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Synthesis of Novel Crown Ethers. Part 1. Coumestan and Coumestan Analog Derivatives of Crown Ethers

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Abstract. The presented ethylenedioxy compounds **5a, 5d, 6a** and **6c** are examples of novel cyclic ethers, while macrocyclic polyethers represent new crown ether analogues. New coumestan-crowns **5a–f**, derivatives of 6,7-dihydroxy-3,4-dihydro-2H-dibenzofuran-1-one and 6,7-dihydroxy-3,3-dimethyl-3,4-dihydro-2H-dibenzofuran-1-one **6a–e** were synthesized from the corresponding *o*-dihydroxy compounds **3a–b**, **4a–b** and ditosylates or dichlorides of di- or triethylene glycol in the presence of K_2CO_3, in DMF/H_2O (15/1) solutions at 65–75 °C for 35 hours. The structure of the macrocyclic ethers obtained were confirmed by ^{1}H-NMR, ^{13}C-NMR, IR spectra and elemental analyses.

Key words: Coumestan, coumarin, crown ethers.

1. Introduction

Recently we have reported the synthesis, characterization, fluorescence spectra of salt solutions and complexing abilities with metal cations of some crown ether derivatives of *o*-dihydroxycoumarins bearing the 2H-1-benzopyran–2-one unit [2]. The dihydroxycoumarin and benzopyrane moieties as part of a crown ether may be valuable components for charge transfer complexes [3]. As part of our novel work on the search for selective and efficient metal ion complexing agents, we have now prepared a new series of crown ether derivatives of *o*-dihydroxycoumestan **3a–b** and dihydroxycoumestan like compounds **4a–b** (Figure1). One of the expected effects is a change in the selectivity of complex formation with cations, including the ionophoric properties of these compounds in ion-selective electrodes **[2e]**.

2. Experimental

All materials and solvents were of analytical reagent grade. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on Gemini Varian 200 MHz instrument in $CDCl_3$ with TMS as internal standard. IR spectra were recorded on a Nicolet 510P FTIR spectrometer.

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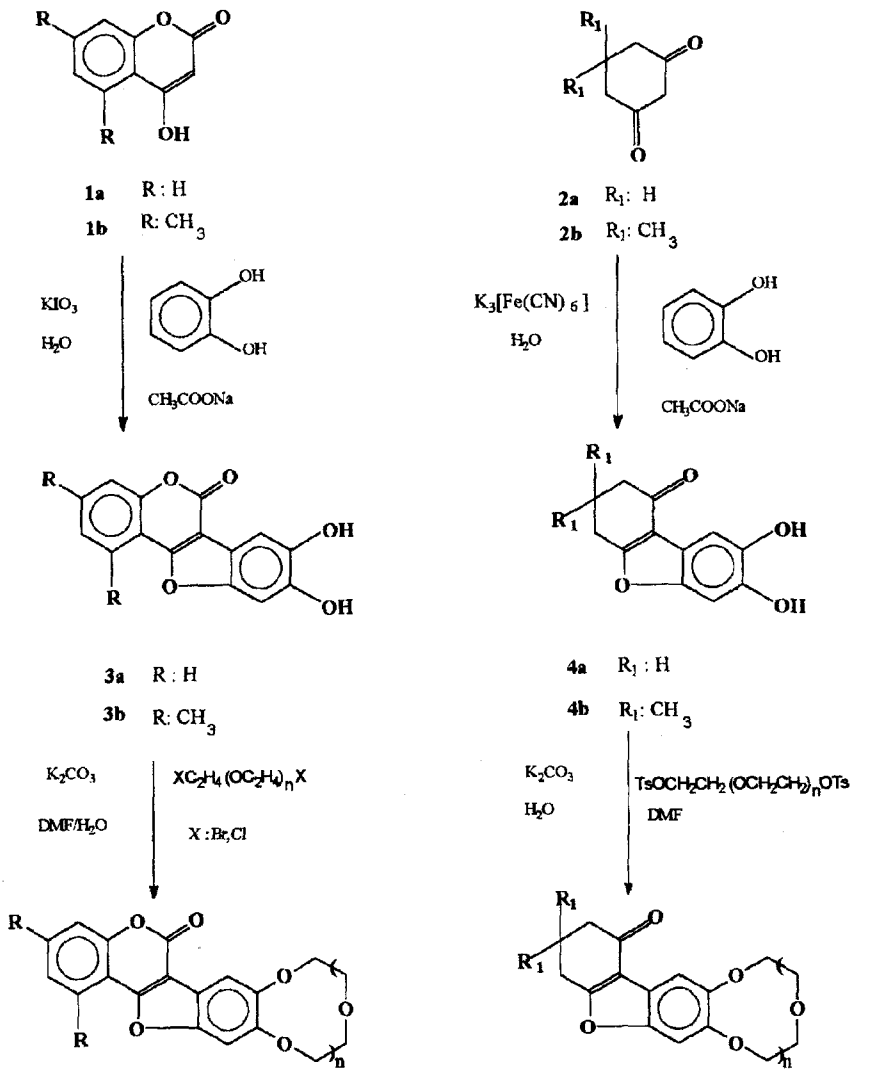

	5a	5b	5c	5d	5e	5f
R	H	H	H	CH_3	CH_3	CH_3
n	0	2	3	0	2	3

	6a	6b	6c	6d	6e
R_1	H	H	CH_3	CH_3	CH_3
n	0	2	0	2	3

Figure 1. Reaction schemes for the preparation of compounds **5** and **6**.

Elementel analyses were carried out by Tubitak laboratories at Gebze, Turkey. The purity of all products have been checked using thin layer chromatography (Kieselgel 60, MERCK, aluminum foil) in a benzene:methanol (10/1) solvent system. Iodine vapour or UV-light was used to detect the spots. Melting points were measured on a BOETIUS apparatus and are uncorrected.

2.1. SYNTHESIS OF INITIAL COMPOUNDS **3a–b** AND **4a–b**

4-Hydroxycoumarin **1a** and 3,5-dimethyl-4-hydroxycoumarin **1b** were prepared from the corresponding phenols by the reaction of malonic acid in $POCl_3$/dry $ZnCl_2$ mixture in 65 and 70% yields, respectively[4]. Treatment of **1a** and **1b** with catechol in an oxidizing mixture $KIO_3/CH_3COONa/H_2O$ gave derivatives of 11,12-dihydroxycoumestan **3a–b** in 70 % yields, respectively [5]. The compounds obtained were purified by crystallization from ethanol. 6,7-Dihydroxy-3,4-dihydro-2H-dibenzopyran-1-one **4a** and 6,7-dihydroxy-3,3-dimethyl-3,4-dihydro-2H-dibenzopyran-1-one **4b** were obtained in good yields through the reaction of cyclohexane-1,3-dione and 5,5-dimethyl-cyclohexane-1,3-dione with catechol in the presence of an equivalent amount of $K_3[Fe(CN)_6]/CH_3COONa/H_2O$, respectively [5].

2.2. SYNTHESIS OF CYCLIC ETHERS AND MACROCYCLIC ETHERS **5a–f, 6a–e**

The typical procedure for the cyclisation reaction leading to ether derivatives of **3a–b** and **4a–b** is as follows. A mixture of *o*-dihydroxy compounds **3a–b** and **4a–b** (5 mmol), 1,2-dibromoethylene or ditosylate (or dichloride) of di- or triethylene glycols (5 mmol) and 10 mmol K_2CO_3 was dissolved in 60 mL DMF/H_2O (15/1) in a 250 mL reaction flask. The mixture was heated for 35 hours at 65–75 °C. The solvent was evaporated in vacuo. Water (30 mL) was added to the residue and the mixture was extracted with $CHCl_3$ (4 × 30 mL). The combined organic extracts were washed with water, dried (over P_2O_5 in a dessicator) and evaporated in vacuo. Chromatography of the crude products (silica gel 60, FLUKA) with chloroform gave pure ethers **5a–f** and **6a–e.** Spectral data and elemental analyses agree with the proposed structures.

Yields, physical properties and spectral data for the novel macrocyclic oligoether derivatives **5a-f** and **6a–e** are given in Table I.

3. Results and Discussion

A variety of substrates possessing a cyclic–1,3-dione moiety **1a-b**, **2a–b** react efficiently with *o*-quinone, generated in situ by the oxidation of catechol with oxidizing agents, to give coupling products **3a–b**, **4a–b**. The results presented in this paper, show that naturally occurring 11,12-coumestan derivatives **3a–b** and some structurally analogous *o*-dihydroxy compounds **4a–b** are easily converted to oligomacrocyclic ethers. The reaction is a nucleophilic substitution reaction between *o*-dihydroxy compounds and ditosylates or dichlorides of ethylene, diethylene and triethylene glycol. The reaction medium of $DMF/H_2O/K_2CO_3$ is the most appropriate polar system to facilitate the reaction. The reactions proceed smoothly between 65–75 °C giving good yields of the desired products. NMR (Figure 2), IR, TLC and elemental analyses confirm the formation of the expected cyclic ethers.

Table I. Properties and spectral characteristics of **5a–f** and **6a–e**.

Comp. no.	Yield %	m.p. (°C)	^{1}H-NMR and ^{13}C-NMR (200 MHz in $CDCl_3$), ppm Elemental analyses	IR Spectra (ν, cm^{-1})
5a	65	232	4.33 (s,4H),7.38(m,2H),7.57(m,2H), 7.93 (s, 1H),7.97 (s,1H) 160.15, 153.79, 153.74, 151.02, 144.19, 142.15, 142.93, 142.89, 131.74,124.95,121.95,117.85,117.37 113.36, 109.19, 100.80, 64.98, 64.51 Calc. %C 69.38, %H 3.42 Found %C 69.57, %H 3.47	3100 (C-H, arom), 2926-2957 (C-H,alkyl), 1736 (lactone), 1630 (C=C), 1286 (C-O, aryl), 1061-1134 (O-C, alkyl)
5b	62	215	3.79 (s,4H), 3.88 (t,4H, J=2.7 Hz), 4.22 (t,4H, J=2.7 Hz),7.22(s,1H) , 7.34 (m,2H), 7.44 (m,1H),7.61(s,1H), 7.89 (d,1H, J=6.53 Hz) 163.0, 160.02, 158.74, 153.60, 151.47, 151.5, 149.88, 131.8, 125.07, 121.86, 117.832, 117.73, 113.23, 112.79, 109.77, 106.53, 101.70, 73.02, 72.51, 71.73, 70.65, 70.20 Calc. %C 65.96, %H 4.74 Found %C 66.01, %H 4.68	3100 (C-H, arom), 2850-2950 (C-H, alkyl), 1734 (lactone), 1278 (C-O, aryl), 1126 (C-H, alkyl)
5c	60	194	4.23 (m,4H), 4.18 (m,4H), 3.79 (m,8H), 7.26 (s,1H), 7.39 (m,2H), 7.50 (s,1H), 7.52 (s,1H), 7.96 (d,1H, J=6.2 Hz) 160.95, 160.37, 156,29, 154.99, 152.44, 150.04, 133,04, 126.53, 123.3, 119.33,117.78, 114.91, 108.24, 106.38, 99.35, 78.38, 73.00, 72.94, 72.80, 72.35, 71.29, 71.21 Calc. %C 64.78, %H 5.20 Found %C 64.90, %H 5.17	3080 (C-H, arom.) 2860-2940 (C-H, alkyl), 1753 (lactone), 1650 (C=C), 1293 (C-O, aryl), 1165 (C-O, alkyl)
5d	70	258	2.41 (s,3H), 2.81 (s,3H),4.32 (s,4H), 6.94 (s, 1H), 7.09 (s,1H),7.13 (s,1H), 7.55 (s, 1H) 161.6,158.8,154.6,150.7,142.8,143.7, 142.7,134.8,128.7,128.3,117.0,110.1, 108.9,105.5,78.1,77.9,77.6,22.1,21.5 Calc. %C 70.81, %H 4.38 Found %C 70.88, %H 3.36	3100 (C-H, arom.), 2959-2956 (C-H, alkyl), 1749 (lactone), 1610 (C=C), 1277(C-O,aryl),1126 (C-O, alkyl)

Table I. Continued.

Comp. no.	Yield %	m.p. (°C)	^{1}H-NMR and ^{13}C-NMR (200 MHz in $CDCl_3$), ppm Elemental analyses	IR Spectra (ν, cm^{-1})
5e	65	205	2.39 (s,3H), 2.79 (s,3H), 3.81 (s,4H), 3.90 (m,4H), 4.26 (m,4H),6.94(s,1H), 7.08 (s,1H), 7.25 (s,1H), 7.65 (s,1H) 161.53, 161.47, 158.94, 154.53, 151.19 150.78, 149.77, 142.30, 134.81, 128.39, 117.5, 115.66, 110.76, 109.53, 105.69, 101.71, 72.54, 71.69, 70.22, 70.05, 69.39 64.01, 22.10, 21.58 Calc. %C 66.07, %H 5.76 Found %C 66.26, %H 5.71	3090 (C-H, arom.), 2940-2960 (C-H, alkyl), 1749 (lactone), 1618 (C=C), 1285 (C-O, aryl), 1076-1135 (O-C, alkyl)
5f	62	248	2.4 (s, 3H), 2.8 (s, 3H), 3.79 (s,4H), 3.95 (t,2H, J=4.72 Hz), 3.97 (t,2H, J=4.3 Hz),4.49 (t,2H, J=4.72 Hz), 4.40 (t,2H, J=4.30 Hz), 6.95 (s,1H), 7.09 (s,1H), 7.15 (s,1H), 7.51 (s,1H) 160.94, 159.15, 154.41, 150.6,149.5, 148.48, 141.9, 134.6, 128.3, 116.0, 115.7, 110.2, 105.9, 104.7, 97.9, 71.6 71.5, 70.8, 69.87, 69.8, 69.7, 22.1, 21.5 Calc. %C 66.07, %H 5.76 Found %C 66.26, %H 5.72	3095 (C-H, arom), 2940-2960 (C-H, alkyl), 1750 (lactone), 1620 (C=C), 1285 (C-O, aryl), 1076-1136 (O-C, alkyl)
6a	26	132	2.24 (p,2H, J=6.5 Hz), 2.53 (t,2H, J=6.0 Hz), 2.93 (t,2H, J=6.53 Hz), 4.24 (s,4H), 6.92 (s,1H), 7.44 (s,1H) 195.03, 171.03, 149.77, 142.50, 117.58, 116.82, 109.09, 100,09, 64.52, 38.22, 24.29, 22.97 Calc. %C 66.85, %H 4.95 Found %C 68.96, %H 4.98	3080 (C-H, arom), 2850-2958 (C-H, alkyl), 1596 (C=C), 1666 (lactone), 1200-1300 (O-C, aryl)
6b	18	154	2.22 (p,2H, J=6.5 Hz), 2.53 (t,2H, J=6.0 Hz), 2.40 (t,2H, J=6.23 Hz), 3.77 (s,4H), 3.83 (m,4H, J=5.86 Hz), 4.16 (m,4H, J=5.86 Hz), 7.06 (s,1H), 7.56 (s,1H) 195.26, 170.98, 150.24, 149.59, 149.28, 118.18, 117.04, 109.94, 101.53, 72.79, 72.60, 71.65, 70.27, 38.53, 24.28, 23.00 Calc. %C 65.06, %H 6.06 Found %C 65.18, %H 5.94	3100 (C-H, arom), 2860-2990 (C-H, alkyl), 1640 (C=O), 1200-1300 (O-C,aryl)

Table I. Continued.

Comp. no.	Yield %	m.p. (°C)	^{1}H-NMR and ^{13}C-NMR (200 MHz in $CDCl_3$), ppm Elemental analyses	IR Spectra (ν, cm^{-1})
6c	48	156	1.08 (s, 6H), 2.32 (s,2H), 2.71 (s, 2H), 4.17 (s, 4H), 6.85 (s, 1H), 7.35 (s, 1H) 194.3, 170.1, 150.0, 142.3, 117.3, 115.4, 108.8,100.12,64.8,64.4,52.4,38.0,35.6,29.0 Calc. %C 69.56, %H 5.83 Found %C 69.64, %H 5.80	3090 (C-H, arom.) 2870-2880 (C-H, alkyl), 1670 (C=O), 1630 (C=C) 1165 (C-O, aryl)
6d	32	132	1.19 (s, 6H), 2.45 (s, 2H), 2.86 (s, 2H), 3.81(s,4H), 3.88 (m,4H, J=4.48 Hz), 4.20 (m,4H, J=4.48 Hz), 7.11 (s,1H), 7.59 (s,1H) 194.5, 170.0, 150.7, 149.6, 149.4, 118.2, 115.9, 109.9, 101.7, 76.6, 72.8, 70.4, 57.6, 38.3, 35.7, 29.1 Calc. %C 66.69, %H 6.67 Found %C 66.81, %H 6.66	3090 (C-H, arom.), 2850-2950 (C-H, alkyl), 1540 (C=C), 1650 (C=O), 1200-1300 (O-C, aryl)
6e	18	108	1.17 (s, 6H), 2.43 (s,2H), 2.84 (s,2H), 3.75 (s, 8H), 3.93 (m,4H, J=4.33 Hz), 4.14 (t,2H, J=4.33 Hz), 4.19 (t,2H, J=4.33 Hz), 7.00 (s,1H), 7.45 (s,1H) 196.23, 170.98, 151.59, 149.93, 149.60, 118.25, 117.53, 107.34, 99.80, 73.06, 73.00, 72.50, 71.52, 71.43, 54.2, 39.83, 37.27, 30.65 Calc. %C 65.34, %H 6.97 Found %C 64.98, %H 6.84	3100 (C-H, arom.), 2978-2876 (C-H, alkyl), 1675 (C=O), 1600 (C=C), 1200-1300 (C-O, aryl)

However, the side products were not necessarily idendified (ca. 5% yield). In general, the yields of the prepared cyclic ethers have been uniformly good and probably depend on the substitution pattern and the stability of substrates **3a–b**, **4a–b** in the reaction medium.

It has been observed that introduction of a coumarin moiety into the crown ether ring has an unpredictable influence on the selectivity of the corresponding ion selective electrodes [1–3]. Crown ethers with a coumestan moiety which contains the coumarin group itself could show selectivity towards alkali or other relevant cations. Such properties of novel crown ethers will be studied soon. To study the behaviour of ion binding with selective electrodes as a function of the structure of the respective coumestan and coumestan like crown ethers it could be assumed that all compounds possess two active sites: the first formed by the polyoxyethylene macrocycle and the second by the electron donating oxygen atoms of the lactone

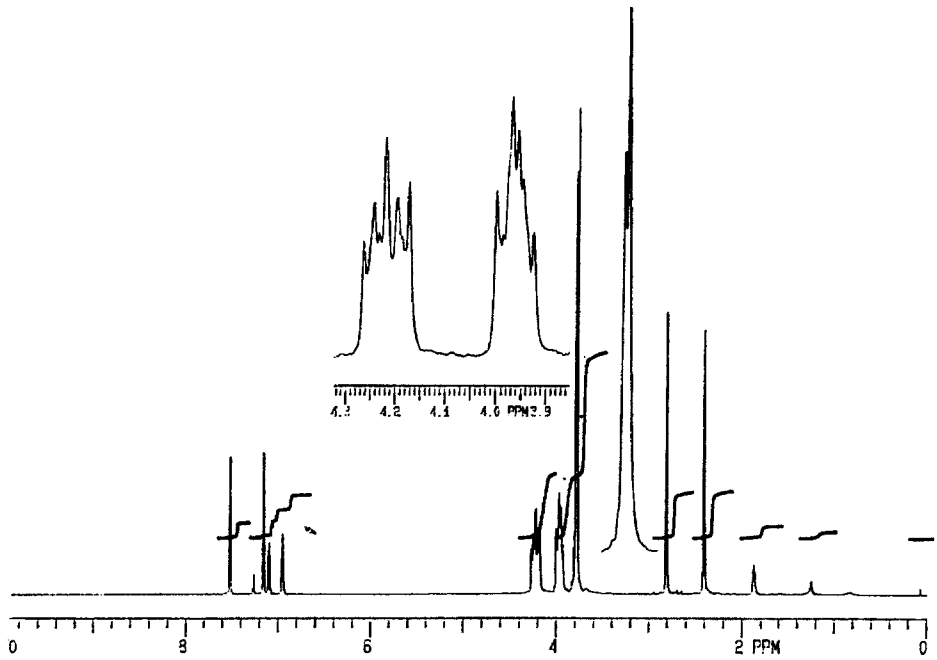

Figure 2. The ^{1}H-NMR spectrum of 5,7-dimethylcoumestano-15-crown-5 **5f** in $CDCl_3$.

ring of coumestan **5a–f** or the α,β-unsaturated cyclohexanone moiety of **6a–e** and both sites might contribute to the selectivity.

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