Modified Crown Ether Catalysts. 2. Synthesis of Alkanoyl-, Aroyl-, α-Hydroxyalkyl- and Alkylbenzo and Alkylcyclohexano Crown Ethers[1]

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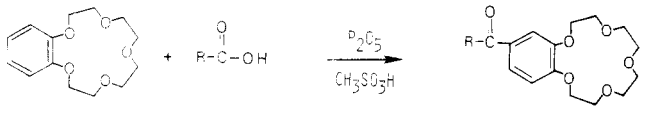
Improved procedures for the synthesis and purification of alkanoyl- and aroylbenzo crown ethers are reported. Several new alkanoyl- and α-hydroxyalkylbenzo crown ethers were prepared. Alkylbenzo crown ethers were prepared in high yield by the Raney nickel catalyzed hydrogen-transfer reductions of the corresponding acyl- or hydroxyalkylbenzo crown ether compounds. The reduction of the tosylhydrazones of acylbenzo crown ethers with sodium borohydride in acetic acid also yielded the corresponding alkyl derivative. Attempted reduction of the acyl- and α-hydroxyalkylbenzo crown ethers by catalytic hydrogenation over palladium catalyst was unsuccessful apparently due to strong binding of the crown ethers to the catalyst. Alkylcyclohexano crown ethers were prepared by catalytic hydrogenation of the aromatic rings of the corresponding alkylbenzo crown ethers.

For several years we have been engaged in a study of the structural parameters that affect the ability of macrocyclic ligands to bind cations, catalyze phase-transfer reactions and transport ions across lipophilic membranes. As a part of this effort we have synthesized a large number of acyl-, α-hydroxyalkyl-, and alkyl-substituted benzo crown ethers. Two alkylcyclohexano crown ethers were also prepared. We have already described the synthesis of some of the alkanoyl-, aroyl- and α-hydroxyalkylbenzo crown ethers.[2] We have subsequently modified and improved those syntheses and have synthesized several new compounds of those types. We have also found that these acyl- and α-hydroxyalkylbenzo crown ethers can be converted in high yields to the corresponding alkylbenzo crown ether compounds. The series of substituted benzo crown ethers reported here and in our eariler paper[2] have been evaluated with regard to performance as phase-transfer catalysts[3] and as neutral-ion carriers in lipophilic membranes.[4]

Improved Procedure for Acylating Benzo Crown Ethers. We originally reported that benzo crown ethers were conveniently acylated with carboxylic acids by the action of Eaton's reagent[5] (phosphorous pentoxide in methanesulfonic acid).[2] The reactions were usually carried



out at room temperature for 5-6 h, giving good yields of acylated products. We have now found that these reactions are more conveniently carried out by dissolving the carboxylic acid in Eaton's reagent at 50 °C and then adding the benzo crown ether. An immediate exothermic reaction ensues. Upon completion, the reaction is quenched by pouring of the mixture onto ice and filtering the crude product.

We have also modified the purification step. The previously used operation of washing with aqueous base often led to the formation of emulsions. This step may be eliminated provided the crude product is subsequently recrystallized from hot alcohol or washed with a solvent in which the excess carboxylic acid is soluble.

Table I. Acylated Benzo Crown Ethers

compd[a]	R[a]	method[b]	yield, %	mp, °C
	Benzo-15-crown-5			
1	CH_3[c]	B	63	95-96.5
2	$CH_3(CH_2)_5$[c]	B	55	49-51
3	$CH_3(CH_2)_{12}$	B	26	55-57
	Dibenzo-18-crown-6			
4	CH_3[c]	B	86	200-208
5	CH_3CH_2	B	66	161-165
6a	$CH_3(CH_2)_2$[c]	B	72[d]	174-182
6b				149-159
7	$(CH_3)_2CH$[c]	B	88	154-160
8	$CH_3(CH_2)_3$	B	100[d]	144-150
9	$(CH_3)_2CHCH_2$	D	80	129-132
10	$(CH_3)_3C$[c]	B	85	146-159
11	$CH_3(CH_2)_4$	B	78	144-147
12a	phenyl	D	100[d]	178-184
12b				197-198
13	$CH_3(CH_2)_5$	B	86	119.5-122
14	$CH_3(CH_2)_7$	B	84	120-122
15	$CH_3(CH_2)_8$[c]	B	75	117-129
16	$CH_3(CH_2)_{10}$	B	79	129-133
17a	$CH_3(CH_2)_{12}$[c]	C/D	71-80	123-127
17b				144-146
18	$CH_3(CH_2)_{16}$[c]	C	75	116-120
	Dibenzo-24-crown-8			
19	CH_3[c]	A	85	150-160
20	$CH_3(CH_2)_3$	B	66	89-91
21a	$CH_3(CH_2)_8$[c]	A/B	50-84	86-92
21b				78-91
22	$CH_3(CH_2)_{10}$	B	53	85-95
23	$CH_3(CH_2)_{12}$	B	85	83-94

[a] See Chart I for the structures of these compounds. [b] Method A, carbonyl chloride and boron trifluoride in nitrobenzene or chlorinated hydrocarbon; method B, carboxylic acid and Eaton's reagent at room temperature; method C, carboxylic acid and Eaton's reagent at 60-80 °C; method D, carboxylic acid pretreated with Eaton's reagent at 50-60 °C. For details see the Experimental Section. [c] Reported in ref 2. [d] Crude yield only.

Table I lists all the acylbenzo crown ether compounds prepared by us and gives their physical properties.[6] The diacyl derivatives of dibenzo-18-crown-6 are relatively in-

(1) Presented in part at the 35th Northwest-5th Biennial Rocky Mountain Joint Regional Meeting of the American Chemical Society, Salt Lake City, UT, June 12-14, 1980.
(2) Parish, W. W.; Stott, P. E.; McCausland, C. W.; Bradshaw, J. S. *J. Org. Chem.* **1978**, *43*, 4577-4581.
(3) Stott, P. E.; Bradshaw, J. S.; Parish, W. W. *J. Am. Chem. Soc.* **1980**, *102*, 4810-4815.
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(5) Eaton, P. E.; Carlson, G. P.; Lee, J. T. *J. Org. Chem.* **1973**, *38* 4071-4073.

(6) A satisfactory elemental analysis was obtained for all new compounds reported in this paper.

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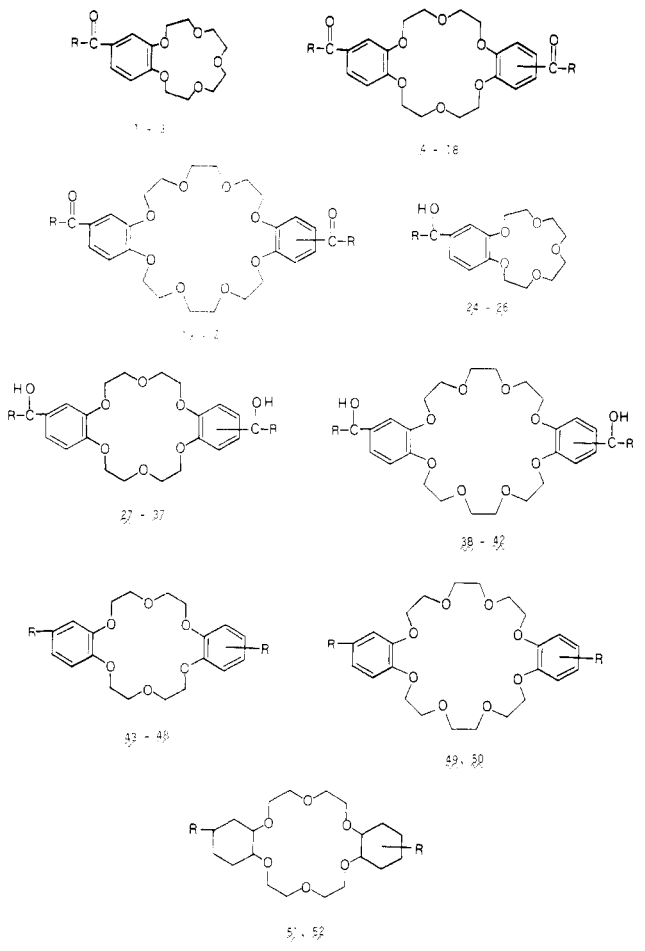
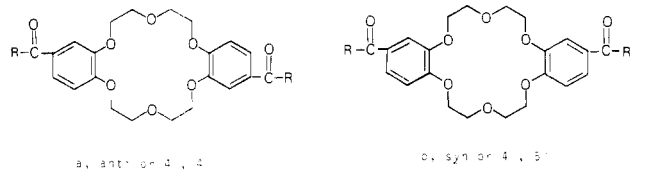
Chart I. Compounds Reported



soluble in most common organic solvents. Recrystallization of large quantities requires inordinately large amounts of solvent. We have, therefore, purified these compounds by a continuous Soxhlet extraction. The two positional isomers present in the crude products could sometimes be separated by this procedure. The physical constants of both isomers of **6**, **10**, and **17** are listed in Table I.



In the case of bis(benzoylbenzo)-18-crown-6 (**12**), the isomers were also separated by using dichloromethane or chloroform as the solvent. We found that the less soluble isomer was present as approximately a 1:1 complex with the chlorinated solvent. The complex with dichloromethane could be precipitated by addition of an equal volume of dichloromethane to a dilute solution of the crude crown ether in chloroform. This complex was able to retain the complexed solvent up to 120 °C.

During the acylation reaction with carboxylic acids in Eaton's reagent, we found the aliphatic ether linkages of the crown ethers were cleaved to form bis(methanesulfonate) and mixed carboxylate–methanesulfonate esters. This side reaction has been briefly investigated and is reported separately.[7] The side reaction occurred extensively only with benzo-15-crown-5 (note lower yields for

(7) Stott, P. E.; Bradshaw, J. S.; Parish, W. W. *Heterocycles*, in press.

Table II. (1-Hydroxyalkyl)benzo Crown Ethers

compd[a]	R[a]	yield, %	mp, °C
	Benzo-15-crown-5		
24	CH_3	86	57-59
25	$CH_3(CH_2)_5$[b]	92	wax
26	$CH_3(CH_2)_{12}$	79	62-65
	Dibenzo-18-crown-6		
27a	CH_3[b]	84	164-167
27b			197-199
28	CH_3CH_2	63	130-140
29	$CH_3(CH_2)_2$	75	135-147
30	$(CH_3)_2CH$	76	110-123
31	$(CH_3)_2CHCH_2$	96	129-132
32	$CH_3(CH_2)_4$	85	135-145
33	$CH_3(CH_2)_5$		95 (134-137)[c]
34	$CH_3(CH_2)_7$	77	125-135
35a	$CH_3(CH_2)_8$[b]	77	120-122
35b			145-148
36	$CH_3(CH_2)_{10}$	87	125-131
37a	$CH_3(CH_2)_{12}$[d]	100	145.5-147
37b	$CH_3(CH_2)_{12}$[e]	100	129-134
	Dibenzo-24-crown-8		
38	CH_3[b]	89	wax
39	$CH_3(CH_2)_5$	*f*	honey
40	$CH_3(CH_2)_8$[b]	75	88-92
41	$CH_3(CH_2)_{10}$	84	80-81
42	$CH_3(CH_2)_{12}$	79	85-94

[a] See Chart I for the structures of these compounds. [b] Reported in ref 2. [c] Metastable between 95 and 134 °C. [d] Prepared from ketone, mp 144-146 °C. [e] Prepared from ketone, mp 123-127 °C. [f] Product dimerized (benzyl ether type products) before workup was complete.

the formation of compounds **1–3**, Table I, Chart I). Fortunately, the acylated benzo-15-crown-5 products were easily extracted from the cleavage products by treatment with hot hexane.

α-Hydroxyalkylbenzo Crown Ethers. Many of the acylbenzo crown ethers were reduced to the corresponding alcohols by the action of sodium borohydride in ethanol. A comlete list of the α-hydroxyalkylbenzo crown ethers thus prepared, along with their physical properties, is given in Table II.

Individual *syn*- and *anti*-α-hydroxyalkyl isomers were prepared both by the reduction of the previously separated diacyl isomers and by the reduction of the mixed diacyl isomers followed by a subsequent separation of the reduced isomeric products. The isomers of bis(α-hydroxyethyl)- and bis(α-hydroxydecyl)dibenzo-18-crown-6 (**27** and **35**) were obtained by the latter method.

Alkylbenzo Crown Ethers. We conveniently reduced the alkanoyl- and α-hydroxyalkylbenzo crown ethers to the corresponding alkylbenzo crown ether compounds by hydrogen transfer from alcoholic solvents catalyzed by Raney nickel.[8,9] Table III lists the alkylbenzo crown compounds and their physical properties. The reduction of α-hydroxybenzo crown ethers could be accomplished in ethanol, but ethanol was unsatisfactory for the reduction of the corresponding alkanoylbenzo compounds. Cyclohexanol, however, could be used for the reduction of all ketones. This latter procedure shortens the synthetic sequence by one step (the sodium borohydride reduction of the ketone to the α-hydroxy compound) but requires steam distillation to subsequently remove the higher boiling solvent. Since the sodium borohydride reduction is straightforward and

(8) Mozingo, R.; Spencer, C.; Folker, K. *J. Am. Chem. Soc.* **1944**, *66*, 1859–1860.
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(10) Pedersen, C. J. *J. Am. Chem. Soc.* **1967**, *89*, 7017–7036.

Table III. Alkylbenzo Crown Ethers

compd[a]	R[a]	method[b]	yield, %	mp, °C
	Dibenzo-18-crown-6			
43a	CH_3	E	48	128-129
43b				145-146
44	$CH_3(CH_2)_4$	F	72	91-94
45	$(CH_3)_2CH(CH_2)_2$	G	72	97-105
46	$CH_3(CH_2)_6$	F	68	89-91
47	$CH_3(CH_2)_9$	F		89.5-91.5
48a	$CH_3(CH_2)_{13}$	F	76	100-100.5
48b				96-97
	Dibenzo-24-crown-8			
49	$(CH_3)_3C$	E	56	87-92
50	$CH_3(CH_2)_9$	F	53	74.5-76

[a] See Chart I for the structures of these compounds. [b] Method E, cyclization of alkyl catechol;[10] method F, Raney nickel reduction of ketone in cyclohexanol; method G, Raney nickel reduction of alcohol in ethanol.

proceeds in a high yield, the direct reduction of the ketone probably does not offer any specific advantage. Some glycolic byproduct was observed in the Raney nickel reduction. No attempt was made to optimize the yields.

We initially tried catalytic hydrogenation to accomplish these reductions because the Clemmenson[11] and Wolff–Kishner[12] reductions often result in ether cleavage.[11,13] Indeed, each of these methods has given relativley low yields of alkylbenzo crown ethers.[14,15]

Literature reports of palladium-catalyzed hydrogenation of aryl alkyl ketones and benzyl alcohols to the corresponding hydrocarbons are common. Even though we easily reduced a model compound (3′,4′-dimethoxybutyrophenone) using palladium, only starting materials were recovered when this procedure was tried on the acyl- or α-hydroxyalkyl crown compounds. When a large excess of palladium was employed, removal of the catalyst also removed the starting material. It is possible that these ligands strongly bind palladium and thus effectively poison the catalyst. Attempts to extract the macrocycle from the catalyst with hot acetic acid, chloroform, or ethanol were all unsuccessful.

The recently reported[16] conversion of the tosylhydrazones of aryl alkyl ketones to the corresponding hydrocarbons by the action of sodium borohydride and acetic acid was also used to form bis(decylbenzo)-18-crown-6 (**47**) from bis(decanoylbenzo)-18-crown-6 (**15**). However, the product from this reaction was yellow and somewhat difficult to purify. The described method was used except that a trace of trifluoracetic acid was necessary to catalyze formation of the tosylhydrazone.

Alkylcyclohexano Crown Ethers. In addition to the above-reported substituted benzo crown ethers, we also prepared two alkylcyclohexano crown ethers (**51**, **52**) by the catalytic hydrogenation of the corresponding alkylbenzo compounds.[10] Four isomers are possible: 4,4′-cis-syn-cis, 4,5′-cis-syn-cis, 4,4′-cis-anti-cis, 4,5′-cis-anti-cis. The crude products were oils that could only be purified by column chromatography to yield somewhat waxy white solids. One of the isomers of bis(methylcyclohexano)-18-crown-6 could be separated as its nitromethane complex by recrystallizing the crude oil from that solvent. NMR spectroscopy of the resulting white crystals showed about 1.25 mol of nitromethane to be present. Such complexes between crown ethers and small neutral organic molecules, including nitromethane, are known.[17] The solvent was liberated by heating the complex briefly at 105 °C to give a white powder, mp 88–91 °C [lit.[18] (mixed isomers) mp 34–50 °C].

The crown ethers described in this report have proven to be useful tools for studying the effects of minor and progressive changes in size, organophilicity, and electron-donating and -withdrawing capacity of crown ethers on their performance as neutral ionophores in phase-transfer catalysis[3] and membrane transport of ionic substances.[4]

Experimental Section

Equipment and Data. All melting ponts were obtained with a Thomas-Hoover Unimelt capilary melting point apparatus and are uncorrected. All infrared spectra were obtained with a Beckman Acculab II, and all NMR spectra were obtained with a Varian EM 390 spectrometer. All elemental analyses were performed by M-H-W Laboratories.

Explicit details of each preparation are not supplied.[6] For yields and melting point data, refer to Tables I–III. Specific details of preparations which are representative of each of the methods discussed are presented below.

2,3:11,12-Bis[4′,4″(or 5″)-pentanoylbenzo]-18-crown-6 (8). A mixture of 36 g (0.1 mol) of dibenzo-18-crown-6, 22 g (0.215 mol) of valeric acid, and 266 g of Eaton's reagent[5] was stirred for 5 h at 25 °C. The reaction was then quenched by being poured onto ice (method B). The crude product [52.5 g (100%); mp 135–144 °C] was extracted for 90 h with hexane in a Soxhlet extractor. The portion extracted into the hexane was 7 g of light tan powder, mp 144–150 °C. This material is presumed to be primarily the anti isomer (lit.[14] mp 150–152 °C).

Anal. Calcd for $C_{30}H_{40}O_8$: C, 68.36; H, 7.63. Found: C, 68.39; H, 7.78.

2,3:11,12-Bis[4′,4″(or 5″)-isopentanoylbenzo]-18-crown-6 (9). A mixture of 18.5 g (0.18 mol) of isovaleric acid and 209 g of Eaton's reagent was stirred and heated to 50 °C, and 30 g (0.08 mol) of dibenzo-18-crown-6 was added (method D). The temperature was maintained at 55 °C first by cooling and later by heating. After 30 min, the red solution was poured onto ice. The crude off-white product (42 g, 96%) was decolorized and recrystallized in 400 mL of 7:3 ethanol–water to give 35 g (80%) of shiny plates, mp 128–133 °C. An analytical sample was obtained by recrystallizing a small sample from heptane; mp 129–132 °C.

Anal. Calcd for $C_{30}H_{40}O_8$: C, 68.36; H, 7.63. Found: C, 68.76; H, 7.71.

2,3:11,12-Bis(4′,4″-benzoylbenzo)-18-crown-6 (12a) and 2,3:11,12-Bis(4′,5″-benzoylbenzo)-18-crown-6 (12b). A mixture of 14.5 g (0.12 mol) of benzoic acid and 140 g of Eaton's reagent at 50 °C was reacted with 20 g (0.056 mol) of dibenzo-18-crown-6 (method D). After 45 min at 50–60 °C, the green reaction mixture was poured onto ice. The crude product (33 g) was stirred in 250 mL of dichloromethane, and the purple slurry was filtered. The solvent turned bright green as it passed through the filter paper. The filtrate was washed with sodium bicarbonate solution, which caused it to turn orange, and evaporated to give 16 g of tan product, mp 174–183 °C. Recrystallization of a sample from ethanol gave a light tan powder (**12a**), mp 178-184 °C (lit.[14] mp 184-186 °C).

Anal. Calcd for $C_{34}H_{32}O_8$: C, 71.82; H, 5.67. Found: C, 71.69; H, 5.93.

The gray solid (18 g) which was insoluble in dichloromethane was dissolved in chloroform and filtered to remove a small amount

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of insoluble material. Addition of an equal volume of dichloromethane caused the solution to turn from yellow to purple, and after a few minutes a white precipitate formed. The mixture was cooled and filtered to give a material whose NMR spectrum indicated that it contained 1 mol of dichloromethane/mol of product. This material gave up its solvent at about 130 °C and then melted at 197–198 °C. Recrystallization of 0.5 g of the chloroform complex in 1000 mL of ethanol gave fine white needles (**12b**), mp 197–198 °C.

Anal. Calcd for $C_{34}H_{32}O_8$: C, 71.82; H, 5.67. Found: C, 71.79; H, 5.68.

2,3:11,12-Bis[4′,4″-(1-hydroxyethyl)benzo]-18-crown-6 and 2,3:11,12-Bis[4′,5″-(1-hydroxyethyl)benzo]-18-crown-6 (27). A slurry of 1.5 g (0.0034 mol) of bis(acetylbenzo)-18-crown-6 **4** and 1.0 g (0.026 mol) of sodium borohydride in 50 mL of ethanol was stirred for 2 h, poured into 250 mL of water, and neutralized with sulfuric acid. The mixture was extracted three times with 25-mL portions of dichloromethane. A white powder (mp 196–198 °C) precipitated from the dichloromethane. The powder was recrystallized from dichloromethane to give 0.15 g of solid (**27b**), mp 197–199 °C. When the solution was allowed to stand, an additional 0.27 g of this material precipitated from the initial extraction solvent. The solid was removed by filtration, and the filtrate was evaporated to give a solid residue. This residue was triturated with hot ethyl ether to give 0.8 g of a white solid (**27a**), mp 164–167 °C. The NMR spectra of both isomers were identical.

Anal. Calcd for $C_{24}H_{32}O_8$: C, 64.27; H, 7.19. Found (**27b**): C, 64.22; H, 7.20. Found (**27a**): C, 64.43; H, 7.36.

2,3:11,12-Bis[4′,4″ or 4′,5″-(1-hydroxytetradecyl)benzo]-18-crown-6 (37a). A slurry of 4 g (0.005 mol) of the higher melting isomer of bis(tetradecanoylbenzo)-18-crown-6 **17b** in ethanol was treated with an excess of sodium borohydride. The crude product (4 g, 100%) was a white powder. Recrystallization from hexane gave white needles, mp 145.5–147 °C. Elemental analysis indicated that inorganic material was present. The product was then treated for 30 min with boiling water and recrystallized from ethanol. The resulting white needles had a melting point of 147 °C.

Anal. Calcd for $C_{48}H_{80}O_8$: C, 73.43; H, 10.27. Found: C, 73.55; H, 10.19.

2,3:11,12-Bis[4′,4″ or 4′,5″-(1-hydroxytetradecyl)benzo]-18-crown-6 (37b). A slurry of 1 g of the lower melting isomer of bis(tetradecanoylbenzo)-18-crown-6 **17a** in 50 mL of ethanol was treated with an excess of sodium borohydride. The crude product (1 g, 100) was an off-white powder, mp 127–136 °C. A sample of the material was recrystallized from hot benzene to give a white powder, mp 129–134 °C.

Anal. Calcd for $C_{48}H_{80}O_8$: C, 73.43; H, 10.27. Found: C, 73.26; H, 10.38.

2,3:14,15-Bis[4′,4″(or 5″)-(1-hydroxydecyl)benzo]-24-crown-8 (40). An excess of sodium borohydride was carefully added to a stirred slurry of 16.5 g (0.0217 mol) of bis(decanoylbenzo)-24-crown-8 (**21**) in 200 mL of ethanol. The mixture was stirred for 3 h at room temperature and then for 30 min at 50 °C. The solution was filtered to remove a fluffy inorganic precipitate, neutralized with sulfuric acid, and extracted with 300 mL of dichloromethane. The organic phase was dried over sodium sulfate and evaporated to give a waxy cream-colored product. The crude product was triturated with acetone, washed with ethanol, and dried. The yield was 12.4 g (75%) of a white powder, mp 88–92 °C.

Anal. Calcd for $C_{44}H_{72}O_{10}$: C, 69.44; H, 9.54. Found: C, 69.06; H, 9.75.

2,3:11,12-Bis(4′,4″-methylbenzo)-18-crown-6 (43a) and 2,3:11,12-Bis(4′,5″-methylbenzo)-18-crown-6 (43b). The method of Pedersen[10] was used to prepare the title compounds from 4-methylcatechol. Fractional crystallization of the crude product from ethanol gave long colorless needles (**43b**), mp 145–146 °C. Evaporation of the filtrate, extraction into hot hexane, evaporation of the hexane, and recrystallization of the residue from ethanol gave a second isomer (**43a**), mp 128–129 °C. The overall yield was 48%.

Anal. Calcd for $C_{22}H_{28}O_6$: C, 68.02; H, 7.26. Found (**43b**): C, 68.02; H, 7.21. Found (**43a**): C, 68.24; H, 7.35.

2,3:11,12-Bis[4′,4″(or 5″)-*n*-pentylbenzo]-18-crown-6 (44). To a slurry of 5 teaspoons of Raney nickel W-2 in 200 mL of cyclohexanol was added 6 g of bis(pentanoylbenzo)-18-crown-6 **8**. The mixture was refluxed for 18 h, and the catalyst was removed by multiple filtrations through a Celite pad. (Care must be taken not to allow the catalyst to become dried on the pad since Raney nickel burns spontaneously in air.) The solvent was removed from the filtrate by steam distillation, and the resulting product was extracted into chloroform and decolorized with Norit. Evaporation of the solvent gave a crude product that was recrystallized from hot ethanol to give 4.1 g (72%) of shiny white crystals, mp 89–92 °C (some residue remained until 104–105 °C). An analytical sample was prepared by a second recrystallization from ethanol; mp 91–94 °C.

Anal. Calcd for $C_{30}H_{44}O_6$: C, 71.97; H, 8.86. Found: C, 71.82; H, 8.87.

2,3:11,12-Bis[4′,4″(or 5″)-isopentylbenzo]-18-crown-6 (45). To a slurry of 6 teaspoons of Raney nickel W-2 in 200 mL of ethanol was added 5 g of bis[(α-hydroxyisopentyl)benzo]-18-crown-6 **31**. The mixture was refluxed overnight and the catalyst was removed by filtration through a Celite pad. The solvent was evaporated to give 4.1 g (87%) of white powder. Recrystallization from a minimum of hot ethanol gave 2.1 g of fluffy white needles, mp 98 °C (a small amount of material remains unmelted until 109–111 °C). Evaporation of the solvent from the filtrate and recrystallization of the residue from hexane gave an additional 1.5 g of product mp 97–105 °C (72% overall yield). A glycolic residue (by IR and NMR) was insoluble in the hot hexane.

Anal. Calcd for $C_{30}H_{44}O_6$: C, 71.97; H, 8.86. Found: C, 72.10; H, 8.97.

2,3:11,12-Bis[4′,4″(or 5″)-*n*-decylbenzo]-18-crown-6 (47). Treatment of 6 g of bis(decanoylbenzo)-18-crown-6 **15** with Raney nickel W-2 in refluxing cyclohexanol gave 1.2 g of crystalline product. The product was obtained by removing the catalyst, chilling the filtrate to −20 °C, and removing the crystallized product by filtration. The majority of the product undoubtedly remained in the cyclohexanol, which was lost in a laboratory accident. A portion of the product was recrystallized from ethanol to give white rosettes, mp 89.5–91.5 °C.

Anal. Calcd for $C_{40}H_{64}O_6$: C, 74.96; H, 10.07. Found: C, 74.94; H, 10.15.

2,3:11,12-Bis[4′,4″-*n*-tetradecylbenzo]-18-crown-6 (48a). Treatment of 4 g of the lower melting isomer of bis(tetradecanoylbenzo)-18-crown-6 **17a** with Raney nickel W-2 in refluxing cyclohexanol gave, after removal of the catalyst and chilling of the solution to −20 °C, 2.2 g of small white needles, mp 97–100 °C. Steam distillation of the solvent from the filtrate and recrystallization of the residue from hexane gave an additional 0.7 g of product. The overall yield was 76%. A second recrystallization from hexane gave an analytical sample of **48a**, mp 100–100.5 °C. A small second crop of long white needles, mp 96-97 °C, was also obtained.

Anal. Calcd for $C_{48}H_{80}O_6$: C, 76.55; H, 10.71. Found: C, 76.72; H, 11.00.

2,3:14,15-Bis[4′,4″(or 5″)-*n*-decylbenzo]-24-crown-8 (50). Treatment of 6 g of bis(decanoylbenzo)-24-crown-8 **21** with Raney nickel in refluxing cyclohexanol gave, after removal of the catalyst and cooling of the solution to −20 °C, 2.75 g of white powder. A second crop of 0.32 g was obtained by recooling the filtrate. The overall yield was 53%. White microcrystals (mp 74.5–76 °C) were obtained by recrystallizing a sample of the product from hexane. The sharpness of the melting point indicates that the material may be only one isomer.

Anal. Calcd for $C_{44}H_{72}O_8$: C, 72.49; H, 9.96. Found: C, 72.67; H, 10.14.

2,3:11,12-Bis[4′,4″(or 5″)-*n*-decylcyclohexano]-18-crown-6 (52). A mixture of 1 g of bis(decylbenzo)-18-crown-6 **47** and 0.3 g of 5% ruthenum on alumina was stirred for 6 h at 160 °C and under 1300 psig of H_2 in 100 mL of 1-butanol. The crude yellow oil was eluted with hexane from a 10-cm acid-washed alumina column. The first 20 mL of product containing eluent was discarded because of contamination by mineral oil from an unknown source. Evaporation of the solvent from the next 80 mL of eluent gave 310 mg of a waxy white product. A portion of this was recrystallized from hexane to give a fine white powder, mp 62–88 °C.

Anal. Calcd for $C_{40}H_{76}O_6$: C, 73.57; H, 11.73. Found (recrystallized product): C, 73.76; H, 11.76. Found (crude product eluted from column): C, 73.73; H, 11.84.

Registry No. 1, 41757-95-3; 2, 67722-63-8; 3, 74965-98-3; 4, 68817-65-2; 5, 68817-66-3; 6a, 67722-68-3; 6b, 67722-67-2; 7, 74966-24-8; 8, 74966-25-9; 9, 74966-26-0; 10, 74966-27-1; 11, 74966-28-2; 12a, 67722-80-9; 12b, 67722-79-6; 13, 68817-64-1; 14, 74966-29-3; 15, 74966-30-6; 16, 74966-15-7; 17a, 67722-76-3; 17b, 67722-75-2; 18, 74966-16-8; 19, 74966-17-9; 20, 74966-18-0; 21a, 67722-84-3; 21b, 67722-83-2; 22, 74966-19-1; 23, 74966-20-4; 24, 41757-96-4; 25, 67722-85-4; 26, 74965-99-4; 27a, 67722-87-6; 27b, 67722-86-5; 28, 74966-21-5; 29, 74966-22-6; 30, 74966-23-7; 31, 74978-11-3; 32, 74966-02-2; 33, 74966-03-3; 34, 74966-05-5; 35a, 67722-89-8; 35b, 67722-88-7; 36, 74966-04-4; 37a, 67722-91-2; 37b, 67722-90-1; 38, 74966-06-6; 40, 70936-91-3; 41, 74966-07-7; 42, 74966-08-8; 43a, 74670-66-9; 43b, 52755-95-0; 44, 74966-09-9; 45, 74966-10-2; 46, 74966-11-3; 47, 74966-12-4; 48a, 74966-00-0; 48b, 74966-01-1; 49, 71035-28-4; 50, 74966-13-5; 52, 74966-14-6; benzo-15-crown-5, 14098-44-3; dibenzo-18-crown-6, 14187-32-7; dibenzo-24-crown-8, 14174-09-5; acetic acid, 64-19-7; heptanoic acid, 111-14-8; tetradecanoic acid, 544-63-8; propanoic acid, 79-09-4; butyric acid, 107-92-6; isobutyric acid, 79-31-2; valeric acid, 109-52-4; isovaleric acid, 503-74-2; pivalic acid, 75-98-9; hexanoic acid, 142-62-1; benzoic acid, 65-85-0; nonanoic acid, 112-05-0; decanoic acid, 334-48-5; dodecanoic acid, 143-07-7; octadecanoic acid, 57-11-4; acetyl chloride, 75-36-5; decanoyl chloride, 112-13-0; 4-methylcatechol, 452-86-8; 4-*tert*-butylcatechol, 98-29-3.

Synthesis of 2,2′-Diacyl-1,1′-biaryls. Regiocontrolled Protection of Ketones in Unsymmetrically Substituted 9,10-Phenanthrenequinones

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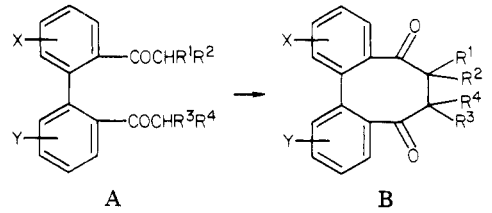
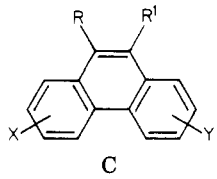
A regiocontrolled monoketalization of unsymmetrically substituted phenanthrenequinones by use of 2,2-dimethyl-1,3-propanediol as the ketalizing reagent has been effected with the help of bromo substitution in one of the aromatic rings at the C-1 or C-8 position. The effect of bromo substitution is of a steric nature and the ketalization enabled the regioselective elaboration of 9,10-tetrasubstituted phenanthrenediols which on subsequent oxidative cleavage afforded the required biaryls with nonidentical (2 and 2′) acyl groups.

A recent synthetic approach leading to bis(benzocyclooctadiene) lignans, members of the schizandrin group, has been based on zinc-induced cyclization reactions of 2,2′-bis(α-bromoacyl) derivatives of 1,1′-biaryls.[1] In connection with our continuing interest in the synthesis of biologically active lignans with the bis(benzocyclooctadiene) structural framework, it was necessary to develop a synthetic route to unsymmetrical biaryls of structure A (where X and Y represent various substituents), possessing nonidentical 2,2′-acyl groups (R^1–R^4 = H, alkyl, alkenyl, or oxygen-containing carbon groups). Introduction of an α-bromo substituent at each acyl group would then provide the substrates needed for the zinc-induced cyclization leading to the tricyclic diketones B, potential intermediates for the



A B



C

elaboration of the natural compounds. From a search of previous work in this area we were not aware of an effective route leading to systems A. The Ullman reaction does not usually provide an effective answer for the coupling of nonidentical aryl moieties, whereas the recently reported coupling of α-haloarylimines[2] and of other haloaryl derivatives[3] did not involve compounds with (latent) ketone groups in both moieties. Moreover, the selective halogenation required by the above-mentioned methods at coupling sites in both moieties is sometimes difficult to bring about in the presence of other substituents in the rings.

A different approach leading to biaryls A can be envisaged via the oxidative cleavage of the 9,10-substituted bond of unsymmetrical phenanthrenes. However, in spite of a large variety of methods for the synthesis of phenanthrenes,[4] no effective route leading to phenanthrenes of structure C with nonidentical C-9 and C-10 carbon groups (R, R^1) and unsymmetrical substitution in the peripheral rings is available.[5]

The present investigation was therefore intended to approach the synthesis of biaryls A by developing a general route for the regiocontrolled substitution of the 9,10-bond of unsymmetrical phenanthrenes. We now describe how this objective can be achieved by a selective ketalization, when a bromine substituent is adjacent to one of the carbonyl functions of the corresponding phenanthrenequinones.

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(5) For a synthesis of some phenanthrenes of this structure via acid-catalysed cyclodehydration which requires, however, a preliminary preparation of biaryls, see C. K. Bradsher and L. S. Wissow, *J. Am. Chem. Soc.*, **68**, 2149 (1946); C. K. Bradsher and W. J. Jackson, *ibid.*, **76**, 4140 (1954). The Perkin–Pschorr sequence to 9-carboxylates,[6] followed by other steps for C-10 substitution, may also possibly provide a route for the regioselective preparation of systems C although no literature examples of such syntheses were found.

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