected. Reaction in benzyl alcohol yielded 3 β -cholesteryl benzyl ether exclusively. On the other hand, 6 β -benzyloxy-3 α ,5 α -cyclocholestane was obtained as the major product from the solvolysis in benzyl alcohol and acetone (1:2, v/v).

Simple solvolysis in ethylene glycol gave rise to some 3 β -cholesteryl hydroxyethyl ether accompanied by elimination products, but the use of ethylene glycol-acetone (1:2) resulted in the predominant formation of 6 β -hydroxyethoxy-3 α ,5 α -cyclocholestane. Solvolyses in 1,3-propanediol, diethylene glycol, and triethylene glycol with acetone also yielded corresponding 3 α ,5 α -cyclocholestan-6 β -yl ether derivatives as major products.

The use of thiol-containing solvents dramatically raised the yield of 3 α ,5 α -cyclosteroids. Thus 3 α ,5 α -cyclocholestan-6 β -yl hydroxyethyl thioether was obtained almost quantitatively when cholesteryl tosylate in mercaptoethanol was heated to reflux briefly. Solvolysis in ethanedithiol yielded the thioether exclusively in the same manner.

Further transformations of some of the above derivatives will be the subject of future communications.



Y=CH ₃ O, KOAc, reflux, 1 h	69%	12%
CH ₃ CH ₂ O, KOAc, reflux, 30 min	51%	12%
(CH ₃) ₂ CHO, KOAc, reflux, 1 h	44%	26%
PhCH ₂ O, NaHCO ₃ , 100°, 30 min	0	≈100%
PhCH ₂ O, acetone, KOAc, reflux, 8 h	≈50%	minor
HOCH ₂ CH ₂ O, KOAc, reflux, 5 min	0	≈30%
HOCH ₂ CH ₂ O, acetone, KOAc, reflux, 4 h	80%	19%
HOCH ₂ CH ₂ CH ₂ O, acetone, NaHCO ₃ , reflux, 4 h	77%	15%
HO(CH ₂ CH ₂ O) ₂ , acetone, KOAc, reflux, 7 h	57%	minor
HO(CH ₂ CH ₂ O) ₃ , acetone, KOAc, reflux, 7 h	41%	minor
HOCH ₂ CH ₂ S, NaHCO ₃ , reflux, 5 min	≈100%	0
HSC ₂ H ₄ S, NaHCO ₃ , reflux, 5 min	≈100%	0

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Ion-Binding Properties of N,N'-Disubstituted Diaza-18-crown-6

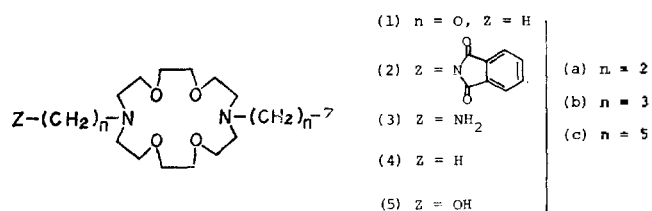
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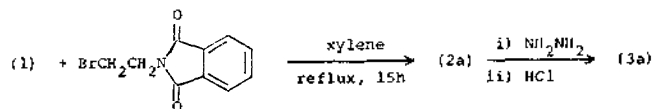
In the course of our study of macromolecular macrocyclic polyethers we have had need to synthesize a series of N,N'-

disubstituted derivatives of diaza-18-crown-6 (1) and to study their ion-binding properties. Some of those derivatives are

known.¹ However a comparison of ion-binding properties of those derivatives of (1) which have different functional substituents is interesting, and we like to report the syntheses of those previously unreported derivatives and the preliminary results of our study of their ion-binding characteristics.



N,N'-Bis-(aminoethyl)-diaz-18-crown-6 (3a) was prepared by the reactions of (1) with *N*-(2-bromoethyl)-phthalimide, followed by hydrazinolysis² (3a, oil, 52% overall yield). In the similar way, reaction of (1) with *N*-(3-bromopropyl) and with *N*-(5-bromopentyl)-phthalimide gave *N,N'*-bis-(aminopropyl)³ and *N,N'*-bis-(aminopentyl) derivatives, respectively (3b, oil, 45% yield; 3c, oil, 41% yield). Reaction of (1) with bromopropane and with bromoethanol gave (4b) (oil, 70% yield) and (5a) (oil, 52% yield). All the spectroscopic data of these compounds were in good agreement with assumed structures.



With some of those derivatives, extraction experiments⁴ were carried out to investigate their ion-binding behaviors and representative results are summarized in Table 1.

As shown in Table 1, all the *N,N'*-disubstituted derivatives of (1) exhibited enhanced extraction efficiencies compared with (1) and the well known dibenzo-18-crown-6, although the selectivities were somewhat less pronounced.⁵ The most interesting to note is the extremely high non-selective extraction efficiency of (3b). No selectivity was observed even when lower concentration of (3b) was applied. This excessive extraction behavior of (3b) is not yet understandable to us. However, a plausible explanation may be that the amino groups in the flexible side arms participate in the formation of

TABLE 1: Extraction of Cation Picrates with Various Crown Ethers^a

Cation	% Cation extracted ^b					
	(1)	DB-18-C-6 ^c	(4b)	(5a)	(2b)	(3b)
Li ⁺	~0	~1	11.2	10.1	6.5	~100
Na ⁺	1.4	2.2	47.4	50.2	29.6	~100
K ⁺	4.2	22.9	67.7	67.8	72.0	~100
NH ₄ ⁺	—	1.9	50.2	17.1	26.3	~100

^aH₂O/CH₂Cl₂ = 50/50(v/v); (picric acid) = 7×10⁻⁵ M; (hydroxide) = 0.01 M; (crown ether) = 35×10⁻⁵ M; at 25 °C. ^bBased on the total amount of cation picrate dissolved in aqueous phase. ^cDibenzo-18-crown-6.

pseudocavity with cations present in rather rigid ring moiety, thereby enhancing the capability to form complexes. With the open flexible complex-forming side arms the specificity towards metal ions of certain ionic size is least expected.

The participation of side chain amino groups in complex formation is further supported by the greatly decreased ion extraction efficiency exhibited by (2)'s, (4)'s and (5)'s. It is interesting to observe that those substituted crown ethers with poor extraction efficiency show rather improved selectivities in complexing with metal ions of different ionic sizes.

The present results are very suggestive information to us in designing the structures of macromolecular crown ethers and studying their metal complexing properties. The full accounts of our study of macromolecular crown ethers will be published elsewhere.

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