Synthesis of a Crown Ether Containing a Pyrrole Subcyclic Unit

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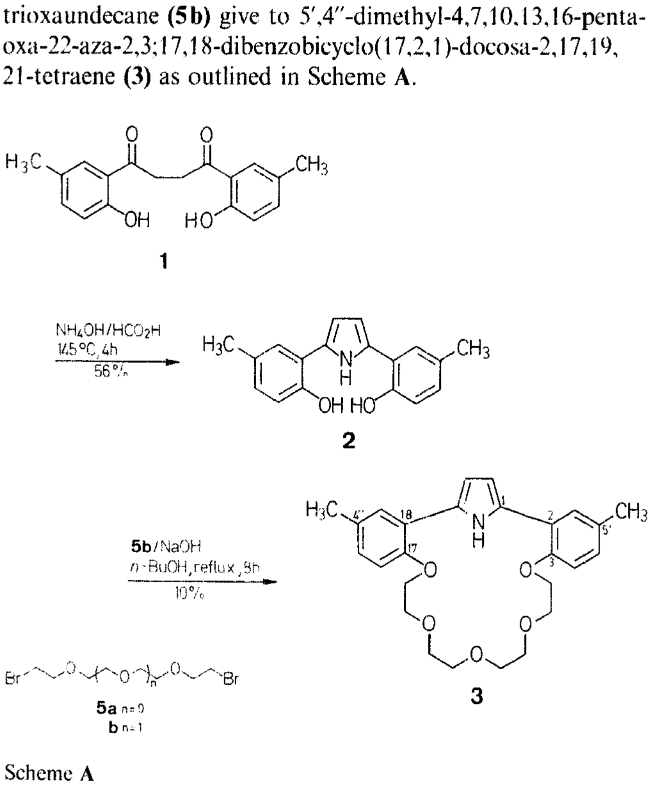
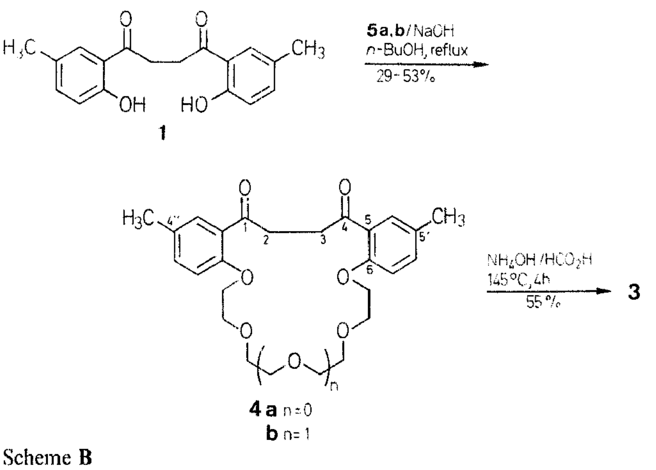
Crown ether 3, containing a pyrrole subcyclic unit, is prepared according to two different synthetic routes. According of the first route, 2,5-bis[3-methyl-2-hydroxyphenyl]pyrrole (2) is cyclized with 1,11-dibromo-3,6,9-trioxaundecane. According to the second route, a crown ether containing a 1,4-diketone unit is prepared first, followed by cyclization to form the pyrrole subcyclic unit. However, if the cavity in the crown ether ring system is small, the cyclization of 1,4-diketone unit does not success.

The Crown ether are an important class of compounds. Only a few papers, however, have reported the synthesis of a crown ether that incorporates a nitrogen heterocyclic ring in its ring system. The synthesis of a crown ether containing a pyridine subcyclic unit has been reported,[1,2] and it was found to exhibit interesting host-guest complexing characteristics. Therefore, the formation of host-guest complexes by a crown ether containing a pyrrole subcyclic unit could be expected as well. Since no reports of such a crown ether has appeared in the literature, we were prompted to undertake its synthesis, and report our results here. First, a pyrrole compound bearing hydroxyl-containing substituents at the 2- and 5-positions was prepared. This compound was then condensed with 1,11-dibromo-3,6,9-trioxaundecane (**5b**) give to 5′,4″-dimethyl-4,7,10,13,16-pentaoxa-22-aza-2,3;17,18-dibenzobicyclo(17,2,1)-docosa-2,17,19,21-tetraene (**3**) as outlined in Scheme **A**.



Scheme **A**

The another synthetic route is similar to the first, only the order of the steps have been reversed. Thus, a crown ether containing a 1,4-diketone moiety is prepared at first, then treated with ammonium formate to form a pyrrole ring as the Paal-Knorr reaction. If the cavity in the crown ether ring system is large enough, the Paal-Knorr reaction occurs readily. In this way **3** was prepared by the cyclization of the 1,4-diketone moiety in the 5′,4″-dimethyl-7,10,13,16,19-pentaoxa-5,6;20,21-dibenzozocyclohencicosa-5,20-diene-1,4-dione **4b**, as outlined in Scheme **B**.



Scheme **B**

However, in the case of the crown ether 5′,4″-dimethyl-7,10,13,16-tetraoxa-5,6;17,18-dibenzocyclooctadeca-5,17-diene-1,4-dione **4a**, the cavity in its ring system is smaller and the cyclization of 1,4-diketone moiety did not occur. This could be due to the difficulty of the reagent for cyclization of 1,4-diketone moiety to diffuse into the small cavity; alternately, the failure could be due to ring strain induced during attempted cyclization.

In summary, two synthetic routes are presented for the synthesis of **3**. According to the first route, the synthesis proceeds from **1** *via* **2** to **3**, with an overall yield of 5.6%. In the second route, proceeding from **1** *via* **4b** to **3**, the overall yield is 29%, much higher than the first one. It is possible that pyrrole ring in **2** is attacked by the vigorous condition of the cyclization to **3**. In second route, this problem is avoided, since the pyrrole subcyclic unit is formed after the cyclization step to the crown ether. For this reason, the second route is the preferable on for the synthesis of **3**.

Melting point are uncorrected. Infrared spectra are recorded on Perkin-Elmer 683 spectrometer. ^{1}H-NMR spectra are determined on Varian EM-360 (60 MHz) and JEOL MH-100 (100 MHz) spectrometers.

1,4-Bis(2-hydroxy-5-methylphenyl)butane-1,4-dione 1:

Diketone **1** is prepared according to the Lit.[3]: m.p. 187–188 °C (Lit.[3] m.p. 189 °C).

IR (KBr): $\nu = 3420, 1635\ \text{cm}^{-1}$.

^{1}H-NMR ($CDCl_3$/TMS): $\delta = 2.3$ (s, 6H, CH_3); 3.5 (s, 4H, CH_2CH_2); 6.75–7.55 (m, 8H_{arom}); 11.8 (s, 2H, OH).

2,5-Bis(2-hydroxy-5-methylphenyl)pyrrole 2:

To 85% formic acid (45 g) contained in a flask under nitrogen atmosphere is added 28% aqueous NH_4OH solution (54 g) dropwise. The reaction mixture is then heated to remove the water from the solution (to a solution temperature of 150 °C). The reaction mixture is cooled to below 130 °C, and **1** (7 g, 0.024 mol) is added as several portions into the stirred solution. The Reaction temperature is gently increased to 145 °C, and stirring at this temperature is continued for 4 h. The reaction mixture is cooled to room temperature, and 28% aqueous NH_4OH solution is added to make the solution basic. The solution is extracted with benzene, and the combined benzene phase dried (Na_2SO_4). The benzene is removed on a rotary evaporator, and the resulting residue is recrystallized from benzene to give pyrrole **2**; yield: 3.7 g (56%); m.p. 210–213 °C.

$C_{18}H_{17}NO_2$	calc.	C 77.41	H 6.14	N 5.02
(279.3)	found	77.60	6.22	5.14

5′,4″-Dimethyl-4,7,10,13,16-pentaoxa-22-aza-2,3;17,18-dibenzobicyclo(17,2,1)docosa-2,17,19,21-tetraene 3:

Procedure I; from Pyrrole **2**: A mixture of **2** (1.73 g, 0.006 mol), *n*-BuOH (100 mL) and NaOH (0.24 g, 0.006 mol) are placed in a flask fixing with a reflux condenser. 1,11-Dibromo-3,6,9-trioxaundecane[4] (**5b**; 1.85 g, 0.007 mol) is added dropwise and the reaction mixture refluxed for 1 h.

A second portion of NaOH (0.24 g, 0.006 mol) and **5b** (1.85 g, 0.007 mol) is then added. The reaction mixture is refluxed for 8 h, cooled to room temperature, and the resultant NaBr separated by filtration. The BuOH is removed on a rotary evaporator and the residue recrystallized from hexane; yield: 0.26 g (10%); m. p. 83–84.5 °C.

$C_{26}H_{31}NO_5$ calc. C 71.37 H 7.14 N 3.20
(437.5) found 71.53 7.21 3.34

^{1}H-NMR (CDCl$_3$/TMS): $\delta = 2.30$ (s, 6H, CH$_3$); 3.6 (s, 8H, OCH$_2$CH$_2$O); 3.8–3.9 (t, 4H, OC$\underline{H}_2$CH$_2$OAr); 4.18–4.27 (t, 4H, CH$_2$OAr); 6.6–7.43 (m, 6H$_{arom}$); 6.93 (s, 2H$_{pyrrole}$); 10.83 (s, 1H, NH).

Procedure II; from 1,4-Diketone 4b: A 28% aqueous NH$_4$OH solution (54 g) is added dropwise to stirred 85% formic acid (45 g). The resulted solution then heated gently until 150 °C to remove the water. The solution is then allowed to cooled to 130 °C and **4b** (1.3 g, 0.003 mol) is added in several small portions under nitrogen. The reaction mixture is maintained at 145 °C for 4 h. After the mixture is cooled to room temperature, 28% aqueous NH$_4$OH solution is added until the reaction mixture is slightly basic. The resultant mixture is extracted with CHCl$_3$ (2 × 50 mL). The combined organic phase is dried (Na$_2$SO$_4$) and the solvent removed by rotary evaporation. The residue is recrystallized from hexane two times to give **3**; yield: 0.69 g (55%); m. p. 84–85 °C.

$C_{26}H_{31}NO_2$ calc. C 71.37 H 7.14 N 3.20
(437.5) found 71.77 7.14 2.93

5′,4″-Dimethyl-7,10,13,16,19-Pentaoxa-5,6;20,21-dibenzocycloheneicosa-5,20-diene-1,4-dione 4b:

A mixture of **1** (6 g, 0.02 mol), *n*-BuOH (150 mL) and NaOH (0.81 g, 0.02 mol) are is heated to reflux under nitrogen. Dibromide **5b** (3.25 g, 0.01 mol) is added, and the reaction mixture is kept under reflux for 1 h. Then another portion of NaOH (0.81 g, 0.02 mol) and **5b** (3.25 g, 0.01 mol) are added. After refluxing for 6 h, the reaction mixture is cooled to room temperature and filtered. The butanol is removed by rotary evaporation, and the residue is recrystallized from EtOAc to give **4b**; yield: 4.86 g (53%); m.p. 127–129 °C.

$C_{26}H_{32}O$ calc. C 68.41 H 7.07
(456.5) found 68.34 7.03

IR (KBr): $\nu = 1680, 1660\ \mathrm{cm}^{-1}$.

^{1}H-NMR (CDCl$_3$/TMS): $\delta = 2.28$ (s, 6H, CH$_3$); 3.55 (s, 4H, COCH$_2$CH$_2$CO); 3.68 (S, 8H, OCH$_2$CH$_2$O); 3.80–3.88 (t, 4H, OC$\underline{H}_2$CH$_2$OAr).
4.16–4.24 (t, 4H, CH$_2$OAr); 6.76–7.62 (m, 6H$_{arom}$).

5′,4″-Dimethyl-7,10,13,16-tetraoxa-5,6;17,18-dibenzocyclooctadeca-5,17-diene-1,4-dione 4a:

The same procedure as for crown ether **4b** is followed; from **1** (12 g, 0.04 mol), *n*-BuOH (150 mL), NaOH (3.84 g, 0.096 mol) and **5a** (13 g, 0.047 mol), product **4a** is obtained; yield: 4.8 g (29%); m.p. 134–136 °C.

$C_{24}H_{28}O_6$ calc. C 69.89 H 6.84
(412.5) found 69.83 6.74

IR (KBr): $\nu = 1685, 1675\ \mathrm{cm}^{-1}$.

^{1}H-NMR (CDCl$_3$/TMS): $\delta = 2.25$ (s, 6H, CH$_3$); 3.43 (s, 4H, COCH$_2$CH$_2$CO); 3.68 (s, 4H, OCH$_2$CH$_2$O); 3.7–3.83 (t, 4H, OCH$_2$CH$_2$OAr);
4.05–4.20 (t, 4H, CH$_2$OAr); 6.7–7.43 (m, 6H$_{arom}$).

The authors acknowledge the financial assistance of the Chinese National Science Foundation

Received: 16 December 1986; revised: 1 April 1987

(1) Newcomb, M., Gokel, G.W., Cram, D.J. *J. Am. Chem. Soc.* **1974** *96*, 6810.
(2) Newcomb, M., Timko, J.M., Walba, D.M., Cram, D.J. *J. Am Chem. Soc.* **1977**, *99*, 6392.
(3) Thomas, F.D. *J. Am. Chem. Soc.* **1958**, *80*, 5864.
(4) Bogatskii, A.V., Luk'yanenko, N.G., Kirichenko, T.I. *J. Org Chem. USSR (Engl. Transl.)* **1980**, *16*, 1124.