(5.8 g, 63%) as a white foam: ^{1}H NMR δ 5.57–5.51 (m, 1 H, vinyl), 4.03–3.82 (m, 8 H, $2CH_2CH_2O$), 3.64–3.53 (m, 2 H, CH_2O), 0.90 (s, 3 H, 18-CH_3); ^{13}C NMR δ 137.4, 124.1, 119.5, 109.5, 65.1, 64.5, 64.3, 64.1, 63.8, 51.5, 50.6, 45.9, 41.8, 39.3, 36.7, 34.0, 33.6, 31.0, 30.7, 30.2, 29.8, 27.2, 22.3, 21.1, 14.7; HRMS m/z (MH^+) calcd 419.2797, obsd 419.2775.

10-[3-[[(4-Methylphenyl)sulfonyl]oxy]propyl]estr-4-ene-3,17-dione (13). To a stirred solution of 11 (1.5 g, 35.8 mmol) in $CHCl_3$ (369 mL, EtOH free) cooled to 0 °C was added pyridine (8.7 mL, 107.6 mmol) followed by TsCl (13.7 g, 71.9 mmol) in portions. After 72 h at 0 °C, the reaction was washed with 0.5 N HCl (200 mL) and H_2O (200 mL) followed by saturated aqueous $NaHCO_3$ (200 mL), dried, and concentrated. The resultant crude 12[20] was dissolved in acetone (300 mL), and $TsOH·H_2O$ (1.2 g, 6.3 mmol) was added. After 20 h, the reaction was concentrated and the residue was partitioned between EtOAc (400 mL) and H_2O (150 mL). The organics were washed with H_2O (100 mL), dried, and concentrated. Chromatography (15% EtOAc/$CHCl_3$) gave 13 (12.6 g, 73% from alcohol 11) as a white foam: ^{1}H NMR δ 7.79 and 7.35 (pr d, 4 H, J = 8.1 Hz, aryl), 5.87 (s, 1 H, vinyl), 4.03 (t, 2 H, J = 5.5 Hz, CH_2O), 2.46 (s, 3 H, aryl-CH_3), 0.92 (s, 3 H, 18-CH_3); IR (KBr) 1738, 1670 cm^{-1}; MS (DCI/CH_4) m/z (rel intensity) 485 (MH^+, 100), 331 (17), 313 (17).

(20) Compound 12 was initially purified by chromatography (35% EtOAc/hexane) but was used crude in subsequent runs to improve the overall yield for the conversion of 11 to 13, and because of the relative instability of 12. For 12: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 and 7.36 (pr d, 4 H, aryl), 5.53–5.49 (m, 1 H, vinyl), 4.03–3.81 (m, 10 H, $2OCH_2CH_2O$ and CH_2O), 2.46 (s, 3 H, aryl-CH_3), 0.83 (s, 3 H, 18-CH_3); MS (DCI/CH_4) m/z (rel intensity) 574 (22), 573 (MH^+, 60), 419 (21), 402 (26), 401 (100), 400 (16), 399 (28), 357 (21), 339 (21), 217 (23), 173 (43), 93 (17). Anal. Calcd for $C_{32}H_{44}O_7S$: C, 67.11; H, 7.74. Found: C, 67.19; H, 7.96.

Anal. Calcd for $C_{28}H_{36}O_5S$: C, 69.39; H, 7.49. Found: C, 69.05; H, 7.83.

(4α,10α)-4,19-Cyclo-*A*-dihomoandrost-4b-ene-4a,17-dione (14). To a stirred solution of LHMDS (1.50 mL of a 1.0 M solution in THF, 1.50 mmol) in additional THF (15 mL) cooled to −78 °C was added a precooled (−78 °C) solution of 13 (242 mg, 0.50 mmol) in THF (10 mL), dropwise. After 40 min, the reaction was allowed to warm slowly to rt. After 1 h at rt, the reaction was poured into 0.5 N HCl (60 mL) and extracted with CH_2Cl_2 (60 mL and 30 mL). The combined organics were washed with 0.5 N HCl (60 mL) and saturated aqueous $NaHCO_3$ (60 mL) followed by brine (50 mL). Chromatography (45% EtOAc/hexane) gave 14 (96 mg, 62%) as a white solid: mp 180–183 °C; ^{1}H NMR δ 6.02 (s, 1 H, vinyl), 0.91 (s, 3 H, 18-CH_3); ^{13}C NMR δ 220.4, 202.6, 167.1, 128.1, 52.1, 51.1, 47.4, 43.1, 40.3, 38.8, 35.7, 34.6, 32.2, 31.4, 29.9, 27.3, 25.3, 21.7, 20.1, 18.8, 13.6; IR (KBr) 1740, 1658 cm^{-1}; MS (DCI/CH_4) m/z (rel intensity) 313 (MH^+, 100), 295 (18).

Anal. Calcd for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03. Found: C, 80.63; H, 9.33.

Acknowledgment. We thank Dr. John C. Huffman of Indiana University for crystallographic studies on 14. Complete crystallographic details are available in microfiche form from the Chemistry Library, Indiana University, Bloomington, Indiana, 47405. Request MSC Report No. 91709.

Supplementary Material Available: NMR spectra and X-ray data for 14 (43 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Medium-Sized Cyclophanes. 21.[1] Preparation and Reduction of *syn*- and *anti*-[3.2]Metacyclophanequinone and *anti*-[4.2]Metacyclophanequinone

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The title compounds, *anti*- and *syn*-[3.2]metacyclophanequinone (**12a**) and (**12b**), were prepared by oxidation of the corresponding *anti*- and *syn*-9,17-dihydroxy-6,14-di-*tert*-butyl[3.2]metacyclophanes (**10a**) and (**10b**) with $Tl(OCOCF_3)_3$ in CF_3COOH. When *anti*-[3.2]quinonophane (**12a**) was reduced with Zn powder in acetic acid, the corresponding tetrahydroxy derivative **14a** was obtained, which was converted to the quinhydrone **13a** by treatment with an equimolar amount of quinonophane **12a** in refluxing THF. The electronic spectrum of **13a** shows a band due to a charge-transfer complex at 400 nm (log ε 2.45). In contrast, attempted reduction of *syn*-quinonophane (**12b**) with Zn powder in acetic acid yielded only a complex mixture of products. It was also found that *syn*-quinonophane was easily converted to the corresponding [2 + 2] cycloadducts **16** and **17** by irradiation with sunlight or tungsten lamp. When oxidation of *anti*- and *syn*-10,18-dihydroxy-7,15-di-*tert*-butyl[4.2]-metacyclophanes (**11a**) and (**11b**) with $Tl(OCOCF_3)_3$ in CF_3COOH was carried out under the same conditions as [3.2]metacyclophanes, both compounds gave *anti*-metacyclophanequinone (**18a**). This finding suggests that the ring inversion to the thermodynamically more stable anti conformation is possible in the [4.2]metacyclophanequinone. While *anti*-[4.2]metacyclophanequinone (**18a**) was reduced with Zn powder in acetic acid, the color change of reaction mixture from pale yellow to reddish brown was observed due to the formation of the corresponding quinhydrone **19**. However, the attempted isolation of the quinhydrone **19** was unsuccessful. Rather, the fully reduced tetrahydroxy derivative **20** was obtained in 91% yield.

Introduction

The first charge-transfer bridged aromatic compound, [2.2]paracyclophanequinone (1) was prepared from [2.2]-paracyclophane by Cram[2] in 1966. Subsequently, the chemistry of the charge-transfer cyclophanes has been extensively studied.[3-8] Staab and Rebafka[5,9] reported that

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(1) Medium-Sized Cyclophanes. Part 20. Yamato, T.; Matsumoto, J.; Kajihara, M.; Tokuhisa, K.; Suehiro, K.; Tashiro, M. *Chem. Ber.*, in press.
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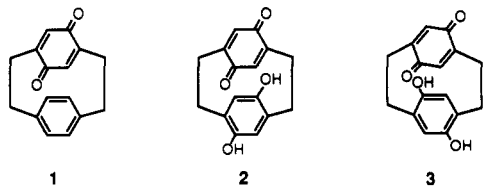


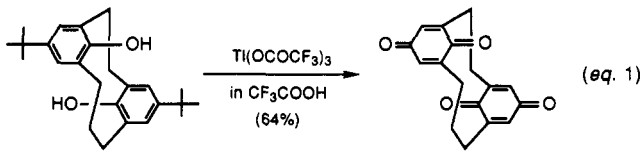
1 2 3

the partial hydrogenation of [2.2]paracyclophanequinones afforded the interesting intramolecular quinhydrones **2** and **3** as black and dark violet crystals, respectively. Likewise, Inazu and co-workers[10] reported the partial hydrogenation of *syn*-[3.3]metacyclophanequinone (**4**) to quinhydrone **5**, brown crystals, whereas the quinhydrone **7** obtained from *anti*-[2.2]metacyclophanequinone (**6**) was almost colorless as a solid, but was colored in solution.[11] Recently, Staab et al.[12] reported that catalytic hydrogenation of *syn*-[2.2]metacyclophanequinone (**8**) did not yield the desired quinhydrone but proceeded by transannular reaction to the isomeric 8,13-dihydroxy-8,16-epoxy[2.2]metacyclophane-5(8*H*)-one (**9**).

All of the previous cases are symmetrically bridged. However, [3.2]metacyclophanequinones have not been synthesized to date. Recently we reported that *syn*- and *anti*-9,17-dihydroxy-6,14-di-*tert*-butyl[3.2]metacyclophanes (**10**) and *syn*- and *anti*-10,18-dihydroxy-7,15-di-*tert*-butyl[4.2]metacyclophanes (**11**) are easily prepared from anisole in only eight steps.[1] These compounds afforded convenient starting materials for the attempted preparation of [3.2]- and [4.2]metacyclophanequinones.

Results and Discussion

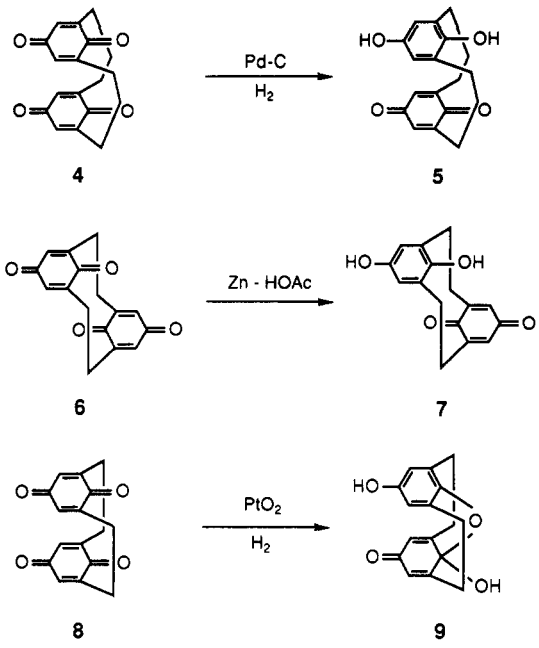
Oxidation of *anti*-9,17-dihydroxy-6,14-di-*tert*-butyl-[3.2]metacyclophane (**10a**) with $Tl(OCOCF_3)_3$[13,14] in CF_3COOH afforded the desired *anti*-[3.2]metacyclophanequinone (**12a**) in 64% yield (eq 1).



10a **12a** (*eq.* 1)

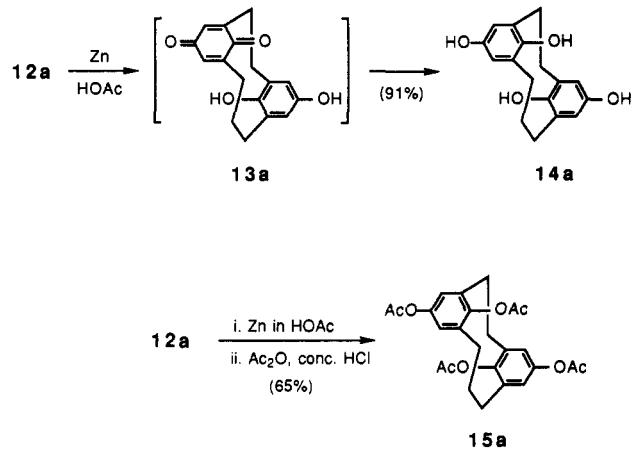
When zinc powder was added to a solution of **12a** in acetic acid, the solution changed color rapidly from yellow to reddish brown in a few minutes. After prolonged reaction the reaction mixture became colorless. The filtrate, after removal of excess zinc, afforded *anti*-6,9,14,17-tetrahydroxy[3.2]metacyclophane (**14a**) as colorless prisms in 91% yield. Reduction of **12a** with zinc powder in a mixture of acetic acid and acetic anhydride in the presence of a small amount of concentrated HCl afforded tetraacetate **15a** in 65% yield. Thus, partial hydrogenation of **12a** gives the colored **13a**, which can be reduced further in a few minutes to colorless **14a**.

Scheme I



4 **5** **6** **7** **8** **9**

Scheme II



13a **14a** **15a**

The ^1H NMR spectrum of **14a** shows that the protons on the oxygen atoms appear as two singlets at 4.79 and 8.36 ppm. The upfield signal is assigned to the internal OH groups, since their protons are shifted upfield by the ring current of the opposite aromatic ring.

We previously reported the reduction of [2.2]metaparacyclophanequinone with zinc powder in acetic acid to give tetrahydroxy[2.2]metaparacyclophane, from which [2.2]-metaparacyclophane quinhydrone was obtained as purplish brown solid by air oxidation.[15] However, **14a** failed to oxidize to the corresponding quinhydrone **13a**. Oxidative disproportionation of **14a** with an equimolar amount of quinone **12a** in refluxing tetrahydrofuran gave **13a** as reddish brown prisms in almost quantitative yield (eq 2). The structure of **13a** is readily confirmed by ^1H NMR.

$$\mathbf{12a} + \mathbf{14a} \xrightarrow[\text{reflux for 1 h}]{\text{THF}} 2 \times \mathbf{13a} \qquad (2)$$

The absorption band characteristic of a benzoquinone structure appeared in the electronic spectra of **12a**, which is absent in the spectrum of **13a** (Figure 1). However, the spectrum of **13a** shows a band due to a charge-transfer

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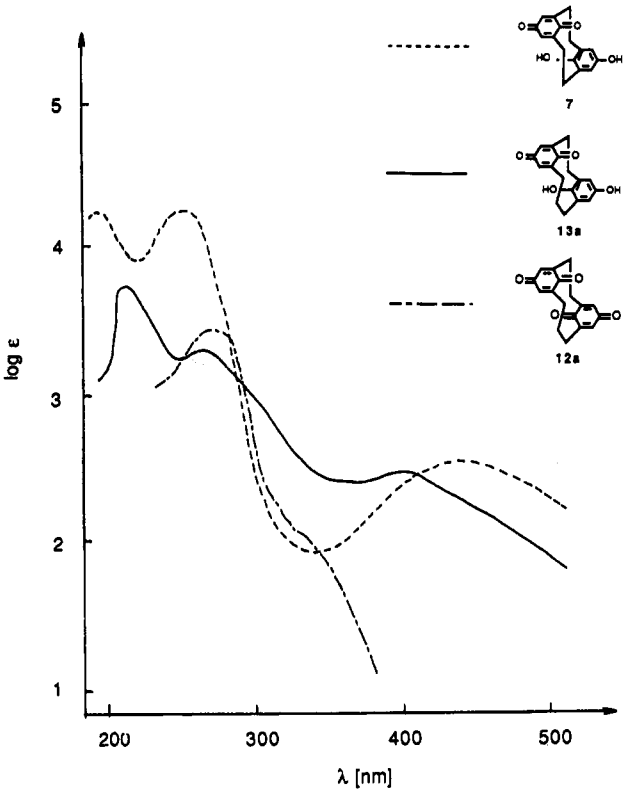
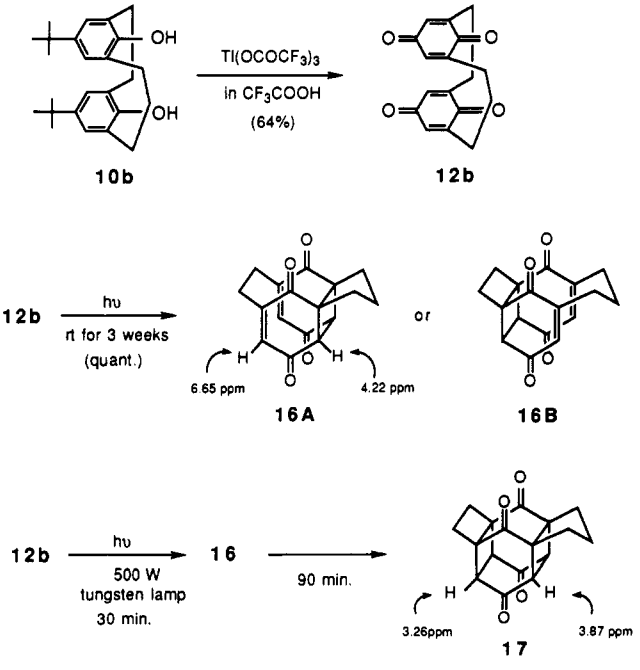


Figure 1. Electronic spectra of [2.2]metacyclophanequinhydrone (**7**) (in EtOH), *anti*-[3.2]metacyclophanequinone (**12a**) (in $CHCl_3$), and *anti*-[3.2]metacyclophanequinhydrone (**13a**) (in EtOH).

Scheme III



complex at 400 nm (log ε 2.45).

The electronic spectrum of **13a** shows a smaller charge-transfer interaction than in [2.2]metacyclophanequinhydrone (**7**) (λ_{max} 459 nm). This would be expected since the transannular interaction between the quinone and the hydroquinone rings of **7** is more favorable than that in **13a** due to the smaller distance between annular positions in **7**.

Oxidation of *syn*-9,17-dihydroxy-6,14-di-*tert*-butyl-[3.2]metacyclophanes (**10b**) with $Tl(OCOCF_3)_3$ in CF_3COOH afforded the anticipated *syn*-[3.2]metacyclophanequinone (**12b**) in 64% yield (Scheme III).

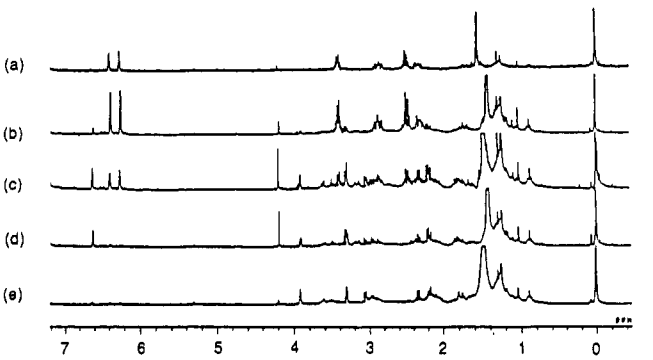
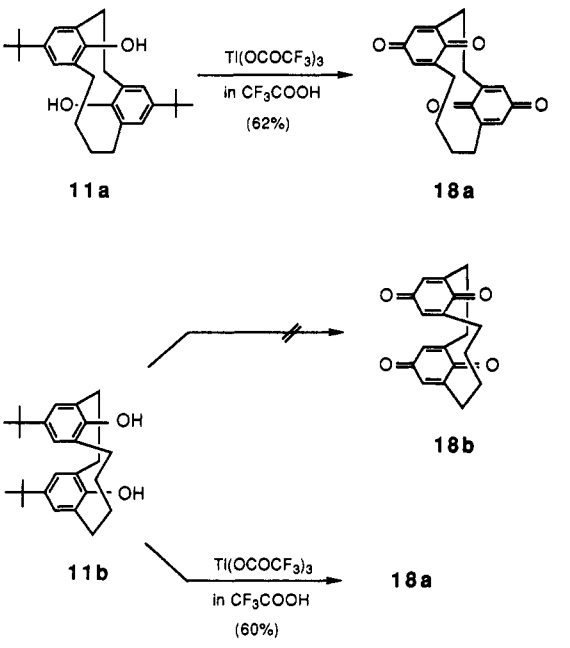


Figure 2. ^1H NMR spectra in irradiation of *syn*-[3.2]metacyclophanequinone (**12b**) in CCl_4 by a 500-W tungsten lamp: (a) before irradiation; (b) after 10 min; (c) after 15 min; (d) after 30 min; (e) after 90 min of irradiation.

Scheme IV



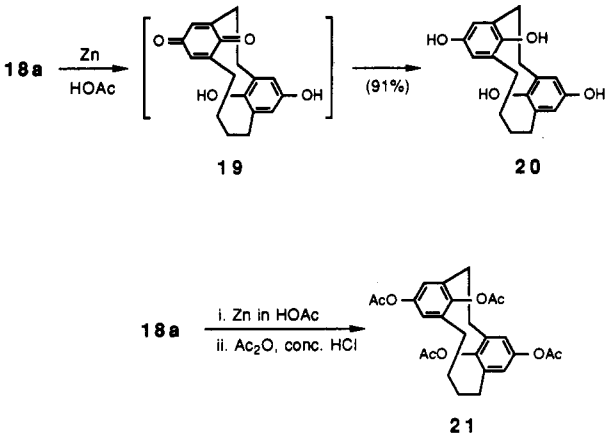
Compound **12b** is labile to sunlight. It was converted completely to the corresponding [2 + 2] cycloadduct **16** in hexane solution within 3 weeks of exposure to direct sunlight. The ^1H NMR spectrum of **16** shows methine protons at 4.22 ppm as a singlet and olefinic protons at 6.65 ppm as a singlet. There are two possible structures (**16A** or **16B**) for compound **16**. However, the second possible structure (**16B**) seems less likely since **16B** contains two four-membered rings, but **16A** contains the less strained five-membered ring.

When a solution of **12b** in carbon tetrachloride was irradiated with a 500-W tungsten lamp at room temperature in a ^1H NMR sample tube, the signals for the corresponding [2 + 2] adduct **16** were observed within 30 min. After irradiation for 90 min, the signals for both olefinic protons disappeared and the signals for two methine protons appeared at 3.26 and 3.87 ppm (Figure 2). The formation of the caged compound **17** is thus proposed.

Attempted reduction of the *syn*-quinonophane (**12b**) with Zn powder gave a complex mixture of products which were not resolved. The reaction mixture changed from pale yellow to reddish brown as in the reduction of the anti confomer **12a**.

When oxidation of *anti*-10,18-dihydroxy-7,15-di-*tert*-butyl[4.2]metacyclophane (**11a**) with $Tl(OCOCF_3)_3$ in

Scheme V



CF_3COOH was carried out under the same conditions as for **10a**, the desired *anti*-[4.2]metacyclophanequinone (**18a**) was obtained in 62% yield. However, like treatment of *syn*-10,18-dihydroxy-7,15-di-*tert*-butyl[4.2]metacyclophane (**11b**) did not give the desired *syn*-[4.2]metaquinonophane (**18b**), but rather the anti conformer **18a** in 60% yield. Thus, ring inversion to the thermodynamically more stable anti conformation is possible in the [4.2]quinonophane system. This hypothesis is supported by inspection of molecular models. A similar observation was reported by Inazu et al. upon oxidation of *anti*-9,18-dihydroxy-6,15-di-*tert*-butyl[3.3]metacyclophane to give *syn*-[3.3]metaquinonophane.[10]

When *anti*-[4.2]quinonophane (**18a**) was reduced with Zn powder in acetic acid, the expected color change of the reaction mixture from pale yellow to reddish brown was observed, due to formation of the intermediate quinhydrone **19**. However the attempted isolation of the quinhydrone **19** was unsuccessful. Instead the tetrahydroxy derivative **20** was obtained in 91% yield. Reduction of **18a** with zinc powder in a mixture of acetic acid and acetic anhydride in the presence of a small amount of concentrated HCl afforded the tetraacetate **21** in 80% yield. Attempted preparation of *anti*-[4.2]metacyclophanequinhydrone (**19**) by oxidative disproportionation of **20** with an equimolar amount of quinone **18a** in refluxing tetrahydrofuran revealed generation of **19** by ^1H NMR, but a pure sample of **19** could not be isolated.

Although attempts to isolate *syn*-[3.2]metacyclophanequinhydrone (**13b**) and *anti*-[4.2]metacyclophanequinhydrone (**19**) were unsuccessful, further studies on the partial reduction of *syn*-[3.2]metacyclophanequinone (**12b**) and *anti*-[4.2]metacyclophanequinone (**18a**) are now in progress.

Experimental Section

All melting and boiling points are uncorrected. NMR spectra were recorded at 270 MHz with Me_4Si as an internal reference. IR spectra were measured as KBr pellets. Mass spectra were obtained at 75 eV using a direct inlet system.

***anti*-[3.2]Metacyclophanequinone (12a).** To a standard solution of 3 mL of trifluoroacetic acid (TFA) containing 1.9 mmol of $Tl(TFA)_3$ was added 150 mg (0.41 mmol) of (**10a**) at 0 °C, and the resulting deep red mixture was stirred at rt for 1.5 h. The reaction mixture was poured into 10 mL of ice–water and extracted with 20 mL of CH_2Cl_2, and the CH_2Cl_2 extracts were washed with water and dried (Na_2SO_4). Concentration of the solution gave a yellow paste. Column chromatography (silica gel 300 mesh) of the paste using $CHCl_3$ as eluent afforded crude quinone **12a**. Recrystallization from hexane gave 74 mg (64%) of quinone **12a**: yellow prisms (hexane); mp 251–252 °C; IR (KBr) 1650, 1622 (C=O) cm^{-1}; ^1H-NMR ($CDCl_3$) δ 2.20–2.95 (10 H, m), 6.48 (2 H, d, J = 2.4 Hz), 6.52 (2 H, d, J = 2.4 Hz); MS (m/e) 282 (M^+). Anal. Calcd for $C_{17}H_{14}O_4$: C, 72.33; H, 5.00. Found: C, 72.03; H, 5.00.

***anti*-6,9,14,17-Tetrahydroxy[3.2]metacyclophane (14a).** To a solution of 100 mg (0.354 mmol) of **12a** in 30 mL of acetic acid was added 1.0 g of zinc powder, resulting in formation of a yellow color that immediately turned reddish brown. The reaction mixture was stirred at rt for a few min until it became colorless. The excess zinc powder was removed by filtration and the solvent distilled in vacuo to leave a brown solid. The mixture was taken up in water. The remaining solid was filtered and washed with water and then hexane to give 30 mg (30%) of tetrol (**14a**). The aqueous solution was extracted with ether several times, dried (Na_2SO_4), and concentrated in vacuo to leave 61 mg (61%) of (**14a**): pale brown prisms; mp 240–245 °C; IR (KBr) 3480, 3360 (OH) cm^{-1}; ^1H-NMR (DMSO-d_6) δ 1.8–2.76 (10 H, m), 4.79 (2 H, s, internal OH, exchanged by D_2O), 6.27 (2 H, d, J = 3 Hz), 6.33 (2 H, d, J = 3 Hz), 8.36 (2 H, s, external OH, exchanged by D_2O); MS m/e, 286 (M^+). Anal. Calcd for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34. Found: C, 71.50; H, 6.25.

***anti*-6,9,14,17-Tetraacetoxy[3.2]metacyclophane (15a).** To a solution of 30 mg (0.086 mmol) of [3.2]metacyclophanequinone (**12a**) in 10 mL of acetic acid was added 0.5 g (7.7 mmol) of zinc powder. The reaction mixture was stirred at rt for a few min. After the yellow solution turned colorless, 10 mL of acetic anhydride and 8 drops of concentrated HCl were added to the reaction mixture. The reaction mixture was stirred at 80 °C for 10 min, filtered, and poured into 100 mL of water. After the aqueous solution was stirred at rt for 1.5 h, it was extracted with 20 mL of CH_2Cl_2, washed with water, dried (Na_2SO_4), and concentrated in vacuo to leave 45 mg of crude **15a**. Recrystallization from hexane–benzene (1:1) gave 25.5 mg (65%) of **15a**: pale brown prisms (hexane–benzene (1:1)); mp 189–194 °C; IR (KBr) 1765 (C=O) cm^{-1}; ^1H-NMR ($CDCl_3$) δ 1.93 (6 H, s), 1.95–1.85 (10 H, m), 2.28 (6 H, s), 6.93 (2 H, d, J = 2.0 Hz), 6.94 (2 H, d, J = 2.0 Hz); MS m/e 286 (M^+). Anal. Calcd for $C_{25}H_{26}O_8$: C, 66.07; H, 5.77. Found: C, 66.36; H, 5.73.

***anti*-[3.2]Metacyclophanequinhydrone (13a).** To a solution of 6.30 mg (0.022 mmol) of **14a** in 10 mL of THF was added 6.21 mg (0.022 mmol) of **12a**. After the reaction mixture was refluxed for 1 h, it was cooled and concentrated to give **13a** in almost quantitative yield. **13a**: reddish brown prisms; mp 208–210 °C; IR (KBr) 3400 (OH), 1650, 1622 (C=O) cm^{-1}; ^1H-NMR (DMSO-d_6) δ 1.9–2.8 (10 H, m), 6.25 (1 H, d, J = 2.4 Hz), 6.28 (1 H, d, J = 2.4 Hz), 6.35 (1 H, d, J = 2.4 Hz), 6.43 (1 H, d, J = 2.4 Hz), 7.62 (1 H, s, internal OH), 8.86 (1 H, s, external OH); MS m/e 284 (M^+). Anal. Calcd for $C_{17}H_{16}O_4$: C, 71.82; H, 5.67. Found: C, 72.03; H, 5.50.

***syn*-[3.2]Metacyclophanequinone (12b).** The oxidation of **10b** was carried out as described above in the preparation of **12a**. Purification by column chromatography (silica gel 300 mesh) using $CHCl_3$ as eluent afforded 74 mg (64%) of **12b**. Attempted recrystallization from hexane was unsuccessful. After 3 weeks in the light of the room, the [2 + 2] cycloaddition product **16** was obtained in quantitative yield.

12b: yellow solid; IR (KBr) 1650, 1622 (C=O) cm^{-1}; ^1H-NMR ($CDCl_3$) δ 2.0–3.0 (8 H, m), 3.3–3.6 (2 H, m), 6.28 (2 H, d, J = 2.4 Hz), 6.41 (2 H, d, J = 2.4 Hz); MS m/e 282 (M^+). Anal. Calcd for $C_{17}H_{14}O_4$: C, 72.33; H, 5.00. Found: C, 72.03; H, 5.00.

16: colorless powder (hexane); mp 198–202 °C; IR (KBr) 1690 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 2.2–3.7 (10 H, m), 4.22 (2 H, s), 6.65 (2 H, s); MS m/e 282 (M^+). Anal. Calcd for $C_{17}H_{14}O_4$: C, 72.33; H, 5.00. Found: C, 72.13; H, 5.13.

Irradiation of 12b To Give 16 and 17. A solution of 1 mg (0.0035 mmol) of **12b** in 1 mL of CCl_4 was irradiated at rt with a 500-W tungsten lamp. The reaction was monitored by ^1H-NMR spectroscopy. The spectrum is shown in Figure 2. After irradiation for 1.5 h, the solvent was removed to give **17** as a colorless powder: ^1H-NMR ($CDCl_3$) δ 2.2–3.7 (10 H, m), 3.26 (2 H, s), 3.87 (2 H, s).

***anti*-[4.2]Metacyclophanequinone (18a).** The oxidation of **11a** and **11b** were carried out as described above in the preparation of **12a**. Recrystallization of the crude quinone from **11a** from hexane gave 75 mg (62%) of **18a**: yellow prisms (hexane); mp >230 °C dec; IR (KBr) 1648 (C=O) cm^{-1}; ^1H-NMR ($CDCl_3$) δ 1.40–1.70 (4 H, m), 1.90–2.10 (2 H, m), 2.40–2.60 (2 H, m), 2.75–2.90 (4 H, m), 6.47 (2 H, d, J = 2.4 Hz), 6.63 (2 H, d, J = 2.4 Hz); MS

m/e 296 (M^+). Anal. Calcd for $C_{18}H_{16}O_4$: C, 72.95; H, 5.44. Found: C, 72.63; H, 5.56.

The reaction mixture from **11b** was treated as described above to afford crude quinone. Recrystallization from hexane gave 73 mg (60%) of **18a**.

***anti*-7,10,15,18-Tetrahydroxy[4.2]metacyclophane (20).** To a solution of 100 mg (0.338 mmol) of **18a** in 30 mL of acetic acid was added 1.0 g of zinc powder. Addition of zinc powder to the mixture produced a yellow to reddish brown color immediately. The reaction mixture was stirred at rt for a few min. After the reaction mixture became colorless, the reaction mixture was treated as described above to give 92 mg (91%) of **20**: colorless prisms; mp >300 °C; IR (KBr) 3500–3350 (broad, OH) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 1.2–1.5 (4 H, m), 1.8–2.0 (2 H, m), 2.5–2.8 (6 H, m), 5.24 (2 H, s, internal OH, exchanged by D_2O), 6.17 (2 H, d, J = 2.8 Hz), 6.41 (2 H, d, J = 2.8 Hz), 8.44 (2 H, s, external OH, exchanged by D_2O); MS *m/e* 300 (M^+). Anal. Calcd for $C_{18}H_{20}O_4$: C, 71.98; H, 6.71. Found: C, 72.14; H, 6.81.

***anti*-7,10,15,18-Tetraacetoxy[4.2]metacyclophane (21).** Metacyclophane **21** was prepared in 80% yield using the same procedure as described above: colorless prisms (hexane–benzene (1:1)); mp 272–274 °C; IR (KBr) 1757 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.24–1.60 (4 H, m), 1.96 (6 H, s), 2.10–2.80 (8 H, m), 2.28 (6 H, s), 6.78 (2 H, d, J = 2.4 Hz), 6.97 (2 H, d, J = 2.4 Hz); MS *m/e* 468 (M^+). Anal. Calcd for $C_{26}H_{28}O_8$: C, 66.66; H, 6.02. Found: C, 66.34; H, 6.31.

Attempted Reaction of 18a and 20 To Give 19. Attempted preparation of *anti*-[4.2]metacyclophane quinhydrone (**19**) was carried out by reaction of **18a** and **20** in refluxing THF by the same procedure as for **13a**. Although the formation of **19** was observed by ^{1}H NMR, isolation of **19** in a pure state was not achieved.

Acid Catalyzed Racemization of 1-(Heterocyclyloxy)-2,3-propanediols

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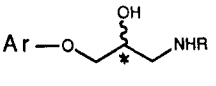
A number of enantiomerically pure heterocyclic ketals **5** have been prepared, and their acid-catalyzed hydrolysis to the corresponding diols **6** has been studied. During this reaction a rearrangement may occur to give racemic products, and so the kinetics of the two competing reactions have been studied to establish optimum conditions. The rate of rearrangement is independent of pH below the pK_a of the heterocycle, whereas the rate of ketal hydrolysis continues to increase as pH is lowered. Brief treatment with strong acid has allowed the formation of very pure diols in high yield.

Introduction

β-Adrenergic blocking drugs are of great importance in the treatment of cardiovascular disease,[1] and one class of drug, the (aryloxy)propanolamines, may be represented by structure **1**, in which the asterisked carbon atom in-



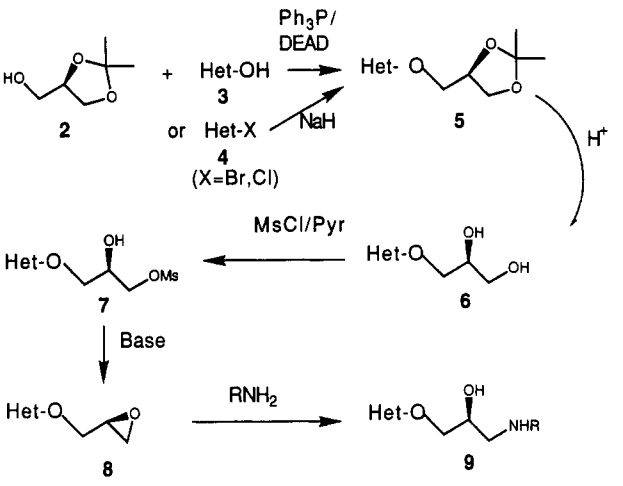
1

dicates that two enantiomers of **1** are possible. In practice most β-adrenergic blocking drugs are sold as racemates, although there is increasing interest in the synthesis and development of pure enantiomers.[2]

One useful synthetic sequence is shown in Scheme I, where the availability of enantiomerically pure glycerol acetonide (**2**) enables the ready synthesis of the heterocyclic ethers **5** from the appropriate hydroxy (**3**) or halo (**4**) heterocycles. These ketal–ethers may be cleaved to diols (**6**) which may be cyclized to epoxides (**8**) by a variety of means, of one of which involves the mesylates (**7**) shown.

An early report by Syntex workers[3] described the synthesis of the *S*-enantiomer of tazolol (**9**, Het = 2-thiazolyl, R = Pr^i) by this route which, however, led to a partially racemic product. The authors ascribed this to a lack of selectivity in the mesylation of **6**, but the reaction was

Scheme I



investigated further by McClure et al.,[4] who proposed that the acid-catalyzed racemization of the diol **6** during prolonged exposure to the hydrolysis conditions was partially responsible for the loss of chiral integrity. The mechanism proposed for this pseudo-Smiles rearrangement[5] is shown in Scheme II and involves the interconversion of (*S*)-**6** to (*R*)-**6** via the intermediate **10**.

As part of our cardiovascular research program we required a number of enantiomerically pure heterocyclic

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